

The Epidemiology of Diabetes Mellitus

The Epidemiology of Diabetes Mellitus An International Perspective

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Foreword by

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FOREWORD

In recent decades, there has been a relative absence of new books in the area of epidemiology of diabetes. Yet, since the publication of Dr Kelly West's landmark book on the *Epidemiology of Diabetes and its Vascular Complications* in 1978, great changes have taken place. The World Health Organization has revised the criteria and classification of diabetes on several occasions, as have the American Diabetes Association. Meanwhile the long-awaited results of the United Kingdom Prospective Diabetes Study (UKPDS) were published and the Diabetes Prevention Program has reported as this book goes to press, alas too late for inclusion in this book. A profusion of studies worldwide have confirmed that an epidemic of Type 2 diabetes, as part of the 'globalization' process, is occurring across the world affecting particularly developing countries.

Some of the most important developments in diabetes have emerged through epidemiology. The rising prevalence and incidence of Type 2 diabetes in many populations has stimulated research on the genetic, environmental, behavioural, socio-economic and cultural factors contributing to the epidemic. This highlights the sociological aspects of epidemiology and public health.

The main intention of this book is to mainly help disseminate the most recent epidemiological data about diabetes mellitus among the many different people involved in diabetes health care, including diabetologists, internists, nurses and other health care providers and health decision makers. A glance at the book's list of contents shows that diabetes has no boundaries, no frontiers and is indeed an international problem.

In the discipline of epidemiology, it's important to consider study methodology and design in interpreting epidemiological reports. Many factors should be considered such as the definition of diabetes mellitus, populations differences and various other adjustments. The editors and authors have paid careful attention to these problems while reviewing the international literature. The importance of standardization of methodology must be emphasized. It is not always possible to make direct

comparison in terms of diabetes risk, prevalence, incidence and complications rates between different populations. However, an international approach focuses primarily on geographically specific aspects of the disease using the same definition.

Epidemiology is not a static science. The recent advances that have been accomplished so far in different epidemiological studies have increased our knowledge about different types of diabetes worldwide. Is it still worthwhile to continue to perform large scale population surveys except in communities where that information is lacking? Some background information is needed before attempting interventions. Although some regions and populations still have to be evaluated, it is time for action. Primary prevention of diabetes mellitus should become a reality.

So, a second and very important aim of this book is to provide the current evidence for primary prevention. The time is ripe to take action in places where the prevalence of diabetes is known and is increasing. This book will hopefully help those who have a specific interest in public health to use adequate tools in measuring the impact of diabetes in a given population. Studies from China, Finland and the USA have clearly shown that weight control and adequate physical activity substantially reduce the risk of developing diabetes. However, it is equally clear that many people do not respond to lifestyle advice. Therein lies a major challenge. The burden that diabetes places on individuals and societies is huge and difficult to evaluate. The medical impact includes mainly the socio-economic costs that treatment of complications and early death impose. The book gives a clear view of this important component of diabetes. In spite of dramatic developments in the treatment of diabetes and its complications, primary prevention of diabetes remains somehow untouched in most countries. The hope is that attitudes will change once this book has been read.

Sir George Alberti

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Jean-Marie Eko 
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Montreal, Leeds, Melbourne
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- Index compiled by Annette Musker*

Introduction

Jean-Marie Ekoé, Rhys Williams, Paul Zimmet

Twenty three years ago Dr Kelly West published the first volume on the epidemiology of diabetes and its vascular complications (1). He left his own unique memorial in a book that critically reviewed more than 2000 papers. This outstanding review gathered most of the contributions, clinical and population-based, on the subject of diabetes epidemiology and highlighted the many gaps in our diabetes epidemiology knowledge at that time.

Much has happened in the last two decades. The present volume bridges the more than twenty years that have elapsed since Dr Kelly West's milestone monograph and we hope it will provide a stimulating 'state of the art' review of recent epidemiological studies spanning the globe.

The book presents and discusses the new diagnostic criteria and classification of diabetes. At the end of the 1970s confusion reigned both with regard to the classification of diabetes and to the appropriate diagnostic tests and their interpretation. Enormous variation in diagnostic cut-off values, in size of the glucose load and clear definition of types of diabetes prevailed. In 1979 and 1980 the National Diabetes Data Group (NDDG) in the USA (2) and the World Health Organization (WHO) Second Expert Committee on Diabetes (3) brought some order. Further revisions have resulted in new recent classification and diagnostic criteria that seem to be more consistent and less controversial (4, 5). One of the major changes in the provisional World Health Organization Consultation report is the disappearance of the Malnutrition Related Diabetes Mellitus (MRDM) as a major category (4). Whilst the protein-deficient pancreatic diabetes (PDPD) variant of MRDM has been dropped, the former fibrocalculous pancreatic diabetes (FCPD) variant is now part of the other types category which include all those types where aetiology is more

clear. A chapter discusses this issue. One major difference remains in Gestational Diabetes Mellitus (GDM). The American Diabetes Association (ADA) has not changed its testing and criteria whilst WHO includes both impaired glucose tolerance (IGT) and new diabetes in pregnancy under the banner of GDM (4, 5). Compared to what was reigning in the 70s this is 'order out of chaos'. However, there is still room for improvement.

The available diagnostic criteria and classification have been widely used since the early 80s in numerous epidemiological studies, allowing comparisons between countries, regions and different populations worldwide. The results of these studies, suggest that the prevalence of diabetes will dramatically increase in the next quarter of this century both in the developed and the developing countries. The World Health Organization (6) suggests an increase worldwide of the prevalence of diabetes in adults of 35% and an increase in the number of people with diabetes of 122%. The developing countries will face an increase of 48% in the prevalence of, and an increase of 170% in the number of people with, diabetes compared to an increase in the prevalence of diabetes of 27% in developed countries, with an increase of 42% in the number of people with diabetes.

Although caution should be expressed regarding these figures due to the lack of suitable survey data, and extrapolations in some places and countries, the epidemic nature of diabetes in the world is supported by studies summarized in this book.

The likely burden of diabetes during the first years of the twenty-first century should not be overlooked: Figures of 135 million adults with diabetes in 1995 rising to probably 300 million in

year 2025 are not far from reality and may even underestimate the magnitude of this major public health problem. Application of new diagnostic criteria will probably add another 2% in the prevalence of diabetes. The greater longevity of women likely explains the fact that there are more women than men with diabetes in many countries. The increasing concentration of diabetes in urban areas of developing countries is notorious and clearly emerges from the reported surveys.

There is now considerable evidence that Type 2 diabetes is lifestyle-related. Given the dramatic change of lifestyle in many developing nations, researchers have had great opportunities to study the genetic and environmental determinants of Type 2 diabetes through both cross-sectional and longitudinal studies. The book presents an extensive overview of these studies and focuses on evidence for prevention of diabetes.

In the last 20 years dramatic changes in the management of Type 1 diabetes have positively modified the natural history of this disorder. The benefits of tight metabolic control have been demonstrated in numerous studies and most conclusively in The Diabetes Control and Complications Trial (DCCT) for Type 1 diabetes (7) and in the United Kingdom Prevention Diabetes Survey (UKPS) for Type 2 diabetes (8–11). An upsurge of interest in diabetes epidemiology that started in the early 80s was immensely reinforced. Although incidence and prevalence data have added only limited information to our further understanding of the aetiology of diabetes, their importance in adding to our knowledge of the public health implications of this disease is considerable. Evidence for prevention is surely emerging and is thoroughly discussed in this volume.

Following the euphoria of the discovery of insulin in the 20s appeared the recognition of most of the disorders due to diabetic complications. The natural progression of the disease to nephropathy and retinopathy led to renal failure and blindness. The consequences of cardiovascular disease and neuropathy resulted in early cardiovascular death, foot disease and amputations. Although it is now possible to reduce the incidence of complications, or, when they occur, retard their progression, their prevalence and incidence remain unacceptably high. The book addresses the magnitude of diabetic complications, time trends and geographical variations.

Proper care of diabetes in the 2000s implies identification of all patients with diabetes and early detection of complications which will enable care providers to take the steps needed to combat the disease. This may not be possible at all in the absence of epidemiological data. This book will therefore be a very useful tool for diabetes care providers, researchers and public health experts. It provides a global picture of the characteristics of the epidemic nature of diabetes and its complications. It is hoped that those of all disciplines involved in diabetes, regardless of their fields of expertise, will find both interest and practical help from its content.

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Part I

Definitions and Evidence for Prevention

The Clinical Syndrome and the Biochemical Definition

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DEFINITION OF THE DIABETIC STATE

Diabetes mellitus is a disease that was recognized in antiquity. Polyuric states resembling diabetes mellitus were described as early as 1550 BC in the ancient Egyptian papyrus discovered by George Ebers (1). The term 'diabetes', which is from the Ionian Greek meaning 'to pass through', was first used by Aretaeus of Cappadocia in the second century AD as a generic description of conditions causing increased urine output (2). The association of polyuria with a sweet-tasting substance in the urine was noted in the fifth to sixth century AD by two Indian physicians, Susruta and Charuka (1, 2). The urine of certain polyuric patients was described as tasting like honey, sticky to the touch and attracting ants. Two forms of diabetes could be distinguished in the Indians' descriptions: one affected older, fatter people and the other thin people who did not survive long; this strongly reminds us the present clinical description of Type 2 and Type 1 diabetes.

The term diabetes mellitus, an allusion to the honeyed taste of the urine, was first used in the late eighteenth century by John Rollo and others (3) to distinguish it from other polyuric states in which the urine was tasteless. The concept that diabetes was a systemic disease arising in the blood was elaborated a century before (in the seventeenth century) by Matthew Dobson, a physician in Liverpool (England) who published a series of experiments showing that the serum of a patient with diabetes, as well as the urine, contained a sweet-tasty substance namely sugar (4).

The nineteenth century is the key century that has greatly contributed to the understanding of

diabetes. Claude Bernard made numerous discoveries in the field of metabolism and diabetes. He described the storage of glucose in the liver as a glycogen and the acute hyperglycemia that followed experimental damage of the medulla oblongata known as 'piqûre' diabetes (5). Oskar Minkowski and Josef Von Mering noted that total pancreatectomy produced diabetes in dogs (6). The pancreatic islets were named after Paul Langerhans by Edouard Lafresse. Langerhans had suggested that pancreatic islets produced a glucose-lowering substance. This substance was named insulin by Jean de Meyer in 1909, almost a decade before insulin was discovered (7). Although diabetes mellitus has been recognized for many centuries and major advances have been accomplished since the discovery of insulin in the understanding of diabetes and metabolism, there was no clear or widely accepted definition of the diabetic state until the early 80s.

In 1980, the World Health Organization (WHO) Expert Committee on diabetes mellitus (8) defined the diabetic state as a state of chronic hyperglycemia which may result from many environmental and genetic factors often acting jointly. Hyperglycemia is due to defects in insulin secretion, insulin action or both. This imbalance leads to disturbances of carbohydrate, fat and protein metabolism. The major effects of diabetes mellitus include long-term damage, dysfunction and failure of various organs. Diabetes mellitus may present with characteristic symptoms: thirst, polyuria, polydipsia, blurring of vision, weight loss, and infections. In its most severe forms, ketoacidosis or a non-ketotic hyperosmolar state may develop and lead to stupor, coma and, in absence of effective treatment, death. Most of the time, symptoms are

not severe, or may be absent, and consequently hyperglycemia of sufficient degree to cause pathological and functional changes may be present for a long time before the diagnosis is made. The long-term complications of diabetes mellitus include progressive development of disease of the capillaries of the kidney and retina, damage to the peripheral nerves and excessive atherosclerosis. The clinical manifestations of these complications therefore include nephropathy that may lead to renal failure, retinopathy with potential blindness, neuropathy with risk of foot ulcers, amputation, Charcot joints, and features of autonomic dysfunction, including sexual dysfunction. People with diabetes are at increased risk of cardiovascular, peripheral vascular and cerebrovascular disease. Diabetes mellitus is thus defined as a set of abnormalities characterized by a state of sustained hyperglycemia. It is a clinical description with a chemical definition. Pathogenic mechanisms and various explanations, to be found, lie behind the sustained hyperglycemia. Processes which destroy the beta-cells of the pancreas with consequent insulin deficiency, and others that result in resistance to insulin action are part of a possible group of processes involved in the development of diabetes.

THE CLINICAL SYNDROME

The usual clinical symptoms of diabetes mellitus, polyuria and polydipsia are the direct result of the high blood glucose concentration. Weight loss in spite of polyphagia, ketoacidosis, visual changes, skin infections, sepsis and pruritus belong to the same list of symptoms. With mild hyperglycemia, these cardinal symptoms are lacking. The description of a clear clinical syndrome bears a very low incidence (1/10 000 per year) and prevalence (9). It is not surprising that few studies have systematically determined the frequency of various symptoms and their relationship to factors such as age, sex and degree of glycemia. The frequency of most symptoms is quite different in previously undiscovered diabetes, as contrasted with people with diabetes who have been under treatment for months or years. Other factors such as intensity of treatment, degree of acceptance of recommended therapy and age of onset, do affect the frequency of the different symptoms (9). The description of a

clear clinical syndrome which encompasses different and probably non-specific symptoms seems to be a poor definition criterion (10). Responses recorded from approximately 1700 diabetics in Bauer's study (10) pertaining to symptoms presented in the beginning of or during the disease, showed no specificity for diabetes. Almost 52% of the patients had none of these 'diabetic symptoms'. No data were gathered in this study on the frequency of these symptoms in the general population or in people without diabetes. Welborn et al.'s study (11) was a controlled study. The authors compared rates of symptoms in known subjects with diabetes and in those found to be either affected or non-affected with diabetes in a survey. An increase of thirst was reported by 12% of the new 'screenees' with diabetes, 13% of known people with diabetes and 5% of people without diabetes. Polyuria was reported by 28% of new cases, 13% of known people with diabetes and 11% of people without diabetes. Visual deterioration was reported by 35% of newly diagnosed cases, 31% of known individuals with diabetes and 25% of people without the disease. A history of pruritus vulvae was reported by 29% of both groups of women with diabetes and 15% of non-affected women.

In the Bedford survey (12), symptoms of diabetes were only slightly more common in those with 2 h blood glucose levels over 6.7 mmol/l (120 mg/dl) than in those with lower values. In several other studies, classical diabetes symptoms are lacking in more than 25% of newly diagnosed diabetics (9).

The clinical recognition of glycosuria as the sole marker of diabetes is also unreliable. Quite a few patients with high renal thresholds or mild hyperglycemia may be missed. Furthermore, the number of false-positives is not minimized by this procedure in certain conditions. Therefore, the prevalence of diabetes will be underestimated when one restricts oneself to the classical syndrome. The use of blood glucose estimation (population screening) greatly raises the prevalence of diabetes when it is used instead of glycosuria determination. West, Keen and others have estimated that between the classical historical phase of ascertainment and the clinical/glycosuric phase, diabetes rates increased at least 10-fold. They increased 10-fold again with the epidemiological blood glucose screening phase (9, 13).

THE BIOCHEMICAL DEFINITION

Hyperglycemia: the Common Factor

The epidemiological attempt to study the natural history and pathogenesis of diabetes as a whole can only rely on one common and stable factor, high blood glucose, despite the wide variation in clinical manifestations and various contributing factors. However, high blood glucose alone does not answer all the questions. Over the past 30 years, evidence has accumulated that numerous and etiologically different mechanisms (genetic, environmental or immunologic processes) may play an important role in the pathogenesis, the clinical course and the emergence of complications of the 'diabetic state' (9, 14). Does correction of hyperglycemia prevent all of the various pathologic changes observed with diabetes? There is some evidence that people with diabetes who are not treated develop more complications than well-controlled patients (9, 15, 16). However, there are few instances in which characteristic complications of diabetes have been described before hyperglycemia was observed. This indicates the vast heterogeneity of diabetes and illustrates the fact that it is not yet clear to what extent the long-term classical diabetic complications are the result of hyperglycemia, the generally accepted and fundamental factor for diabetes, or related factors such as, for instance, insulin deficiency, plasma or tissues osmolality changes, glycated proteins and lipid abnormalities. Despite these questions, hyperglycemia remains the most important factor required for the diagnosis of diabetes.

SIGNIFICANCE OF BLOOD GLUCOSE IN POPULATION

In different populations, the distribution of blood glucose may vary greatly. In one of the early studies of diabetes epidemiology performed in the USA and based on medical history, urine glucose tolerance in a defined community, Wilkerson and Krall reported a large variation in the distribution of blood glucose values within the eight screening age groups (17). One pertinent fact was observed: higher levels of blood glucose were apparent with aging. In the 75–79 years age group, 50% of subjects had high blood glucose. This has been

confirmed in other health surveys (18). Where does diabetes start? In most populations, the degrees of hyperglycemia used for diagnosis of diabetes are based upon the findings in large, normal population samples and validated by prospective observations on outcome (13). However, there are still, to some extent, arbitrary lines across a continuous distribution of values in most populations (e.g., distribution of capillary blood glucose). Most unselected Caucasian populations display a unimodal distribution of glycemia: 80–85% of people have normal blood glucose, 2–4% are in the diabetes range. Between these two extremes remains a third category of people neither frankly diabetic nor non-diabetic. These people have an unpredictable future. It has been recognized by both the National Diabetes Data Group (19) and the World Health Organization (8, 20) that this category of 'borderline diabetics' includes a wide variety of subclasses that forms the new 'impaired glucose tolerance' class which will be discussed in more detail in the next chapter.

Epidemiological observations of Pacific Islanders (9, 21, 22), Arizona Pima Indians (23) and Tamil-speaking South African East Indians (24) and other non-Caucasian populations have brought to light new patterns of blood glucose distribution. They have shown that blood glucose values were bimodally distributed. In the Pima and Nauru population studies, a 100 g glucose load was used. The 2 h plasma glucose values were bimodally distributed. When the 2 h plasma glucose was related to the rate of microvascular disease, it became evident that from about 11 mmol/l (180–200 mg/dl) of blood glucose, microvascular disease (retinopathy) increased significantly.

In conclusion, the study of the distribution of blood glucose in a population seems to be prerequisite to any study of diabetes in that population. It has been a common observation that in populations with a high prevalence rate of diabetes, blood glucose values are bimodally distributed in those populations with a cut-off point around (11.1 mmol/l (200 mg/dl)).

It has also been assumed that in a general population, low levels of circulating insulin were apparent when blood glucose was around 11.1 mmol/l (200 mg/dl) (9, 13, 21–23). Mild, long-standing hyperglycemia might be a marker of a silent ongoing process resulting in damage of key organs.

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Diabetes Mellitus: Diagnosis and Classification

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DIAGNOSIS AND DIAGNOSTIC CRITERIA

Diabetes mellitus may present with clear and classical symptoms (thirst, polyuria or keto-acidosis) or may be accompanied by specific complications. The lack of sensitivity and specificity of some of these 'diabetic symptoms' has already been discussed (see previous chapter). However, when the symptoms and/or specific complications are present, the diagnosis of diabetes is confirmed by a single, unequivocally elevated blood glucose measurement as shown in Figure 3.1 (1). Severe hyperglycemia found under conditions of acute infective, traumatic or other stress may be transitory and should not in itself be regarded as diagnostic of diabetes. If a diagnosis of diabetes is made, one must feel confident that the diagnosis is fully established since the consequences for the individual are considerable and lifelong (2). For the asymptomatic persons at least one additional plasma/blood glucose measurement with a value in the diabetic range is essential, either fasting, from a random (casual) sample, or from the oral glucose tolerance (OGTT). Levels of blood glucose below which a diagnosis of diabetes is virtually excluded have also been defined (Figure 3.1).

If different samples fail to confirm the diagnosis of diabetes mellitus, the person should be reassessed and retested until the diagnostic situation becomes clear. Additional factors such as family history, age, ethnicity, adiposity and concomitant disorders should be considered before deciding on a diagnostic or therapeutic course of action (2). A single abnormal blood glucose value should never be used as the sole basis of diagnosis of diabetes in an asymptomatic subject. An alternative to the single blood glucose estimation or OGTT has long

been sought to simplify the diagnosis of diabetes. Glycated hemoglobin reflecting average glycemia over a period of weeks, was thought to provide such a test. In certain cases, it gives equal or almost equal sensitivity and specificity to glucose measurement. However, lack of standardization and its unavailability in many parts of the world make it difficult to recommend it as a good alternative at this time (2, 3).

In a collaborative study involving nine British towns over 2 years, of 254 newly diagnosed cases of diabetes aged 18–50 years, 81% were diagnosed on one single random/casual blood glucose measurement of 11.1 mmol/l (200 mg/dl) or more (4). Furthermore, a diagnosis of diabetes was established from casual blood glucose estimation without any glucose tolerance test in 800 patients (90%) attending the Diabetic Clinic at King's College Hospital in London (5).

When symptoms are lacking and blood glucose levels are less markedly elevated (e.g., glucose concentration in a casual or random blood sample between 4.4 and 10.0 mmol/l for venous whole blood), measurements made after fasting or after a glucose load may be necessary to confirm or refute the diagnosis of diabetes. An entire investigation is needed if symptoms are questionable. In case of a medical, obstetrical or family history of diabetes, a single elevated blood glucose measurement may or may not be decisive. An oral glucose tolerance test (OGTT) is indicated in this situation (Table 3.1). Table 3.2 shows the diagnostic values of OGTT for diabetes mellitus and other categories of glucose tolerance abnormalities.

Collecting and interpreting epidemiologic data implies a complete understanding of diagnostic methods and the criteria applied. It is therefore appropriate to review briefly the indications of one

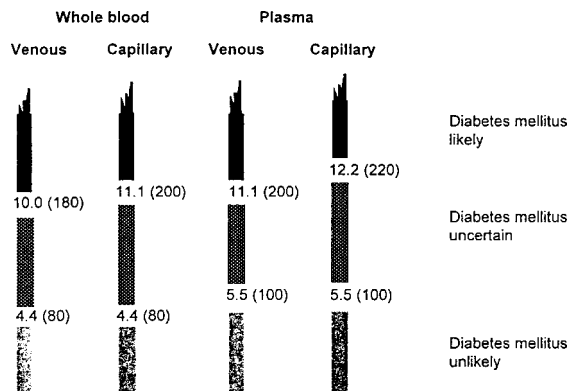


Figure 3.1 Unstandardized (casual, random) blood glucose values in the diagnosis of diabetes in mmol/L (mg/dL). Reproduced from the 1985 WHO Study Group Report (1) by permission

of the most widely used and misused methods of diagnosis: the OGTT.

THE DEMONSTRATION OF AN ABNORMAL BLOOD GLUCOSE LEVEL USING AN ORAL GLUCOSE TOLERANCE TEST (OGTT)

No marker other than a high blood glucose level has been discovered to identify the diabetic state. The diagnosis depends heavily on the demonstration of abnormal blood glucose levels. Symptoms and signs of diabetes and urine glucose tests are non-specific tests for diabetes although they should be taken into account when present.

Before performing the OGTT, it has been assumed that a random (or casual) blood glucose level should be obtained (Figure 3.1). Plasma venous glucose levels greater than 11.1 mmol/l (200 mg/dl) are usually diagnostic irrespective of time of day or status of fasting, provided the elevated blood glucose values are confirmed.

The Oral Glucose Tolerance Test (OGTT)

Conn and Fajans believed that the diagnosis of diabetes in a completely asymptomatic patient could be made only on the basis of a carefully performed glucose tolerance test (6, 7). Ten years earlier, Soskin believed that the OGTT was 'practically worthless as it was used and inter-

preted' (8). These conflicting statements illustrate the fact that, as a clinical diagnostic tool, the OGTT has been grossly overemphasized and misused. It is now apparent that the OGTT is useful in clearly defined situations as summarized in Table 3.1. For instance, the OGTT has been of prime importance in many epidemiological surveys of diabetes and is still one of the best instruments in such studies.

However, from a clinical viewpoint, the OGTT may be performed in specific circumstances. An equivocal random or casual blood glucose level (the diabetes mellitus uncertain zone as defined by the 1985 WHO Study Group on Diabetes Mellitus, Figure 3.1) deserves an OGTT. The establishment of a diagnosis is highly necessary in this situation. The OGTT might also be included as part of a special clinical investigation, or be needed for medico-legal reasons. If an OGTT is performed, it is sufficient to measure the blood glucose values while fasting and at 2 h after a 75 g oral glucose load (Annexes 1 and 2) (2). For children the oral glucose load is related to body weight, i.e. 1.75 g/kg.

Diabetes in children usually presents with severe symptoms, very high blood glucose levels, marked glycosuria, and ketonuria. In most children the diagnosis is confirmed without delay by blood glucose measurements and treatment (insulin injections) is initiated immediately. A small proportion of children and adolescents, however, present with less severe symptoms and may require a fasting blood glucose and/or an OGTT for diagnosis. Diagnostic interpretations of the fasting and 2 h post-load concentrations in non-pregnant subjects are shown in Table 3.2. The diagnostic criteria in children are the same as for adults but in

Table 3.1 Indications of oral glucose tolerance test (OGTT)

- When a 'random' blood glucose is equivocal
e.g.:
Fasting blood glucose: * > 6.1–7.0 mmol/l < (IFG)
Post-prandial blood glucose: * > 7.8–11.0 mmol/l
- As part of special clinical investigation
e.g.:
Fasting glycosuria in pregnancy
Data collection in certain endocrine or other diseases
- For experimental and epidemiological purposes
- To exclude diabetes mellitus or impaired glucose tolerance

IFG: Impaired Fasting Glycemia

*: Venous plasma values

Table 3.2 Values for diagnosis of diabetes mellitus and other categories of hyperglycemia

	Glucose concentration mmol/l (mg/dl)			
	Whole blood		Plasma	
	Venous	Capillary	Venous	Capillary
Diabetes mellitus (DM):				
Fasting	≥ 6.1 (≥ 110)	≥ 6.1 (≥ 110)	≥ 7.0 (≥ 126)	≥ 7.0 (≥ 126)
or				
2 h post-glucose load	≥ 10.0 (≥ 180)	≥ 11.1 (≥ 200)	≥ 11.1 (≥ 200)	≥ 12.2 (≥ 220)
or both				
Impaired glucose tolerance (IGT):				
Fasting concentration (if measured)	< 6.1 (< 110)	< 6.1 (< 110)	< 7.0 (< 126)	< 7.0 (< 126)
and				
2 h post-glucose load	≥ 6.7 (≥ 120) and < 10.0 (< 180)	≥ 7.8 (≥ 140) and < 11.1 (< 200)	≥ 7.8 (≥ 140) and < 11.1 (< 200)	≥ 8.9 (≥ 160) and < 12.2 (< 220)
Impaired fasting glycemia (IFG):				
Fasting	≥ 5.6 (≥ 100) and < 6.1 (< 110)	≥ 5.6 (≥ 100) and < 6.1 (< 100)	≥ 6.1 (≥ 110) and < 7.0 (< 126)	≥ 6.1 (≥ 110) and < 7.0 (< 126)
2 h (if measured)	< 6.7 (< 120)	< 7.8 (< 140)	< 7.8 (< 140)	< 8.9 (< 160)

For epidemiological or population screening purposes, the fasting of 2 h value after 75 g oral glucose may be used alone. Glucose concentrations should not be determined on serum unless red cells are immediately removed, otherwise glycolysis will result in an unpredictable underestimation of the true concentrations. Glucose preservatives do not totally prevent glycolysis. If whole blood glucose is used, the sample should be kept at 0–4 °C or centrifuged immediately, or assayed immediately.

practice, an OGTT is rarely required to make a diagnosis of Type 1 diabetes.

NEW CRITERIA IN DIAGNOSTIC VALUE FOR FASTING PLASMA BLOOD GLUCOSE CONCENTRATIONS

The main change in the diagnostic criteria for diabetes proposed by both the American Diabetes Association (ADA) and the World Health Organization (WHO) from their previous identical recommendation is the lowering of the diagnostic value of the fasting plasma glucose concentration to 7.0 mmol/l (120 mg/dl) from the former level of 7.8 mmol/l (140 mg/dl) and above. For whole blood the proposed new level is 6.1 mmol/l (110 mg/dl) and above, from the former 6.7 mmol/l (120 mg/dl).

The recommended criteria in Table 3.2 allow a diagnosis of diabetes on the basis of an elevation of the 2 h blood glucose (2 h BG) (alone or with the fasting value in the ‘true’ overnight fasting state) provided there is confirmation. When the

FBG meets the diagnostic criteria for diabetes, it is unusual for the 2 h BG to fail to do so (9). However, the converse is not true. Several investigators have found that a large number of subjects meeting the 2 h BG criterion had a normal FBG (10). The new fasting criterion is chosen to represent a value which, in most persons, is of approximately equal diagnostic significance to that of the 2 h post-load concentration, which remains the same.

This equivalence has been established from several population-based studies (4, 11–13) and it also represents an optimal cut-off point to separate the components of bimodal frequency distributions of fasting plasma glucose concentrations seen in several populations. Furthermore, several studies have shown increased risk of microvascular disease in persons with fasting plasma glucose concentrations of 7.0 mmol/l (126 mg/dl) and over (12) and of macrovascular disease in persons with such fasting concentrations, even in those with 2 h values of 7.8 mmol/l (140 mg/dl) (14).

Both FBG and 2 h post-load show relative advantages and are complementary when true fasting can be assured.

EPIDEMIOLOGICAL STUDIES

For the purpose of diabetes epidemiology studies, a single 2 h load glucose value after a 75 g oral glucose load after an overnight fast is often adequate since true fasting cannot be assured in certain conditions, and because of the strong correlation between fasting and 2 h values, epidemiological studies or diagnostic screening have in the past been restricted to the 2 h values only (Table 3.2).

OGTT may be difficult to perform for various reasons, e.g. logistic, economic, etc. In that case fasting plasma glucose alone can be used for epidemiological purposes. However, it should be known that some of the individuals identified by fasting values may be different from those identified by the 2 h values, and that overall prevalence may be somewhat different (15) although not always (11, 16). Both the 2 h and fasting value should be used if possible.

CLASSIFICATION OF THE DIABETES MELLITUS SYNDROME AND OTHER CATEGORIES OF GLUCOSE INTOLERANCE

Previous Classifications

In 1965, a WHO Expert Committee on Diabetes Mellitus published the first WHO report containing a classification of patients according to age of recognized onset (17). Since that time, several pathogenic mechanisms have been described and long-term studies have shown different courses and outcomes of different types of diabetes. Many of the subsequent reclassifications proposed attempted to take into account various aspects of diabetes which, in fact, sometimes reflected the specific interests of particular investigators. A great deal of confusion arose from this and it became quite difficult to construct a simple classification that met all interests. In order to overcome these setbacks and establish a new classification that included all possible forms of diabetes mellitus and glucose intolerance, a revised classification of diabetes was formulated by the National Diabetes Data Group (NDDG) (18). This was reviewed, amended and adopted in the second report of the WHO Expert Committee in 1980 (19) and in a modified form in 1985 (1). The

1980 and 1985 classifications of diabetes and allied categories of glucose intolerance included clinical classes and two statistical risk classes (1, 19). The 1980 Expert Committee proposed two major classes of diabetes mellitus and named them insulin-dependent diabetes mellitus (IDDM) or Type 1, and non-insulin-dependent diabetes mellitus (NIDDM) or Type 2 (19). In the 1985 Study Group Report the terms Type 1 and Type 2 were omitted, but the classes IDDM and NIDDM were retained and a new class of malnutrition-related diabetes mellitus (MRDM) was introduced (1). The 1985 WHO classification was essentially based on clinical descriptions (e.g. insulin-dependent, non-insulin-dependent, gestational) and did not include terms that might indicate etiological mechanisms (such as Type 1 or Type 2). The question whether certain clinical forms of diabetes (such as the so called 'tropical diabetes') were given adequate priority to correct hierarchic order that was raised many years before probably led to the introduction of MRDM although more precise epidemiological data and a better assessment were needed, and called for.

Both the 1980 and 1985 reports included other types of diabetes and impaired glucose tolerance (IGT) as well as gestational diabetes mellitus (GDM). The 1985 classification was widely accepted, is used internationally, and represents a compromise between clinical and etiological classifications. Furthermore, it allows classification of individual subjects and patients in a clinically useful manner even when the specific cause of etiology is unknown. The newly proposed WHO and ADA classifications or staging of diabetes still include clinical descriptive criteria but a complementary classification according to etiology is not recommended by either organization (1, 3).

New Classifications

The ADA classification and the proposed WHO classification encompass both *clinical stages*, *etiological types* of diabetes mellitus and *other categories* of hyperglycemia (Table 3.3). Diabetes may progress through several clinical stages during its natural history regardless of its etiology. The clinical staging reflects this specific aspect. Moreover, individual subjects may move from stage to stage in either direction (Figure 3.2). Even in the

Table 3.3 Etiological classification of diabetes mellitus

-
- I. Type 1 diabetes * (β -cell destruction, usually leading to absolute insulin deficiency)
 - A. Immune mediated
 - B. Idiopathic
 - II. Type 2 diabetes * (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance)
 - III. Other specific types
 - A. Genetic defects of β -cell function
 1. Chromosome 20, HNF-4 α (MODY1)
 2. Chromosome 7, glucokinase (MODY2)
 3. Chromosome 12, HNF-1 α (MODY3)
 4. Chromosome 13, IPF-1 (MODY4)
 5. Mitochondrial DNA 3243 mutation
 6. Others
 - B. Genetic defects in insulin action
 1. Type A insulin resistance
 2. Leprechaunism
 3. Rabson–Mendenhall syndrome
 4. Lipomatrophic diabetes
 5. Others
 - C. Diseases of the exocrine pancreas
 1. Fibrocalculous pancreatopathy
 2. Pancreatitis
 3. Trauma/pancreatectomy
 4. Neoplasia
 5. Cystic fibrosis
 6. Hemochromatosis
 7. Others
 - D. Endocrinopathies
 1. Cushing's syndrome
 2. Acromegaly
 3. Pheochromocytoma
 4. Glucagonoma
 5. Hyperthyroidism
 6. Somatostinoma
 7. Aldosteronoma
 8. Others
 - E. Drug- or chemical-induced
 1. Nicotinic acid
 2. Glucocorticoids
 3. Thyroid hormone
 4. α -adrenergic agonists
 5. β -adrenergic agonists
 6. Thiazides
 7. Dilantin
 8. Pentamidine
 9. Vacor
 10. α -interferon therapy
 11. Diazoxide
 12. Others
 - F. Infections
 1. Congenital rubella
 2. Cytomegalovirus
 3. Others
 - G. Uncommon forms of immune-mediated diabetes
 1. Insulin autoimmune syndrome (antibodies to insulin)
 2. Anti-insulin receptor antibodies
 3. 'Stiff-man' syndrome
 4. Others
 - H. Other genetic syndromes sometimes associated with diabetes
 1. Down's syndrome
 2. Klinefelter's syndrome
 3. Turner's syndrome
 4. Wolfram's syndrome
 5. Friedreich's ataxia
 6. Huntington's chorea
 7. Laurence–Moon–Biedl syndrome
 8. Myotonic dystrophy
 9. Porphyria
 10. Prader–Willi syndrome
 11. Others
 - IV. Gestational diabetes mellitus (GDM)
-

*Patients with any form of diabetes may require insulin treatment at some stage of their disease. Such use of insulin does not, of itself, classify the patient.

absence of information concerning the underlying etiology, persons with diabetes or those who are developing the disease can be categorized by stage according to clinical characteristics. The classification by etiological type results from improved understanding of the cases of diabetes.

The new classification takes into account the various degrees of hyperglycemia in individual subjects with any of the disease processes which may lead to diabetes. These are glycemic stages ranging from *normoglycemia* (normal glucose tolerance) to *hyperglycemia* (established diabetes where insulin is requested for survival). All individuals with the disease can be categorized according to clinical stage and this is achievable in all circumstances (2). The stage of glycemia may change over time depending on the extent of the underlying disease processes (Figure 3.2). As shown in Figure 3.2 a disease process may be present but may not have progressed far enough to cause hyperglycemia. The etiological classification reflects the fact that the defect or process which may lead to a manifest disease, diabetes, may be identifiable at any stage in the development of diabetes even at the stage of normoglycemia. For instance, the presence of islet cell antibodies in a normoglycemic individual makes it likely that individual has the Type 1 autoimmune process.

For Type 2 diabetes, there are not many good highly specific indicators. Future research will probably reveal some of them.

The same disease process can cause various degrees of 'dysglycemia' such as impaired fasting glycemia (IFG) and/or impaired glucose tolerance (IGT) without fulfilling the criteria for the diagnosis of diabetes (2). Weight reduction, exercise and/or oral agents treatment can result in adequate glycemic control in some persons with diabetes. These persons, therefore, do not require insulin. Other persons require insulin for adequate glycemic control but can survive without it. By definition these persons have some residual insulin secretion. Patients with extensive beta-cell destruction (no residual insulin secretion) do require insulin for survival. The severity of the metabolic abnormality can either *regress* (e.g., with weight reduction), *progress* (e.g., with weight gain) or *stay the same*.

CHANGES IN TERMINOLOGY

Both ADA and the proposed WHO classification have eliminated the terms 'insulin-dependent diabetes mellitus' and 'non insulin-dependent diabetes mellitus' and their acronyms 'IDDM' and 'NIDDM' on the basis that these terms have

Types	Stages	Normoglycemia Normal glucose tolerance	Hyperglycemia			
			Diabetes Mellitus			
			IGT and/or IFG	Not insulin requiring	Insulin: for control	Insulin: for survival
Type 1 Autoimmune Idiopathic		←				→
Type 2 * Predom. insulin resistance Predom insulin secretory defects		←			→	→
Other specific types *		←			→	→
Gestational hyperglycemia*		←			→	→

Figure 3.2 Disorders of glycemia: etiological types and clinical stages. * In rare instances, patients in these categories (e.g.: Vacor toxicity, Type 1 presenting in pregnancy) may require insulin for survival

been confusing and frequently resulted in misclassification, patients being classified on treatment rather than on pathogenesis (Table 3.3). The terms '*Type 1* and '*Type 2*' are retained (using Arabic rather than Roman numerals). People with any form of diabetes may require insulin treatment at some stage of their disease.

The etiological type named Type 1 encompasses the majority of cases which are primarily due to *pancreatic islet beta-cell destruction* and are prone to ketoacidosis. Type 1 includes those cases attributable to an autoimmune process, as well as those with beta-cell destruction and which are prone to ketoacidosis for which neither an etiology nor a pathogenesis is known (idiopathic). Those forms of beta-cell destruction or failure to which specific causes can be assigned are not included in this type of diabetes (e.g., cystic fibrosis, mitochondrial defects).

The form named Type 2 includes the common major form of diabetes which results from defect(s) in insulin secretion, almost always with a major contribution from insulin resistance. The class malnutrition-related diabetes (MRDM) has been deleted in the proposed WHO classification. The former subtype of MRDM, protein-deficient pancreatic diabetes (PDPD or PDDM) needs more studies for a better definition. The other former subtype of MRDM, fibrocalculous pancreatic diabetes (FCPD), is now classified as a disease of the exocrine pancreas, fibrocalculous pancreatopathy which may lead to diabetes. Chapter 18 on MRDM in this book discusses this issue.

The class impaired glucose tolerance (IGT) is reclassified as a stage of impaired glucose regula-

tion (Table 3.4), since it can be observed in any hyperglycemic disorder, and is itself not diabetes.

Gestational diabetes is retained but now encompasses the groups formerly classified as gestational impaired glucose tolerance (GIGT) and gestational diabetes mellitus (GDM) according to the new proposed WHO criteria (2).

CLINICAL CLASSIFICATION OF DIABETES MELLITUS AND OTHER CATEGORIES OF GLUCOSE TOLERANCE

Table 3.3 summarizes the etiological classification of diabetes mellitus. Etiological and clinical stages are presented in Figure 3.2.

The concepts for new staging/etiological classification were proposed by Kuzuya and Matsuda (20). Their proposals sought to separate clearly the criteria related to etiology and those related to degree of deficiency of insulin or insulin action and to define each patient on the basis of these two criteria.

The newly suggested WHO classification and the new ADA classification bring in both clinical stages of hyperglycemia as well as etiological types (Figure 3.2 and Table 3.3). The classification by etiological type results from new knowledge as to the causes of hyperglycemia including diabetes. The actual staging proposed reflects that any etiological type of diabetes can pass or progress through several clinical phases (both asymptomatic and symptomatic) during its natural history. Moreover individuals may move (in either direction), from stage to stage (Figure 3.2).

Table 3.4. Glucose levels for diagnosis of glucose tolerance abnormalities

Category	FPG mmol/l	(mg/dl)	PG 1 h after 75 g glucose load		PG 2 h after 75 g glucose load	
			mmol/l	(mg/dl)	mmol/l	(mg/dl)
Impaired fasting glucose (IFG)	6.1–6.9	(10–124)	N/A		N/A	
Impaired glucose tolerance (IGT)	<7.0	(<126)	N/A		≥7.8	(<140)
Diabetes mellitus (DM)	≥7.0	(≥126)	N/A		≥11.1	(<200)
Gestational diabetes* (GM)	≥5.3	(95.4)	≥10.6	(≥191)	≥8.9	(≥200)

FPG = Fasting plasma glucose PG = Plasma glucose N/A = not applicable.

*A diagnosis of gestational diabetes mellitus requires two abnormal values among the three measurements according to the American Diabetes Association and the Canadian Diabetes Association.

THE NEWLY PROPOSED STAGING CLASSIFICATION

The new classification proposes that hyperglycemia, regardless of the underlying cause, can be sub-categorized into the following.

Diabetes Mellitus

Diabetes mellitus, regardless of underlying cause, is subdivided into:

Insulin requiring for survival (corresponding to the former clinical class of 'Insulin-Dependent Diabetes Mellitus: IDDM') e.g. C-peptide deficient.

Insulin requiring for control, i.e. for metabolic control, rather than for survival, e.g. some endogenous insulin secretion but insufficient to achieve normoglycemia without added exogenous insulin and not insulin requiring; i.e. those who may be treated and controlled satisfactorily by non-pharmacological methods or drugs other than insulin. These two categories correspond to the former 'Non-Insulin-Dependent Diabetes Mellitus: NIDDM'.

Impaired Glucose Regulation

Impaired Glucose Tolerance (IGT) and Impaired Fasting Glycemia (IFG, Non-diabetic Fasting Hyperglycemia)

Impaired glucose tolerance (IGT) was considered a class in the previous WHO classification but is now categorized as a stage in the natural history of disordered carbohydrate metabolism. A stage called 'impaired fasting hyperglycemia' or impaired fasting glycemia (IFG) or 'non-diabetic fasting hyperglycemia' is now recognized as these people also appear to be at greater risk for progression to diabetes and macrovascular disease, although prospective data are sparse and early data suggest a lower risk of progression than IGT (21). IFG refers to fasting glucose concentrations which are lower than those required to diagnose diabetes mellitus but higher than the 'normal' reference range.

IGT and IFG are not clinical entities in their own right (mostly in the absence of pregnancy for

IGT), but rather risk categories for future diabetes and/or cardiovascular disease (22, 23). IGT and IFG represent impaired glucose regulation which refers to a metabolic intermediate between normal glucose homeostasis and diabetes. Individuals who meet criteria for IGT or IFG may be euglycemic in their daily lives as shown by normal or near-normal glycated hemoglobin levels (2). IGT is often associated with the metabolic syndrome (insulin resistance syndrome) (24). An individual with a fasting plasma glucose concentration of 6.1 mmol/l (110 mg/dl) or greater (whole blood 5.6 mmol/l; 100 mg/dl) but less than 7.0 mmol/l (126 mg/dl) (whole blood 6.1 mmol/l; 110 mg/dl) is considered to have *impaired fasting glycemia* (IFG). If an OGTT is performed, some individuals with IFG will have IGT. Some may have diabetes but this cannot be determined without an OGTT. If resources allow, it is recommended that those with IFG have an OGTT to exclude diabetes (2).

Normoglycemia

A fasting venous plasma glucose concentration of less than 6.1 mmol/l (110 mg/dL) has been chosen as 'normal' (Table 3.2). These values are observed in people with normal glucose tolerance and values above this are associated with progressively greater risks of developing micro and macrovascular complications (13, 14, 23, 25).

The etiological processes which often lead to diabetes mellitus begin, and may be recognizable, in some subjects who have normal glucose tolerance. Recognition of the pathological process at an early stage may be useful if progression to more advanced stages can be prevented. The proposed classification includes a stage of normoglycemia in which persons who have evidence of the pathological processes which may lead to diabetes mellitus or in whom a reversal of the hyperglycemia has occurred, are classified (Figure 3.2, Table 3.3).

THE NEWLY PROPOSED ETIOLOGICAL TYPES

The etiological types listed represent processes, or disorders which may result in diabetes mellitus.

Type 1

Type 1 indicates the processes of beta-cell destruction that may ultimately lead to diabetes in which 'insulin is required for survival' in order to prevent the development of ketoacidosis, coma and death. While the Type 1 process is characterized by the presence of autoantibodies to glutamic acid decarboxylase (GAD), islet cell, insulin or ICA512 which identify the autoimmune process associated with beta-cell destruction, in some cases, no evidence of antibodies is present and these are classified as 'Type 1 idiopathic'.

Type 2

Type 2 is the commonest form of diabetes and is characterized by disorders of insulin resistance and insulin secretion, either of which may be the predominant feature. Both are usually present at the time that the diabetes is clinically manifest. The specific reasons for the development of these is not yet known.

Other Specific Types

The other specific types (Table 3.3) are less common, but are those in which the underlying defect or disease process can be identified in a relatively specific manner, particularly those where a monogenic defect has been identified, e.g., in MODY.

1. *Type 1 Diabetes* (beta-cell destruction, usually leading to absolute insulin deficiency).

This category is composed of:

- a. *Immune-Mediated Diabetes Mellitus*: This form of diabetes, previously encompassed by the terms insulin-dependent diabetes, Type 1 diabetes, or juvenile-onset diabetes, results from a cellular mediated autoimmune destruction of the beta-cells of the pancreas. The rate of destruction is quite variable. It can be rapid in children but a slowly progressive form, previously known as LADA, is well described in adults (26, 27).

Markers of immune destruction, including ICA, and/or IAA, autoantibodies to GAD and IICA 512 are present in 85–90% of individuals when fasting hyperglycemia is initially detected, and often many years before (28). The peak incidence of this form of Type 1 diabetes occurs in childhood and adolescence but the onset may occur at any age ranging from childhood to the ninth decade of life (29). Patients are rarely obese when they present with this type of diabetes. However, the presence of obesity is not incompatible with the diagnosis. Other autoimmune disorders such as Grave's disease, Hashimoto's thyroiditis and Addison's disease may be associated with Type 1 diabetes mellitus (30).

- b. *Idiopathic*: There are some forms of Type 1 diabetes which have no known etiologies. Some of these patients have permanent insulinopenia and are prone to ketoacidosis, but have no evidence of autoimmunity (31). This form is more common among individuals of African and Asian origin (32). In another form found in Africans, an absolute requirement for insulin replacement therapy in affected patients may fluctuate with time, and come and go, and patients periodically develop ketoacidosis (32).
2. *Type 2 diabetes* (ranging from predominantly insulin resistance with relative insulin deficiency to predominantly an insulin secretory defect with/without insulin resistance)

This form of diabetes mellitus, previously referred to as NIDDM or adult-onset diabetes, is a term used for individuals who have relative (rather than absolute) insulin deficiency. People with Type 2 diabetes frequently are resistant to the action of insulin (33, 34). At least initially, and often throughout their lifetime, these individuals do not need insulin treatment to survive. Type 2 diabetes is frequently undiagnosed for many years because the hyperglycemia is often not severe enough to provoke noticeable symptoms of diabetes. Nevertheless, such patients are at increased risk of developing macrovascular and microvascular complications. There are probably many different causes of this form of diabetes, and it is likely that the number of patients in this category will decrease in the future as identification of specific pathogenic

processes and genetic defects permits better differentiation and a more definitive classification. Although the specific etiologies of this form of diabetes are not known, autoimmune destruction of the pancreas does not occur and patients do not have any other known causes of diabetes as listed in Table 3.2.

Most patients with this form of diabetes are obese, and obesity itself causes insulin resistance (35, 36). Many of those not obese by traditional criteria, e.g. body mass index (BMI), may have an increased percentage of body fat distributed predominantly in the abdominal region (36, 37). Ketoacidosis seldom occurs in Type 2 diabetes and when seen, it usually arises in association with the stress of another illness such as infection (38, 39).

Often, insulin secretion is defective in these patients and insufficient to compensate for the insulin resistance. On the other hand, insulin action is essentially normal in some individuals, but insulin secretion is markedly impaired. Insulin resistance may improve with weight reduction, increased physical activity and/or pharmacologic treatment of hyperglycemia but is not restored to normal (40, 41).

The risk of developing Type 2 diabetes increases with age, obesity, and lack of physical activity (42, 43). It occurs more frequently in women with prior GDM, in those with hypertension or dyslipidemia, and its frequency varies in different ethnic subgroups (42–45). Type 2 diabetes is often associated with strong familial, likely genetic, predisposition (44–46). The genetics of Type 2 diabetes are quite complex and not clearly defined. Some patients who present a clinical picture consistent with Type 2 diabetes have been shown to have autoantibodies similar to those found in Type 1 diabetes. This form of diabetes may masquerade as Type 2 diabetes if antibody determinations are not made (26). Patients who are not obese or who have relatives with Type 1 diabetes and are Caucasian (Northern European origin) may be suspected of having late onset Type 1 diabetes (2).

Other Specific Types

These include identified *genetic, exocrine pancreatic, endocrine, and drug-induced* causes. A more comprehensive breakdown is provided in Table 3.3.

Genetic Defects of β -cell Function

The diabetic state may be associated with monogenetic defects in β -cell function. These forms are characterized by onset of mild hyperglycemia at an early age (generally < 25 years). They are inherited in an autosomal dominant pattern. Patients with these forms of diabetes, formerly referred to as maturity-onset diabetes of the young (MODY), have impaired insulin secretion with minimal or no defect in insulin action (47, 48). Abnormalities at three genetic loci on different chromosomes have been identified to date. The most common form is associated with mutations on chromosome 12 in a hepatic transcription factor referred to as hepatocyte nuclear factor (HNF)-1 α (49). A second form is associated with mutations in the glucokinase gene on chromosome 7 p (50, 51) and results in a defective glucokinase molecule. Glucokinase converts glucose to glucose-6-phosphate, the metabolism of which in turn stimulates insulin secretion by the beta-cell. Thus, glucokinase serves as the 'glucose sensor' for the beta-cell. Due to defects in the glucokinase gene, increased levels of glucose are necessary to elicit normal levels of insulin secretion. A mutation in the HNF-4 α gene on chromosome 20 q characterizes the third form (52). HNF-4 α is a transcription factor which is involved in the regulation of the expression of HNF-12. A fourth variant has recently been ascribed to mutations in another transcription factor gene, IPF-1, which in its homozygous form leads to total pancreatic agenesis (53). Specific genetic defects in other individuals who have a similar clinical presentation are currently being investigated.

In addition, point mutations in mitochondrial DNA have been found to be associated with deafness (54). The most common mutation occurs at position 3243 in the tRNA leucine gene leading to an A to G substitution. An identical lesion occurs in the MELAS syndrome (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like syndrome). However, diabetes is not part of this syndrome, suggesting different phenotypic expressions of this genetic lesion (55).

Genetic abnormalities that result in the inability to convert proinsulin to insulin have been identified in a few families. Usually such traits are inherited in an autosomal dominant pattern (56, 57) and the resultant carbohydrate intolerance

is mild. Mutant insulin molecules with impaired receptor binding have also been identified in a few families. These are also associated with autosomal inheritance and either normal or only mildly impaired carbohydrate metabolism (58, 59).

Genetic Defects in Insulin Action

These causes of diabetes are unusual and result from genetically determined abnormalities of insulin action. The metabolic abnormalities associated with mutations of the insulin receptor may range from hyperinsulinemia and modest hyperglycemia to severe symptomatic diabetes (60, 61). Acanthosis nigricans may be present in some of these individuals. Women may have virilization and have enlarged cystic ovaries. This syndrome was termed Type A insulin resistance in the past (60). Two pediatric syndromes that have mutations in the insulin receptor gene with subsequent alterations in insulin receptor function and extreme insulin resistance are called leprechaunism and the Rabson–Mendenhall syndrome (61). Leprechaunism has characteristic facial features while the Rabson–Mendenhall syndrome is associated with abnormalities of teeth, nails and pineal gland hyperplasia. In patients with insulin-resistant lipodystrophic diabetes alterations in the structure and function of the insulin receptor cannot be demonstrated. Therefore it is assumed that the lesion(s) must reside in the post-receptor signal transduction pathways.

Diseases of the Exocrine Pancreas

Pancreatitis, trauma, infection, pancreatic carcinoma and pancreatectomy are some of the acquired processes of the pancreas that can cause diabetes. Any process that diffusely injures the pancreas may cause diabetes (62, 63). With the exception of cancer, damage to the pancreas must be extensive for diabetes to occur. However, adenocarcinomas that involve only a small portion of the pancreas have been associated with diabetes. This implies a mechanism other than single reduction in beta-cell mass (64). Depending on their extension, cystic fibrosis and hemochromatosis will also damage beta-cell and impair insulin secretion (65, 66). Fibrocalculous pancreatopathy

may be accompanied by abdominal pain radiating to the back and pancreatic calcification on X-ray and ductal dilatation (see Chapter 18 on malnutrition-related diabetes mellitus). Pancreatic fibrosis and calcified stones in the exocrine ducts are found at autopsy (67).

Endocrinopathies

Insulin action can be antagonized by several hormones (e.g.: growth hormone, cortisol, glucagon, epinephrine). Diseases associated with excess secretion of these hormones can cause diabetes (e.g.: acromegaly, Cushing's syndrome, glucagonoma and pheochromocytoma) (68). These forms of hyperglycemia resolve when the hormone excess is removed. Somatostinoma and aldosteronoma-induced hypokalemia can cause diabetes at least in part by inhibiting insulin secretion (69, 70). Hyperglycemia generally resolves following successful removal of the tumour.

Drug or Chemical-induced Diabetes

Insulin secretion may be impaired by many drugs. They may not, by themselves, cause diabetes but may precipitate diabetes in persons with insulin resistance (71, 72). Classification is ambiguous in such cases as the primacy of β -cells destruction or where insulin resistance is unknown. Pancreatic β -cells destruction may occur with the use of certain toxins such as Vacor (a rat poison) and pentamidine (73–75). There are also many drugs and hormones which can impair insulin action. The list shown in Table 3.3 is not all-inclusive, but reflects the more commonly recognized drug-, hormone-, or toxin-induced forms of diabetes and hyperglycemia.

Infections

Certain viruses have been associated with β -cells destruction. Diabetes occurs in some patients with congenital rubella (76). Coxsackie B, cytomegalovirus and other viruses (e.g.: adenovirus and mumps) have been implicated in inducing diabetes (77–79).

UNCOMMON BUT SPECIFIC FORMS OF
IMMUNE-MEDIATED DIABETES MELLITUS

Diabetes may be associated with several immunological diseases with a pathogenesis or etiology different from that which leads to the Type 1 diabetes process. Post-prandial hyperglycemia of a severity sufficient to fulfill the criteria for diabetes has been reported in rare individuals who spontaneously develop insulin autoantibodies. However, these individuals generally present with symptoms of hypoglycemia rather than hyperglycemia (80). The ‘stiff man syndrome’ is an autoimmune disorder of the central nervous system, characterized by stiffness of the axial muscles with painful spasms. Affected people usually have high titres of the GAD autoantibodies and approximately one third to half will develop diabetes (2,3). Patients receiving interferon alpha have been reported to develop diabetes associated with islet cell autoantibodies and, in certain instances, severe insulin deficiency (81–83).

Anti-insulin receptor antibodies can cause diabetes by binding to the insulin receptor thereby reducing the binding of insulin to target tissues (84). However, these antibodies also can act as an insulin agonist after binding to the receptor and can thereby cause hypoglycemia (85). Anti-insulin receptor antibodies are occasionally found in patients with systemic lupus erythematosus and other autoimmune diseases (86). As in other states of extreme insulin resistance, patients with anti-insulin receptor antibodies often have acanthosis nigricans. In the past, this syndrome was termed Type B insulin resistance.

Other Genetic Syndromes Associated with
Diabetes

Many genetic syndromes are accompanied by an increased incidence of diabetes mellitus. These include the chromosomal abnormalities of Down’s syndrome, Klinefelter’s syndrome, and Turner’s syndrome. Wolfram’s syndrome is an autosomal recessive disorder characterized by insulin-deficient diabetes and the absence of beta-cells at autopsy (87). Additional manifestations include diabetes insipidus, hypogonadism, optic atrophy, and neural deafness. These and other similar disorders are listed in Table 3.3.

GESTATIONAL DIABETES MELLITUS

Gestational diabetes is carbohydrate intolerance resulting in hyperglycemia of variable severity with onset or first recognition during pregnancy. The definition applies irrespective of whether or not insulin is used for treatment or the condition persists after pregnancy. It does not exclude the possibility that the glucose intolerance may antedate pregnancy but has been previously unrecognized (2, 3).

Women who become pregnant and who are known to have diabetes which antedates pregnancy do not have gestational diabetes but have ‘diabetes mellitus and pregnancy’ and should be treated accordingly before, during, and after the pregnancy (2, 3).

Fasting and post-prandial glucose concentrations are normally lower in the early part of pregnancy (e.g.: first trimester and first half of second trimester) than in normal, non-pregnant women. Elevated fasting or post-prandial plasma glucose levels at this time in pregnancy may well reflect the presence of diabetes which has antedated pregnancy, but criteria for designating abnormally high glucose concentrations at this time have not yet been established. The occurrence of higher than normal plasma glucose levels at this time in pregnancy mandates careful management and may be an indication for carrying out an OGTT (Table 3.5 and Annex 1). Nevertheless, normal glucose tolerance in the early part of

Table 3.5. Diagnosis of GDM with a 100 g or 75 g glucose load according to the ADA

	mmol/l	mg/dl
100 glucose load		
Fasting	5.3	95
1 h	10.0	180
2 h	8.6	155
3 h	7.8	140
75 g glucose load		
Fasting	5.3	95
1 h	10.0	180
2 h	8.6	155

Two or more of the venous plasma concentrations must be met or exceeded for a positive diagnosis. The test should be done in the morning after an overnight fast of between 8 and 14 h and after at least 3 days of unrestricted diet (≥150 g carbohydrate per day) and unlimited physical activity. The subject should remain seated and should not smoke throughout the test (see Annex 1).

pregnancy does not itself establish that gestational diabetes may not develop later.

Individuals at high risk for gestational diabetes include older women, those with a previous history of glucose intolerance, those with a history of large for gestational age babies, women from certain high-risk ethnic groups (e.g.: Hispanic American, Native American, Asian American, African American, Pacific Islander) and any pregnant woman who has elevated fasting, or casual, blood glucose levels (2,3). It may be appropriate to screen pregnant women belonging to high-risk populations during the first trimester of pregnancy in order to detect previously undiagnosed diabetes. Formal systematic testing for gestational diabetes is usually done between 24 and 28 weeks of gestation.

Diagnosis of Gestational Diabetes

To determine if gestational diabetes is present in pregnant women, a standard OGTT should be performed after overnight fasting (8–14 h) by giving 75 g anhydrous glucose in 250–300 ml water (Annex 1). Plasma glucose is measured fasting and after 2 h. Pregnant women who meet WHO criteria for diabetes mellitus or IGT are classified as having Gestational Diabetes Mellitus (GDM). After the pregnancy ends, the woman should be reclassified as having either diabetes, or IGT, or normal glucose tolerance based on the results of a 75 g OGTT 6 weeks or more after delivery (3). It should be emphasized that such women, regardless of the 6-week post-pregnancy result, are at increased risk of subsequently developing diabetes. The significance of IFG in pregnancy remains to be established. Any woman with IFG, however, should have a 75 g OGTT. A fasting plasma glucose load >7.0 mmol/l (126 mg/dl) or a casual plasma glucose >11.1 mmol/l (200 mg/dl) meets the threshold for the diagnosis of diabetes, if confirmed on a subsequent day, and precludes the need for any glucose challenge. In the absence of this degree of hyperglycemia, according to the ADA, evaluation for GDM in women with average or high-risk characteristics should follow one of the two approaches (3).

One-step approach: OGTT without prior plasma or serum glucose screening.

Two-step approach: Perform an initial screening by measuring the plasma or serum glucose concentration 1 h after a 50 g oral glucose load (glucose challenge test [GCT]) and perform a diagnostic OGTT on that subset of women exceeding the glucose threshold value on the GCT. When the two-step approach is applied a glucose threshold value >7.8 mmol/l (140 mg/dl) identifies approximately 80% of women with GDM and the yield is further increased to 90% by using a cutoff of >7.2 mmol/l (130 mg/dl). With either approach, the diagnosis of GDM is based on OGTT. 100 g or 75 g load and the glucose threshold values are listed for fasting, 1 h, and 2 h (Table 3.5).

The prevalence in the US of GDM may range from 1 to 14% of pregnancies (3), depending on the ethnic group studied with the prevalence higher in populations with highest Type 2 diabetes susceptibility. Overall, it may complicate about 4% of all pregnancies, resulting in ≈ 135 000 cases annually. GDM represents nearly 90% of all pregnancies complicated by diabetes (3).

The criteria cited above for abnormal glucose tolerance in pregnancy which are widely used in the US were proposed by O'Sullivan and Mahan in 1964 (88). In 1979, the National Diabetes Data Group (NDDG) revised the O'Sullivan and Mahan criteria, converting whole blood values to plasma values. Carpenter and Coustan suggested that the NDDG conversion of the O'Sullivan and Mahan values from the original Somogyi–Nelson determinations may have resulted in values that are too high. They proposed cutoff values for plasma glucose that appear to represent more accurately the original O'Sullivan and Mahan determinations (89). The 75 g OGTT provides values for plasma glucose concentrations that are similar to the Carpenter–Coustan extrapolations of the 100 g OGTT (3).

Recommendations from the American Diabetes Association's Fourth International Workshop-Conference on Gestational Diabetes Mellitus in 1997 support the use of the Carpenter–Coustan diagnostic criteria as well as the alternative use of a diagnostic 75 g 2 h OGTT (Table 3.5). The 75 g is probably more practical.

CONCLUSIONS

The most substantive change in diagnostic criteria for glucose intolerance is that the fasting plasma glucose (FPG) concentration for the diagnosis of diabetes has been lowered from 7.8 mmol/l (140 mg/dl) to 7 mmol/l (126 mg/dl).

A new category of impaired FPG of 6.1 to 7.0 mmol/l (111 mg/dl to 126 mg/dL) has been created as the ADA recommended abolition of the oral glucose tolerance test (OGTT). This suggestion has not been supported by the 1999 WHO report (2).

The OGTT is not used very often to diagnose diabetes in a clinical setting and has been mainly used for clinical research and epidemiological studies. Diabetes can usually be diagnosed without an OGTT, but this is not the case for IGT. While in many settings, the logistics and costs of measuring glycated hemoglobin are less than those of obtaining fasting blood or performing an OGTT, the current disadvantage of glycated hemoglobin is the lack of standardization of methodology as well as the fact there is no universal reference standard for interlaboratory calibration (2). In addition, there are fewer outcome data available than for the OGTT. However, these limitations may be overcome in the near future, so that further evaluation of the properties of HbA_{1c} measurements for screening and diagnosis could justify postponing a change in screening recommendations.

There are several arguments for abolishing the OGTT as a routine screening test for Type 2 diabetes. First, the complexity of the current diagnostic criteria reflects both the difficulty in distinguishing diabetic from non-diabetic patients on the basis of a single measurement, and the considerable test/retest variability of the OGTT.

However, a major argument for continuing the OGTT relates to the identification of high-risk subjects, i.e. those with IGT for clinical trials of Type 2 diabetes prevention. In addition, the 2 h plasma glucose value from the OGTT was in particular recommended by WHO for epidemiological studies, to overcome uncertainties about whether study subjects were fasting or not.

Blood glucose is a continuum, and therefore the choice of a distinct cutpoint will always be somewhat arbitrary. The determination of diagnostic cutpoints which gave rise to the NDDG and

WHO recommendations was based on studies performed which evaluated the association between 2 h plasma glucose and the subsequent development of the microvascular complications of diabetes.

The diagnostic cutpoint of 11.1 mmol/l for the 2 h plasma glucose concentration was originally adopted for two reasons. First, the bimodality of glucose distributions in populations with high prevalence of diabetes suggested that 11.1 mmol/l represented the cutpoint separating the two components of the bimodal frequency distributions. Second, when the prevalence of microvascular complications was plotted against the 2 h plasma glucose it became obvious that the former sharply increased at about 11.1 mmol/l.

Using the WHO cutpoint values to define Type 2 diabetes, it became apparent that FPG and 2 h plasma glucose detect different sectors of the hyperglycemic state. The 1985 WHO FPG criterion for diabetes (7.8 mmol/l or 140 mg/dl) represents a greater degree of hyperglycemia than the 2 h plasma glucose criterion for diabetes (11.1 mmol/l or 200 mg/dl). The effect of the change will have variable, but not great effects on diabetes prevalence in most populations.

The new World Health Organization/ADA recommendations will be welcomed as a basis on which to build. They are based on the accumulated work of many researchers. The rapid advances in molecular biology in the last decade have provided the means to extend our knowledge of the basis for the metabolic and clinical heterogeneity of diabetes. The classification should provide a more rational platform for phenotyping and choosing appropriate therapies for persons with diabetes. Inevitably, the classification and criteria will need to be revised in future years as new evidence-based data emerge.

ANNEX 1 THE ORAL GLUCOSE TOLERANCE

The oral glucose tolerance test (OGTT) is principally used for diagnosis when blood glucose levels are equivocal, during pregnancy, or in an epidemiological setting to screen for diabetes and impaired glucose tolerance.

The OGTT should be administered in the morning after at least 3 days of unrestricted diet

(greater than 150 g of carbohydrate daily) and usual physical activity. The test should be preceded by an overnight fast of 8–14 h, during which water may be drunk. Smoking is not permitted during the test. The presence of factors that influence interpretation of the results of the test must be recorded (e.g.: medications, inactivity, infection).

After collection of the fasting blood sample, the subject should drink 75 g of anhydrous glucose (or partial hydrolysates of starch of the equivalent carbohydrate content) in 250–300 ml of water over the course of 5 minutes. For children, the test load should be 1.75 g of glucose per kg body weight up to a total of 75 g of glucose. Blood samples must be collected 2 h after the test load.

Unless the glucose concentration can be determined immediately, the blood sample should be collected in a tube containing sodium fluoride (6 mg per ml whole blood) and immediately centrifuged to separate the plasma; the plasma should be frozen until the glucose concentration can be estimated. For interpretation of results, refer to Tables 3.2 and 3.5)

ANNEX 2 METHODS FOR MEASURING SUBSTANCES IN BLOOD AND URINE

Measurement of Glucose in Blood

Reductimetric methods (the Somogyi–Nelson, the ferricyanide and neocuprine autoanalyser methods) are still in use for blood glucose measurement. The *o*-toluidine method also remains in use but enzyme-based methods are widely available, for both laboratory and near-patient use. Highly accurate and rapid (1–2 min) devices are now available based on immobilized glucose oxidase electrodes. Hexokinase and glucose dehydrogenase methods are used for reference.

Whole blood samples preserved with fluoride show an initial rapid fall in glucose of up to 10% at room temperature, but subsequent decline is slow; centrifugation prevents the initial fall. Whole blood glucose values are 15% lower than corresponding plasma values in patients with a normal hematocrit reading, and arterial values are about 7% higher than corresponding venous values.

The use of reagent-strip glucose oxidase methods has made bedside estimation of blood glucose very

popular. However, the cost of the reagent-strips remains high. Some methods still require punctilious technique, accurate timing, and storage of strips in airtight containers. Reasonably quantitative results can be obtained even with visual color-matching techniques. Electrochemical and reflectance meters can give coefficients of variation of well under 5%. Reagent-strip methods have been validated under tropical conditions, but are sensitive to extreme climatic conditions. Diabetes may be strongly suspected from the results of reagent-strip glucose estimation, but the diagnosis cannot be confidently excluded by the use of this method. Confirmation of diagnosis requires estimation by laboratory methods.

Patients can easily collect small blood samples themselves (either in specially prepared plastic or glass capillary tubes or on filter-paper), and self-monitoring using glucose reagent-strips with direct color-matching or meters is now widely practiced. Patients should be properly trained in the appropriate techniques to avoid inaccurate or misleading results.

The insulin-treated patient is commonly requested to build up a 'glycemic profile' by self-measurement of blood glucose at specific times of the day (and night). A '7-point profile' is useful, with samples taken before and 90 min after breakfast, before and 90 min after lunch, before and 90 min after an evening meal, and just before going to bed. Occasionally patients may arrange to wake at 03 h to collect and measure a nocturnal sample. The complete profile rarely needs to be collected within a single 24 h period, and it may be compiled from samples collected at different times over several days.

Measurement of Glucose in Urine

Insulin-treated patients who do not have access to facilities for self-measurement of blood glucose should test urine samples passed after rising, before main meals, and before going to bed. Patients with Type 2 diabetes do not need to monitor their urine so frequently. Urine tests are of somewhat limited value, however, because of the great variation in urine glucose concentration for given levels of blood glucose. The correlation between blood and urine glucose may be improved a little by collecting short-term fractions

(15–30 min) or the urine output. Benedict's quantitative solution or self-boiling, caustic soda/copper sulphate tablets may be used or the more convenient, but costly, semi-quantitative enzyme-based test-strips.

Ketone Bodies in Urine and Blood

The appearance of persistent ketonuria associated with hyperglycemia or high levels of glycosuria in the diabetic patient points to an unacceptably severe level of metabolic disturbance and indicates an urgent need for corrective action. The patient should be advised to test for ketone bodies (acetone and aceto-acetic acid) when tests for glucose are repeatedly positive, or when there is substantial disturbance of health, particularly with infections. Rothera's sodium nitroprusside test may be used or, alternatively reagent-strips that are sensitive to ketones. In emergency situations such as diabetic ketoacidosis, a greatly raised concentration of plasma ketones can be detected with a reagent-strip and roughly quantified by serial 1 in 2 dilution of plasma with water.

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Prevention of Type 1 Diabetes Mellitus

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INTRODUCTION

The ultimate goal of understanding the epidemiology of any disease is to use that information in the development of programs aimed to prevent or eradicate the disease in question. Such is certainly the case for Type 1 diabetes mellitus. Progress in our understanding of the epidemiology of Type 1 diabetes, including its etiology, genetic and non-genetic influences, changing incidence and prevalence, is reviewed in other chapters in this volume. These factors will be discussed here only as they relate to the purpose of this chapter, the case for implementation of programs for prediction and prevention of Type 1 diabetes.

The clinical symptoms of Type 1 diabetes are the overt expression of an insidious pathogenetic process which began years earlier. The consequence of immune-mediated destruction of the pancreatic islet insulin-secreting beta-cells, clinical disease becomes apparent only when a majority of beta-cells have been destroyed. The pathogenesis of Type 1 diabetes is generally thought to involve genetic predisposition to the disease, non-genetic (environmental) factors that appear to act as triggers in genetically susceptible individuals, activating immune mechanisms specifically targeted against pancreatic islet beta-cells. This may be an oversimplification. Rather, the pathogenesis of type 1 diabetes appears to involve a disruption of balance between forces propelling the progression of disease and forces retarding or preventing that progression (Figure 4A.1). This delicate balance appears to be in place for genetic factors, environmental factors, and immune regulation. Thus, there have been identified genes that confer susceptibility or predisposition to the disease, and genes that confer protection against development of the disease. Likewise, there are apparent

environmental insults which have the potential of triggering development of disease in genetically susceptible individuals, while other environmental factors appear to be associated with protection from development of disease. In addition, there seem to be complex regulatory interactions amongst various elements of the immune response, with some elements of the immune circuitry being responsible for beta-cell destruction and others regulating that response and leading to beta-cell protection.

DETERMINANTS

Genetic

There are both genetic and environmental determinants of the Type 1 diabetes disease process. The major genetic susceptibility locus for Type 1 diabetes, IDDM1, is localized within the HLA (human leukocyte antigen) region on the short arm of chromosome 6 (1). IDDM1 provides at least 50% of the genetic susceptibility to Type 1 diabetes (1,2). The susceptibility within the IDDM1 locus is mostly conferred by alleles of the HLA-DQ locus in the HLA class II region (3). However, a number of studies have shown that alleles at the DRB1 locus are also important and significantly modulate diabetes susceptibility. The HLA molecules DQA1*0301-DQB1*0302 (also known as DQ8), DQA1*0501-DQB1*0201 (also known as DQ2), DRA-DRB1*0401 (also known as DR4) and DRA-DRB1*0301 (also known as DR3) confer susceptibility to Type 1 diabetes.

A second gene, termed IDDM2, has been mapped to the VNTR (variable number of tandem repeats) minisatellite locus at the 5' end of the insulin gene on the short arm of chromosome

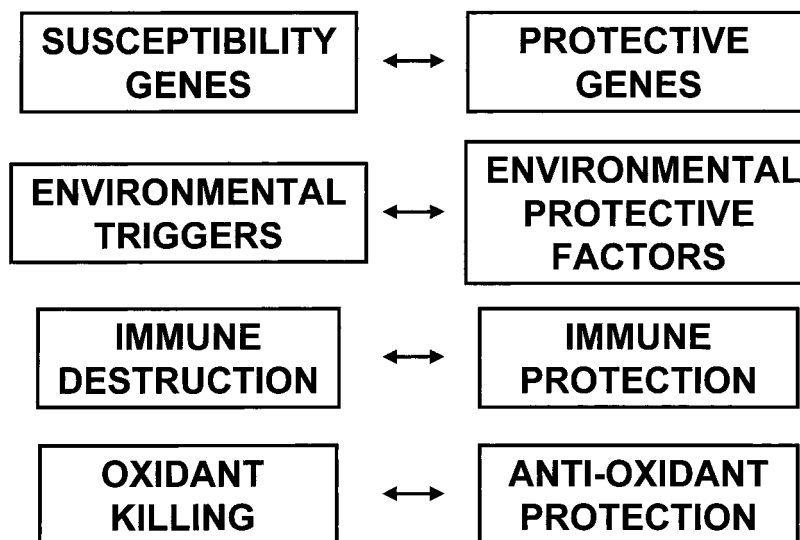


Figure 4A.1 Elements in the pathogenesis of Type 1 diabetes. Type 1 diabetes emerges when the disease-promoting elements in the left-hand column outweigh the protective elements in the right-hand column, i.e. when the balance of forces favors processes which eventuate in immune destruction of islet beta-cells

11, and accounts for about 10% of the genetic predisposition (4). At least 13 other minor loci have been discovered mostly through microsatellite typing and linkage analysis in large collections of diabetic families with affected sib-pairs, and may contribute to diabetes risk (5).

The best characterized loci, IDDM1 (HLA) and IDDM2 (INS-VNTR), encode true susceptibility genes. Yet, there is also clear evidence that certain alleles provide genetic resistance from the development of diabetes. In particular, genetic protection from Type 1 diabetes is associated with specific alleles at the IDDM1 (6) and IDDM2 loci (7,8). For example, the HLA molecule DQA1*0102-DQB1*0602 (also known as DQ6). There usually is dominance of protection over susceptibility for genes encoded at these loci. It is a fair speculation that IDDM1 may be involved in antigen presentation and control immune responsiveness to one or more islet cell antigens, while IDDM2 may control insulin gene expression in the thymus and in turn selectively influence immune responsiveness to insulin. These two susceptibility loci may influence the specificity of the autoimmune response rather than a generic predisposition to autoimmunity.

That genetics plays an important role in the development of Type 1 diabetes has been demonstrated from a number of careful studies. There is a

higher concordance rate for Type 1 diabetes in monozygotic twins (35–50%) than in dizygotic twins (5–10%) (9). In siblings of probands of Europoids with Type 1 diabetes, the risk is 6% (10), while offspring of diabetic parents have a 3% risk if the mother has the disease, and a 6% risk if the father has the disease (11). The cumulative concordance or recurrence risk of Type 1 diabetes up to the age of 40 years in dizygotic twin pairs is twice as high as in ordinary first-degree relatives of patients up to the same age (12). The much higher concordance rate for diabetes among monozygotic than dizygotic twins implies that there is an inherited component to a disease. Yet, the substantial (50–65%) discordance rate in monozygotic twins indicates that environmental factors also must play a role in human Type 1 diabetes.

In contrast to the familial predisposition noted above, in the general population, the risk is much less. For example in the United States amongst Europoids the overall risk is 0.2 to 0.4%. However, there is considerable racial and ethnic variation in Type 1 diabetes incidence (e.g. 3.3 per 100 000 in African Americans in San Diego, CA, to 20.6 per 100 000 in whites in Rochester, MN), and about 40% of the incidence rate variation in the United States can be explained by racial composition (13).

A recent study examined the frequency of various islet cell antibodies—*islet cytoplasmic antibodies (ICA)*, *insulin autoantibodies (IAA)*, and *glutamic acid decarboxylase antibodies (GADA)* in 18 monozygotic and 36 dizygotic twin pairs with one or both partners having Type 1 diabetes (14). There was no difference between the prevalence of these three islet cell autoantibodies in dizygotic (26%, 49%, and 40%) and monozygotic (20%, 50%, and 40%) twins without diabetes, suggesting that islet cell autoimmunity is environmentally rather than genetically determined. Moreover, the prevalence of these antibodies was higher in the non-diabetic monozygotic and dizygotic twins than in other first degree relatives (~4%, 3%, and 4%) of patients with Type 1 diabetes (12). This implies that there is etiological importance to the prenatal or early postnatal period during which twins are exposed to the same environment, in contrast with that experienced by first-degree relatives.

Environmental

Many factors suggest that environmental factors are important determinants of Type 1 diabetes. It has already been noted that environmental factors are implicated by the discordance rate in monozygotic twins and the higher prevalence of autoimmunity in non-diabetic twins than in other first-degree relatives. Other indicators that environmental factors are involved include the seasonal variation in disease onset (15) and the rising incidence of Type 1 diabetes in Europe and many other parts of the world over the past 20–30 years (16, 17). Although in most areas, there has been an overall increase in incidence rates, in two studies—one in Finland and one in England—there has been a marked increase amongst children aged under 5 years (18, 19).

The rapid changes in incidence seen in populations that are for the most part genetically stable suggests a major role for environmental factors encountered early in life, e.g. before birth or in early postnatal life.

Viral Infection

Viruses have long been implicated as possible environmental determinants in Type 1 diabetes.

Direct effects of viruses, causing beta-cell destruction, are possible (20). In one dramatic case, a Cocksackie-B variant was isolated from pancreatic tissue in a young boy who succumbed within 10 days of the onset of Type 1 diabetes, and the viral isolate produced diabetes in experimental animals (21). In two other cases of death in young children shortly after diabetes onset, there was demonstration of superantigen involvement (22), which suggests acute viral infection. Yet, these examples of direct effects of viruses are exceedingly rare, and most likely do not account for many cases of Type 1 diabetes.

On the other hand, there is evidence that maternal viral infection during pregnancy is a risk factor for childhood-onset Type 1 diabetes. As many as 10–12% of children with congenital rubella develop Type 1 diabetes (23, 24). The patients who develop Type 1 diabetes have the typical genetic background, and manifest the usual immunologic abnormalities (25). Congenital cytomegalovirus infection has also been implicated in Type 1 diabetes (26). Careful studies from Sweden and Finland, using maternal cord blood, have found that maternal enteroviral infection during pregnancy, especially Cocksackie-B virus infection (but also echo virus), is a risk factor for Type 1 diabetes (27, 28, 29). Thus, children of mothers who expressed viral antibodies at delivery are at increased risk for developing childhood onset Type 1 diabetes. A fetal viral infection may initiate autoimmunity or cause persistent infection that may lead to progressive beta-cell destruction.

One mechanism by which viral infection may influence the immune response is through molecular mimicry. There is a homologous domain in the Cocksackie-B virus protein 2C (p. 2C) and the islet autoantigen glutamic acid decarboxylase (GAD) (30). There is T-cell reactivity to GAD peptide sequences shared with Cocksackie virus protein in recent-onset Type 1 diabetes (31). Moreover, it has recently been shown that this homologous domain is highly conserved in the Cocksackie B-like enteroviruses (32). These are very prevalent enteroviruses and therefore exposure to the mimicry motif will be a frequent event throughout life. It has also been shown that the p. 2C domain binds to the diabetes associated HLA-DR3 molecule (32). It is thus possible that this molecular mimicry may be limited to the HLA-DR3 positive subpopulation of Type 1 diabetic patients.

There are other examples of possible molecular mimicry involving viruses and islet antigens. These include a homologous domain in insulin and a retrovirus sequence (33), a homologous domain in an islet tyrosine phosphatase IA2 and a rotavirus sequence (34), a homologous domain in a 52 kD islet protein and a rubella protein (35), and a homologous domain in a 38 kD islet protein and cytomegalovirus (36).

There are other mechanisms, too, by which viral infections may induce immune reactions, and lead to beta-cell destruction (37). These include induction of expression of HLA class II molecules with subsequent antigen presentation, retrovirus or slow virus infections, or alteration of T-cell receptors.

Viral infections also may serve as a stress factor, bringing Type 1 diabetes to clinical recognition. In a nationwide incident case control study in Sweden, the odds ratios for Type 1 diabetes for children exposed to 0, 1–2, or over 2 infections during the last year before diagnosis of diabetes revealed a linear increase (OR = 1.0, 1.96 and 2.55 for 0, 1–2 and over 2 infections, respectively), which remained significant when standardized for possible confounders such as age and sex of the children, maternal age and education and intake of antibiotics and analgesics (38). This study also found a protective effect of measles vaccination.

Chemical Toxins

Several chemical toxins have been shown to have the potential of destroying beta-cells. Amongst these are the nitrosourea compounds, including the drug streptozotocin, the rotenticide Vacor (N-3-pyridyl-methyl-N-p-nitrophenyl urea) (39) and other nitrosourea compounds (40). Unfortunately, such compounds are ubiquitous in our environment, and represent only one class of chemical compounds that may have the potential of leading to Type 1 diabetes.

Another group of potentially toxic substances is the nitrates and nitrites. One study suggested that maternal consumption of nitrates and nitrites around the time of conception may influence the eventual development of Type 1 diabetes (41). In this case the nitrates and nitrites were contained in smoked mutton, consumed

disproportionately as part of holiday festivities. The notion is that a developing embryo, when exposed to these toxins, suffers an initial beta-cell insult, which enhances the risk of diabetes, appearing years later. Similar studies in animals support this interpretation (42, 43). In the Swedish nationwide study, a high intake of foods rich in nitrosamine conferred risk, and the frequency of infections and a high nitrosamine intake tended to interact, indicating a synergistic effect with an odds ratio of 11.8 (44).

Neonatal Nutrition

One potential environmental influence is neonatal nutrition. It has been proposed that consumption of cow milk proteins may increase susceptibility to Type 1 diabetes (45). A number of studies have examined the relationships amongst breast milk feeding, introduction of cow milk proteins, and the frequency of Type 1 diabetes, with conflicting results (46–48). A meta-analysis has suggested both that exclusive breast feeding may be protective and that early cow milk consumption may confer risk (49). A small prospective Finnish study has suggested that exclusive breastfeeding may reduce the likelihood of disease development (50). Although controversial and not reproducible, in one study a group of diabetic children were found to have elevated levels of antibodies directed against bovine serum albumin, which may be the relevant cow's milk protein (51). A suggested mechanism is molecular mimicry between the beta-cell surface protein ICA-69 and a 17 amino acid sequence of bovine serum albumin (51). These studies have led the investigators to propose that neonatal exposure to cow's milk may lead to the initiation of the immunologic attack against pancreatic islet beta-cells and the development of Type 1 diabetes. As a consequence, they have proposed and initiated a controlled clinical trial in infants who are first-degree relatives of individuals with Type 1 diabetes, in which the treatment group will receive a cow's milk-free formula and the control group will receive conventional formula containing cow's milk (52). This trial is known as TRIGR, Trial to Reduce IDDM in Genetically at Risk. It plans to enroll several thousand newborns and follow them for up to a decade.

DISEASE PROCESS

The Type 1 diabetes disease process is one of selective destruction of the insulin-producing beta-cells in the pancreatic islets of Langerhans (53, 54). The current concept is that islet beta-cells are destroyed by an immune response mediated by T-lymphocytes that react specifically to one or more beta-cell proteins (autoantigens). The exact mechanisms have not yet been clearly defined, as there appear to be complex regulatory interactions amongst various elements of the immune response, and it is unclear which elements of the immune circuitry are responsible for beta-cell destruction and which are responsible for beta-cell protection. The prevalent view is that islet cell destruction is enhanced by CD8+ cytotoxic T-lymphocytes stimulated by T-helper-1 (Th1) subset of CD4+ T-lymphocytes, with inhibition of islet destruction by T-helper-2 (Th2) subset of CD4+ T-lymphocytes and CD8 $\gamma\delta$ suppressor T-lymphocytes. Thus, the pathogenetic sequence potentially could be altered either by downregulation of destructive forces or by enhancement of protective forces. This explains why both immunosuppressive and immunostimulatory (or immunomodulatory) approaches may be beneficial. Also, there is some debate as to whether Type 1 diabetes is an antigen specific autoimmune disease or an inflammatory disease that arises because beta-cells are inherently less able to withstand local environmental insults than are other cell types. In fact, the development of Type 1 diabetes likely involves collaboration amongst islet cell specific and non-specific mechanisms, including a complex orchestration of the entire immunologic repertoire. Diabetes develops in a highly tissue specific, cytokine-rich environment of insulinitis. Immune activation appears to involve presentation (by antigen presenting cells in the context of MHC class II molecules) to the immune system of a diabetogenic peptide.

As a consequence of antigen (immunogen) presentation, there is activation of a Th1 subset of CD4+ T-lymphocytes. The cytokines produced by Th1-cell activation, interleukin-2 (IL-2) and interferon- γ (IFN- γ), activate cytotoxic T-lymphocytes and cytotoxic macrophages to kill islet beta-cells by a variety of mechanisms. These killing mechanisms include oxygen free radicals, nitric oxide, destructive cytokines (interleukin-1 [IL-1], tumor necrosis factor- α [TNF- α], tumor necrosis

factor- β [TNF- β], and interferon- γ [IFN- γ]), and CD8+ cytotoxic T-lymphocytes that interact with a beta-cell autoantigen-MHC class I complex.

Once the initial immune destruction commences, secondary and tertiary immune responses also are activated, with virtually the whole immunologic army attacking beta-cells. In the process, many beta-cell proteins serve as antigens that generate both cellular and humoral immune responses, thus rendering nearly impossible the task of identifying putative 'primary' triggering antigens. Although the diabetogenic peptide is as yet unknown, there are several candidates, including insulin, glutamic acid decarboxylase (GAD), and islet tyrosine phosphatases (IA2 and IA2 β). After initiation of the immune response by an antigen acting as an immunogen, there is an amplification cascade, with both intramolecular epitope (or determinant) spreading and intermolecular antigen spreading. Ultimately, then, several different antigens are immunologic targets and also may be used as immunologic modulators (tolerogens or regulators).

Prevention strategies to be discussed herein are those designed to interrupt the pathogenetic sequence, the Type 1 diabetes disease process.

STAGES IN DEVELOPMENT

The development and course of Type 1 diabetes can be divided into a number of stages, the earlier of which are depicted in Figure 4A.2. The Type 1 diabetes process in any individual may progress through some or all of them. The purpose of dividing the disease into these stages is to note that interruption of the sequence at any stage, preventing the development of the next stage, is likely to be an important advance. Primary prevention may not be possible, in the strictest sense, particularly if the disease process is initiated *in utero*.

Stage 1. The first stage is genetic susceptibility, modulated by genetic protection. This stage is identified by finding of susceptibility genes without dominant protective genes.

Stage 2. In the second stage, an environmental trigger initiates autoimmunity. This eventuates in an anti-beta-cell cellular immune response leading to an immune mediated islet infiltrate (insulinitis), with consequent beta-cell injury, impairment of

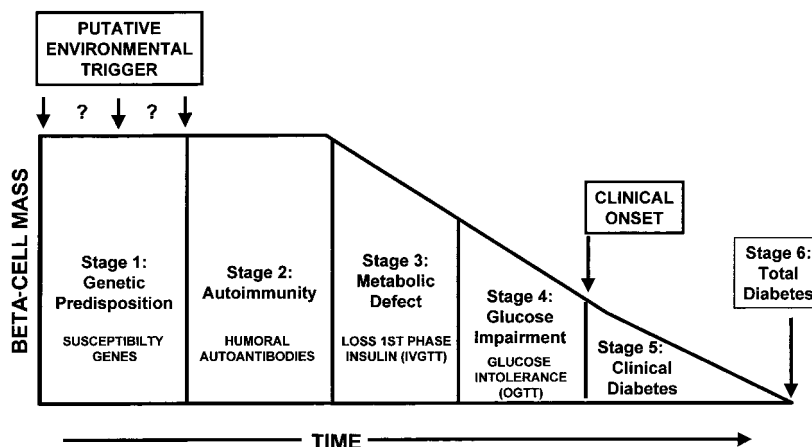


Figure 4A.2 Schematic depiction of the evolution of Type 1 diabetes through stages, as discussed in text

beta-cell function, and some loss of beta-cell mass. As beta-cells are injured, a presumably secondary humoral immune response develops, with the appearance of beta-cell autoantibodies. The principal antibodies are islet cytoplasmic antibodies (ICA), insulin autoantibodies (IAA), glutamic acid decarboxylase antibodies (GADA), and antibodies to islet tyrosine phosphatases (IA2 and IA2 β). (The antibodies to IA2 include the antibody ICA512 directed at a component of IA2, while the antibodies to IA2 β include one directed against an insulin granule membrane protein, phogrin [phosphatase homologue of granules from rat insulinoma].) This stage is identified by the presence of autoantibodies.

Stage 3. In the third stage, there is sufficient impairment of beta-cell function and/or loss of beta-cell mass to result in loss of first-phase insulin response (FPIR) during an intravenous glucose tolerance test (IVGTT). This stage is identified by loss of FPIR in an IVGTT.

Stage 4. In the fourth stage, there is impaired glucose tolerance (IGT) and/or impaired fasting glucose (IFG), but without overt diabetes. This stage is identified by glucose levels either fasting (IFG) or after a glucose challenge (IGT), that are elevated above the upper limit of normal, but have not reached the diagnostic threshold for diabetes.

Stage 5. The fifth stage is marked by the clinical onset of Type 1 diabetes. At the beginning of this stage it is estimated that over 80% of beta-cell function and/or mass has been lost, but the residual beta-cell function (evidenced by c-peptide

production) remains an important contributor to metabolic homeostasis. These individuals are identified by hyperglycemia exceeding the diagnostic threshold for diabetes, and by measurement of intact c-peptide secretion.

Stage 6. The onset of the sixth stage is marked by loss of all beta-cell function and mass (evidenced by lack of any c-peptide response to provocative challenge), and has been called 'total' diabetes. Diabetes becomes more difficult to control. As beta-cell function is lost and 'total' diabetes evolves, antibodies tend to decrease in titer and/or disappear. These individuals are identified by fluctuating glycemia and by absence of c-peptide secretion.

Stage 7. In the seventh stage, diabetic complications (retinopathy, nephropathy, neuropathy) develop. These individuals are identified by clinical and laboratory abnormalities signifying the presence of these complications.

Stage 8. In the eighth stage, one or another diabetic complication has progressed to blindness, renal failure, amputation, or other clinical disability.

PREVENTION STRATEGIES

Although it is possible to consider intervention at any of these stages, the tertiary intervention needed to forestall complications will not be considered in this chapter. Rather, the focus will be on interrupting the Type 1 diabetes disease

process. In this regard, there are several possible prevention strategies which could alter the natural history of the disease. These include:

1. Identification and elimination of environmental triggers. This might include eradication of maternal viral infections, perhaps by immunization of mothers prior to conception. It also might include elimination of cow's milk proteins from neonatal formulae.
2. Identification and enhancement of environmental protective factors. This might include promotion of breastfeeding.
3. Interruption of the immunologic sequence leading to beta-cell destruction. This could involve immune modulation that decreases destructive or increases protective forces, tolerization to beta-cell antigens, or development of anergy to these. It could also involve blockage of destructive elements (e.g. cytokines or free radicals) or promotion of beta-cell survival.

It is possible to consider using these at various stages of the disease, such as:

1. Immune intervention begun shortly after diagnosis (during Stage 5) when there is still some residual beta-cell function, in an effort to modify the severity of clinical manifestations, halt the destruction of beta-cells, and perhaps allow residual beta-cells to recover their function.
2. Identifying those at risk for the development of diabetes, during the preclinical period (Stages 2 or 3), and designing an intervention which might arrest the immune destruction before it becomes clinically evident, and thus prevent the disease syndrome.

In attempting to identify those at risk, to test interventions, much attention has focused on relatives (principally first-degree relatives) of people with Type 1 diabetes. In relatives, case finding is much easier because they have a 10–20-fold increased risk over the general population, making identification of high-risk individuals easier. Yet, even amongst relatives, except for monozygotic twins, the odds of identifying an individual potentially at risk are very small, as only 3–4%

of relatives will have identifiable autoimmunity (12). Yet, a problem is in newly diagnosed Type 1 diabetes, there is a first-degree family history of Type 1 diabetes only in 10–15% of children. For example, in one series from England, 12.8% of children had a first-degree relative with the disease, the relative affected being the father in 4.5%, the mother in 2%, and a sibling in 4.5% (19).

It should be noted that all evidence suggests that the pathogenetic sequence is the same in sporadic non-familial cases (55,56) as it is in relatives (57, 58). Thus, the same interventions would likely apply. The differences are that of case-finding and the need to have screening approaches with sufficiently high positive predictive value to be used in the general population. Amongst relatives, for example, autoantibody screening represents a relatively simple way of initiating the process of risk assessment. On the other hand, the logistics of autoantibody screening, presumably on a repetitive basis, usually would preclude this as the initial step in risk assessment in the general population. Here, two options seem likely:

1. A case-finding strategy, perhaps involving genetic screening at birth, followed by autoantibody screening in those genetically at risk, followed by appropriate intervention. This case-finding approach is being taken in the DAISY (Diabetes Autoimmunity Study in the Young) (59), DIPP (Diabetes Prediction and Prevention Project) (60), and NOBADIA (Norwegian Babies against Diabetes) (61) studies. In such a strategy, treatment (e.g. vaccination) would be only of susceptible individuals.
2. A population strategy. In this scenario, one might have a treatment approach (e.g. vaccination) sufficiently safe and effective that the entire population could be treated.

With time, it should be possible to implement one or both of these strategies. The prevention of Type 1 diabetes is a realistic possibility for the future.

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Epidemiology, Evidence for Prevention: Type 2 Diabetes

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INTRODUCTION

The prevalence of Type 2 diabetes is rising all over the world, with an ageing population living an increasingly sedentary lifestyle, and consuming, in relation to their energy expenditure, foods too high in fat and refined carbohydrates (1, 2). Many developing countries already have high Type 2 diabetes prevalence and diabetes complications, which typically form the greatest social and health care costs of diabetes. With increasing urbanization of lifestyle these rates become even higher than in European populations (3, 4).

Because of this scenario, there is an urgent need for strategies to prevent the emerging global epidemic of Type 2 diabetes. As there seem to be more reviews on prevention of Type 2 diabetes than actual studies of prevention, this chapter will be more orientated towards a case study illustrating the information available to address the issues that confront public health authorities in terms of Type 2 diabetes prevention. In fact, there has only been one major population-based intervention reported, the DaQing study in China (5). For this chapter, we briefly discuss general issues related to Type 2 diabetes prevention and focus on some of the evidence for considering the possibility of interventions targeted at one community at particularly high risk, the Australian Aboriginal and Torres Strait Island people (6).

IMPORTANCE OF CLASSIFICATION IN THE PREVENTION OF TYPE 2 DIABETES

Research, management and prevention of both Type 1 and 2 diabetes depend on an appropriate

and contemporary classification (1, 2, 7). Furthermore, a hallmark in understanding the aetiology of a disease, studying its natural history and investigating the contribution of genes is the ability to identify and differentiate the various forms. In the past, many clinical, molecular biology and prevention studies for Type 2 diabetes were undertaken with inadequate and inappropriate care in relation to classification (1). The latest World Health Organization (WHO) recommendations on diabetes criteria and classification have just been published (8) and are discussed in Chapter 1 above. This is the first revision in 13 years and the report has recommended major changes in both diagnostic criteria and the way diabetes is classified.

The outcome of the revised classification should be better description and comparison of diabetes between countries and also improved management of diabetes due both to earlier diagnosis and to better classification of cases for more appropriate therapy. Correct classification and phenotyping is also essential to ensure correct interpretation of primary prevention studies (1, 9). For example, recent studies on antibodies to glutamic acid decarboxylase and other markers of autoimmunity highlighted the poor classification of diabetes in adults, making many genetic and clinical research studies, as well as pharmaceutical trials of hypoglycaemic agents for treatment of Type 2 diabetes 'polluted' by participants with latent autoimmune diabetes in adults (LADA), and maturity-onset diabetes in the young (MODY) (1, 9, 10). It should be mandatory to screen all participants with anti-GAD and other autoantibodies in future Type 2 diabetes studies.

PRIMARY PREVENTION OF TYPE 2
DIABETES

Prevention of diabetes can be considered at three different levels. Primary prevention covers activities aimed at preventing diabetes from occurring in susceptible populations or individuals. Secondary prevention is aimed at early diagnosis and effective control of diabetes in order to avoid or at least delay the progress of the disease, and tertiary prevention includes those measures undertaken to prevent complications and disability due to diabetes (6, 11).

Studies in a number of populations, including Europeans, Native Americans, Indian, Chinese and African-born Mauritians, Samoans, Nauruans and Melanesian Papua New Guineans have shown that individuals with IGT have a higher risk of progressing to Type 2 diabetes (between 2- and 7-fold higher) than persons with normal glucose tolerance (3, 11). Therefore, persons with IGT have formed the target group for interventions aimed at preventing Type 2 diabetes in several studies. These have been of two main types—behavioural interventions based on changing diet and increasing physical activity, and/or therapeutic interventions using pharmaceutical agents to try and improve glucose tolerance and insulin sensitivity (6, 11). The factors that most consistently predict progression from IGT to Type 2 diabetes in published studies are elevated fasting and 2 h blood glucose and fasting insulin concentrations, decreased insulin response, and obesity (3, 4, 11). Thus interventions aim to influence one or more of these factors and thereby reduce risk of Type 2 diabetes.

Another very important reason for interventions to prevent Type 2 diabetes is that much of the morbidity and mortality from diabetes-related CVD is preventable (1). However, the clock starts ticking for CVD many years before Type 2 diabetes manifests clinically (12). In subjects who progressed to diabetes at the 5-year follow-up, examination of their baseline profile of CVD risk factors revealed that they already had significant elevations of key risk determinants (Table 4.1) (13). We have shown that a community-based lifestyle approach in Mauritius reduces some of the key risk factor determinants for Type 2 diabetes and CVD such as eating behaviour, sedentary activity, serum lipids and cigarette smoking (1). The study has reinforced the knowledge of when the risk factors for CVD in Type 2 diabetes begin to operate (12, 13). Therefore, there is great potential for early intervention to reduce the huge burden of CVD in Type 2 diabetes. This is particularly important as, with the success of primary prevention of CVD in non-diabetics, the proportion of CVD in the community due to diabetes has been increasing (14).

Behavioural Interventions
(Exercise and/or Diet)

A number of short-term studies have demonstrated improvements in metabolic parameters among people with IGT after interventions aimed at changing diet and increasing physical activity. They are reviewed in detail elsewhere (3, 4, 6, 11). The results of these studies suggest, but by no means prove, that in the longer term it may be

Table 4.1 Mauritius age-adjusted baseline cardiovascular disease (CVD) characteristics measured in 1987 in men with normal glucose tolerance developing Type 2 diabetes in 1992

CVD risk factor (baseline 1987)	1992 Status	
	Normal glucose tolerance	Converted to diabetes
Body mass index (kg/m ²)	22.4	24.3 **
Waist-hip ratio	0.88	0.91 **
Diastolic blood pressure (mmHg)	78.3	82.0 *
Fasting insulin (mU/L)	4.1	6.5 **
2-h insulin (ng/ml)	20.2	35.6 **
2 h plasma glucose (mmol/l)	5.2	6.3 **
Fasting plasma triglycerides (mmol/l)	1.3	1.9 **

* *p* < 0.05 ** *p* < 0.001

possible to reduce the incidence of Type 2 diabetes. A study from the USA (15), although not population-based, showed that weight reduction in morbidly obese subjects who underwent gastric bypass was associated with a reduced risk of developing diabetes relative to the control group who considered but did not undergo surgery for non-medical reasons. However, the subjects in this study are not representative of the wider population where intervention would be considered.

The Swedish Malmö Study was the first to show that it was feasible to carry out a diet and exercise programme for 5 years in men with IGT and reduce the incidence of Type 2 diabetes by 50% compared with the non-randomized control group (16). In a high-risk Indian community in Tanzania, in which the benefits of exercise and a healthy diet were promoted, the 6-year incidence of Type 2 diabetes in men and women with IGT was a seemingly low 2.2% (17). As there was no control group in this study, it is not possible to determine the programme's effectiveness. The best evidence yet that Type 2 diabetes can be prevented in people with IGT comes from a randomized intervention study reported from DaQing, China (5). Over 6 years there were significant and similar reductions in the incidence of diabetes in subjects with IGT who were randomized to diet, exercise or combined diet–exercise treatment groups (Figure 4.1).

Very recently, Eriksson et al. (18) have reported on the study design and one-year interim report on

the feasibility of a major Finnish initiative, the Diabetes Prevention Study. The aim of the study is to assess the efficacy of an intensive diet–exercise programme in preventing or delaying Type 2 diabetes in subjects with IGT. A total of 523 overweight IGT subjects have been randomized to a control or intervention group. The interim results show the efficacy and feasibility of the intervention programme. Both weight and plasma glucose (both fasting and post-glucose load) were significantly lower in the intervention group. Favourable changes were also noted in blood pressure, lipids and anthropometric indices (18).

Pharmacological Interventions

Two British trials in the 1960s using oral hypoglycaemic agents in association with some dietary modifications in Bedford (tolbutamide) (19) and Whitehall (phenformin) (20) did not show any benefit over 10 years or 5 years follow-up, respectively. Another study in women with post-gestational IGT (21) found that the addition of chlorpropamide to a diet treatment did not change later rates of glucose intolerance. As no control group was included the effects of diet alone could not be assessed. These negative results were in contrast to the findings of Sartor et al. (22), who showed that diet alone, or diet and tolbutamide, significantly reduced the incidence of Type 2 diabetes in males with IGT. However, this trial had a number of flaws, including poor randomization of control and treatment groups. Moreover, when analysed properly according to 'intention to treat', there did not appear to be any advantage in using tolbutamide.

The efficacy of primarily non-pharmacologic interventions such as used in the Chinese IGT intervention study (5) supports the view that interventions in persons with IGT should be given a high priority. In response, the National Institutes of Health, USA, have now funded a major multicentre IGT intervention to examine the potential for Type 2 diabetes prevention, the Diabetes Prevention Program (DPP) (23). Besides lifestyle interventions, they had intended to assess the role of pharmacological intervention with metformin and troglitazone. Troglitazone had been shown to improve insulin sensitivity in people with Type 2 diabetes (24), and a more recent study

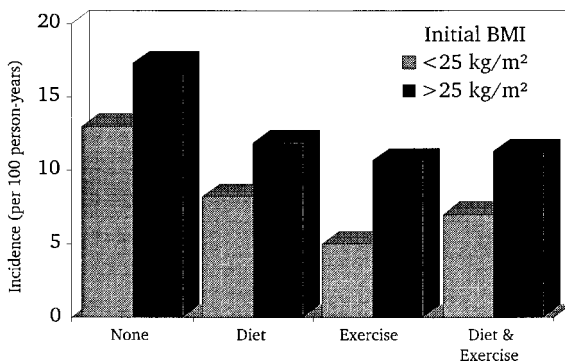


Figure 4.1 Effects of diet and exercise in preventing Type 2 diabetes in people with impaired glucose tolerance over 6 years in DaQing, China

Source: Adapted from Pan X, Li G, Hu Y et al. The DaQing IGT and Diabetes Study. *Diabetes Care* (1997); 20: 537–544, by permission

had demonstrated its effectiveness in improving the glycaemic response after a glucose load in people with IGT (25). However, because of reports of potential liver toxicity, the troglitazone arm of the study was suspended.

The α -glucosidase inhibitor, acarbose, is also being tested currently in a primary prevention trial (26).

Population-based Prevention Projects

Socio-economic factors have a major influence on nutrition, physical activity and health and thus on individual and community disease patterns (6). An excellent example of this is the dramatic rise in prevalence of CVD that has followed the epidemics of Type 2 diabetes, obesity and other NCDs in developing and newly developed nations (1). This has resulted in chronic disease epidemics that have occurred concurrently with modernization of lifestyle. Examples of the latter can be found in the native Canadian community (27), the Maoris of New Zealand (28) and the Aboriginal and Torres Strait people of Australia (6, 29). Prevention programmes are urgently required in each of these communities as diabetes and its micro- and macrovascular complications impose huge socio-cultural problems and become an unacceptable economic burden (1, 4). Table 4.2

Table 4.2 Aetiological determinants and risk factors for Type 2 diabetes

A. Genetic Factors
B. Demographic determinants Sex, Age, Ethnicity
C. Behavioural and lifestyle-related risk factors Obesity (including distribution and duration of obesity) Physical inactivity Diet Stress Westernization, urbanization, modernization
D. Metabolic determinants and intermediate risk categories of Type 2 diabetes Impaired glucose tolerance, impaired fasting glycaemia Insulin resistance Pregnancy-related determinants (parity, gestational diabetes, diabetes in offspring of women with diabetes during pregnancy, intrauterine environment)

shows the key behavioural and environmental risk determinants that need to be addressed in such programmes.

The intervention studies discussed above were carried out in a number of ethnic groups and populations. Although none have been carried out in Australian Aborigines there is no reason to believe that the possibility of improving metabolic parameters and preventing Type 2 diabetes in Aboriginal populations both in Australia and other developed countries would be any less. The studies to date have been focused on people with IGT who are already at increased risk of Type 2 diabetes. There are no data available from any population as to whether community-wide programmes encouraging healthy diet and exercise can successfully reduce the incidence of Type 2 diabetes. However, given the potential benefits of healthy lifestyle programmes in influencing risk factors for a range of non-communicable diseases, including Type 2 diabetes, coronary heart disease, stroke and certain cancers (11, 30), there are strong grounds for advocating a strengthening of such programmes in Aboriginal communities (6). Certainly there are examples of healthy lifestyle promotion programmes targeting Aboriginal people from across Australia and these have been reviewed in detail by de Courten et al. (6). Several of these appear there as models of community-based initiatives. For example, at Ernabella in South Australia, a group of women with diabetes have been instrumental in teaching others in nearby communities about cooking good food and a healthy way of life. Community-driven projects such as these may be the most effective means of bringing about lifestyle improvements in Aboriginal people.

In remote Aboriginal communities where all food is provided by a single store, the influence of the store manager and store policy on the available diet of the community is paramount (31). Lee et al. (32) reviewed the Arnhem Land Progress Association's Nutrition Policy which is aimed at improving the availability and affordability of 'healthy' foods, after 3 years and found varying degrees of success among five stores. In those communities where stores complied best with the policy, providing promotional and educational material alongside the food, dietary improvements were evident. In the Minjilang community, part of the store policy project, a more intensive community-

based intervention programme was run for 12 months. The programme there involved community elders and other community members and used several simultaneous strategies to promote healthy food and physical activity. During the 12 months of the intervention the diet improved (based on store turnover data), and metabolic, anthropometric and haematologic parameters among community members reflected these changes. After 3 years the Minjilang community still appeared to be consuming a healthier diet than a control community where no intervention had taken place (33). The authors stressed the importance of community control and ownership in the ongoing success of the programme.

Unfortunately, too often there is scant formal evaluation information available to demonstrate the success or otherwise of such programmes. O'Dea et al. (34) have shown, as summarized in Table 4.3, in a small study of both healthy and diabetic groups, that metabolic parameters associated with Type 2 diabetes and CVD can be improved, at least in the short term, by lifestyle changes in Aborigines. Similar results were seen in a project involving Hawaiian Polynesians (35).

These studies, in conjunction with the intervention trials discussed above strongly support the possibility of preventing Type 2 diabetes in Abori-

ginal communities through lifestyle changes. However, it is clear that it is neither practical nor acceptable for the majority of Aboriginal people to 'revert' to traditional patterns of food intake and physical activity to lower risk of Type 2 diabetes and CVD. Appropriate ways of lifestyle change, tailored to the prevailing circumstances in which Aboriginal people live, need to be identified to utilize the positive impact of a healthy lifestyle as demonstrated in these studies (34, 36).

New drugs may one day prove beneficial for prevention of Type 2 diabetes in Aboriginal communities. Their use in apparently healthy but yet at risk persons has to be limited for safety reasons to clinical trial settings. Hence the current focus on people already identified with IGT and therefore at increased risk for diabetes and cardiovascular disease (6). However, this presupposes widespread screening of Aboriginal people with the oral glucose tolerance tests in order to identify persons with IGT. Such an exercise applied to a total population would be extremely difficult in both financial and practical terms, and may not be justifiable (6). Staged screening approaches to increase the 'yield' in screened positive people using less invasive initial screening steps (such as random blood sugar tests and/or pre-screening questionnaires for risk assessment)

Table 4.3 A summary of the important paper of O'Dea et al. (1980) describing the effects of reversion to traditional diet

Number, age and sex of subjects	13 full-blood Aboriginal men and women. 14 Caucasians were included as comparison.
Sample selection/design	The Aborigines spent 12 weeks living a relatively traditional lifestyle with one of the authors (KA). Used guns and simple fishing gear but consumed no alcohol or store food. At the conclusion of the 12 weeks in the bush starch tolerance tests were carried out. 3 months after return to urban life starch tolerance again tested. Alcohol avoided prior to starch tolerance tests.
Criteria for IGT and diabetes	Any subject whose glucose was >10 mmol/l during the test was arbitrarily designated as diabetic; 3 Aborigines and 4 whites in this category.
Results	All Aborigines for whom baseline data were available (10/13) lost weight during the study. The most weight was lost by those most overweight, i.e. women. Food was varied and plentiful during study and relied heavily on animal sources—perhaps because the gun and fishing equipment made these easier to obtain. ≤20% CHO, ≥30% fat and 50% protein. In the urban setting the diet was high in fat, alcohol, and refined CHO and low in protein (≤10%). Caucasians consumed low–mod alcohol, CHO 45–50%, fat 35–40%, protein 10–15% diet. Aborigines had lower serum cholesterol than whites, which did not fall during study. Triglycerides increased with urban diet and were higher than whites in urban setting. Fasting plasma glucose in Aborigines was lower than in Caucasians, in bush or urban setting, and not changed by lifestyle change. Starch test showed that in urban Aborigines there was a more immediate increase in plasma glucose than in traditional Aborigines or Whites. Thereafter rates of change were similar. Insulin responses were steepest in urban Aborigines, intermediate in traditional Aborigines and showed no change in first 15 mins for Caucasians. Differences were maintained thereafter and cannot be attributed to relative obesity in Aborigines.

are currently under evaluation. Therefore, realistic hopes for primary prevention of Type 2 diabetes in Aboriginal communities remain with population-wide healthy lifestyle programmes. What are needed now are demonstrated effective strategies to bring about changes in diet and physical activity which can reduce rates of Type 2 diabetes and CVD risk factors in Aboriginal communities. These are unlikely to work in isolation from initiatives to improve general living conditions and address the social and political issues confronting Aboriginal people today (6).

EXPERIENCES IN OTHER INDIGENOUS POPULATIONS

Given the paucity of information on intervention programmes available for Aboriginal communities (6), it is useful to briefly review experiences in similar populations. One of the best documented is that in Native Americans, the Zuni Diabetes Program in New Mexico. This is a community-based exercise programme initiated in July 1983, and now offering 48 aerobic sessions over 5 days each week (37). Sessions specifically for people with Type 2 diabetes or for the general public are provided. Participants are recruited by personal invitation, recommendations from medical staff and community advertising. Special events are held throughout the year sponsored by community agencies and local businesses. Indian Health Service staff coordinate the program which also employs community members to run the exercise sessions.

A prospective evaluation has not been performed to determine whether the programme is reducing the incidence of Type 2 diabetes. However, results from a small sample of Zuni Indians with Type 2 diabetes suggest that the programme successfully facilitated weight loss, with participants losing 4.09 ± 4.9 kg and non-participants losing 0.91 ± 3.9 kg over a 50-week period (37). While the weight lost was not great in magnitude, it was accompanied by a drop in mean fasting plasma glucose concentration of 2.4 mmol/l. The ability of the programme to attract and retain 30 people for a mean attendance of 37 weeks suggests that such programmes can be successful. The authors postulate that some of the characteristics of this programme that have made it successful are

the reinforcement of exercise behaviour through multiple classes at a range of sites, community exposure to the exercise message and the ongoing nature of the programme (37). It may also be that the involvement of community members as group leaders has helped acceptance of the programme.

Ethnographic methods were used to assist in the development of a community-based diabetes prevention programme in an isolated Native American community on the Sandy Lake reserve in northern Ontario (38). An understanding of the socio-cultural context of diabetes is essential for prevention of Type 2 diabetes in the Sandy Lake population, and also in other indigenous populations, such as Australian Aborigines. Therefore, answers to questions regarding local terms used to talk about diabetes, perceptions of causes, consequences and treatment of diabetes and how this information can be used in preventive programmes were sought, using ethnographic methods.

Diabetes was perceived to be a common problem in the community but it was considered to be of intermediate severity because of its chronic rather than acute nature, i.e. it did not require a trip to the hospital or cause severe pain. The Sandy Lake community identified 'bad diet' and eating too much 'white man's' food as causes of diabetes but did not link lack of physical activity and obesity directly with diabetes (38). There was less understanding of what made certain foods good or bad in terms of nutrient content. Diabetes was considered a white man's illness which could be treated by eating more bush food and less white man's food. However, despite the consistency of this view, store purchases suggested that this was not commonly done.

Socio-cultural Perspectives of the Prevention of Type 2 Diabetes

Whatever the views or perceptions of European Australians, Aboriginal people undeniably perceive that progress in overcoming their social, education and health problems will not occur without recognition of their rights to, and access to, land (6). Whilst major High Court decisions have delivered some legal weight to Aboriginal claims and aspirations, the fact that these judgments and their intent remain under question suggests that non-Aboriginal Australians have not

yet accepted the Aboriginal views linking land and reconciliation to health problems and other areas of inequality. Given the long history of Aboriginal health problems, and the importance that they place on land rights and reconciliation, it seems reasonable to conclude that there will indeed not be substantial improvements until these fundamental issues are resolved (39).

SUMMARY

The evidence for the potential of pharmaceutical interventions to prevent diabetes awaits confirmation from clinical studies in high-risk groups (23,26). These trials may not be applicable if community-based approaches are recommended in populations with high diabetes prevalence and associated diseases. There are a number of issues to be considered in planning preventive strategies, some of them emerging from cultural differences and the special socio-economic circumstances under which Aborigines and other indigenous people live. Community-based preventive programs and initiatives do exist; however, a critical evaluation of success is missing and outside the scope of this review. There are a number of general issues, which can reduce the success of prevention campaigns, e.g.:

- Psychological factors such as illusion of immortality, which can impact on the commitment for prevention.

- Insufficient knowledge about prevention, resulting in apathy of participants and decision-makers alike.
- Low priority for research and funding for prevention amongst politicians, academics and institutions.
- Vested commercial interest in certain aspects of lifestyle and nutrition.
- Socio-economic factors which can inhibit changes in diet and lifestyle.
- Economic benefits of curative medicine, which de-emphasizes prevention.
- Late benefits of prevention, which are often initially intangible, but require upfront financial investment. Support for prevention is therefore difficult to obtain in politics governed by the quest for short-term results.

The demographic, behavioural and environmental causes of Type 2 diabetes are being increasingly well described (1,3,11). The specific roles of obesity, lack of physical activity, and, to a lesser extent, nutritional factors such as low-fibre diet, high-saturated fat, etc. and perhaps low birth-weight, can explain a significant proportion of the aetiology of Type 2 diabetes (Table 4.4) (3). These findings provide clues for strategies to prevent Type 2 diabetes. The genetics of Type 2 diabetes remain poorly understood, despite major advances in the understanding of the single gene mutations causing MODY (1).

Pharmacological compounds, e.g. biguanides, α -glucosidase inhibitors and thiazolidinediones, may

Table 4.4 Proposed behavioural and environmental determinants of Type 2 diabetes based on findings from cross-sectional or longitudinal studies

Determinant	Strength of association	Control for confounding factors
High body mass index	High	Adequate
Increased central obesity	High	Adequate
Physical inactivity	Intermediate	Not complete
Excessive intake of		
● energy	Intermediate	Not satisfactory
● simple carbohydrates	Weak	Not satisfactory
● saturated fats	Intermediate	Not satisfactory
● alcohol	Weak	Not satisfactory
Low intake of		
● dietary fibre	Intermediate	Not satisfactory
● certain trace elements	Weak	Not satisfactory
Use of some antihypertensive drugs	Intermediate	Not complete

prove useful in the prevention of the deterioration from IGT to Type 2 diabetes. However, at least for economic reasons, these are unlikely to be helpful in the developing world in the near future. However, the epidemiological studies that have demonstrated aetiological roles for a number of potentially modifiable factors related to lifestyle, such as physical activity, obesity and diet, hold out some hope of being able to stem the tide.

Intervention studies based on modifications of diet and exercise are starting to show promising results, but almost certainly need to be combined with socio-political changes. This seems necessary in order to implement changes of lifestyle outside a clinical trial setting which should persuade large enough numbers of people of different cultures to avoid sedentary lifestyles and to follow healthy diets.

At present there are approximately 110 million people with diabetes in the world but this number will reach around 234 million by the year 2010, the majority of them with Type 2 diabetes (2). Thus there is an urgent need to implement strategies to prevent the emerging global epidemic of Type 2 diabetes. Tackling diabetes must be seen as part of an integrated programme that addresses other lifestyle-related disorders. The prevention and control of Type 2 diabetes and the other major non-communicable diseases can be cost- and health-effective through an integrated approach to NCD disease prevention and control.

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Methodology for Physical Activity Assessment

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Recent epidemiological studies have related physical activity to improved glucose tolerance, insulin sensitivity and reduced prevalence and incidence of diabetes in various ethnic groups (see (1,2) for a review of the literature). Physical activity is also thought to protect against a wide range of other diseases and adverse outcomes, including cardiovascular disease, stroke, colon cancer, functional decline, and all-cause mortality (3–11). Additionally, physical inactivity has been related to overall obesity (12), body fat distribution (13,14), blood pressure (15–17), lipid abnormalities (18), and hemostatic factors (19), which are also concerns for people with diabetes.

With this evidence of the multifactorial significance of physical activity for health, the measurement of physical activity has become an increasingly important part of epidemiologic methodology. Many researchers are interested in measuring physical inactivity as a potential risk factor in the development of diseases. Public health interventionists rely on physical activity assessment to identify subgroups at greatest risk for disease and/or to monitor the progress of intervention efforts. Both researchers and interventionists would like to be able to identify the specific levels of physical activity likely to provide the most protection. This issue was the focus of a National Institutes of Health workshop, in which a panel of experts in physical activity epidemiology emphasized the need to clarify and specify 'the type, pattern, intensity, frequency, and total amount of physical activity required to enhance functional status and provide mental and physical health benefits' and 'the need to identify variations in dose–response relationships between different populations' as they relate to disease prevention

(20). For all of these issues, physical activity measurement is a crucial link and sometimes a lingering hurdle.

WHAT IS PHYSICAL ACTIVITY?

Physical activity has been defined by Caspersen et al. as 'any bodily movement produced by skeletal muscles that results in energy expenditure' (21). Components of total energy expenditure in a relatively sedentary individual include basal metabolic rate, which typically encompasses 50–70% of total energy, and the thermic effect of food, which accounts for another 7–10% (22). The remaining 20–43% is composed of energy expended through some type of 'physical activity', which can then be subdivided into energy expended in general activities of daily living (such as bathing, feeding, and grooming) and occupation, transportation, sporting and other leisure activities (see Figure 5.1).

Since the relative contribution of each of these components can vary considerably both within and among individuals and populations, valid and appropriate measurement of physical activity becomes a challenging task. This measurement is further complicated by the fact that there are several health-related dimensions of physical activity (23). For example, in addition to quantifying physical activity based on the amount of energy expended, it can be quantified based on the *manner* in which energy is expended. In other words, physical activity can be measured according to its effects on different systems of the body by assessing attributes such as aerobic intensity, muscular resistance, degree of weight-bearing, and range of motion involved (see Figure 5.2). These

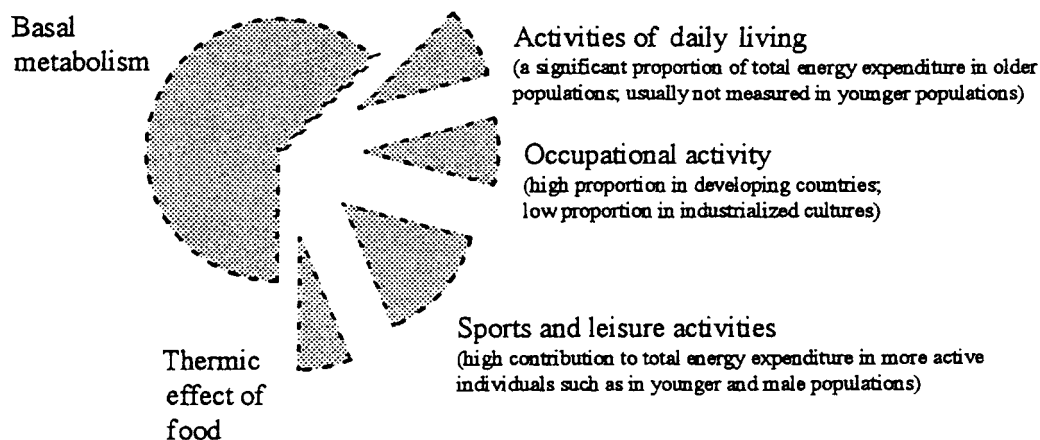


Figure 5.1 Schematic representation of components of total energy expenditure

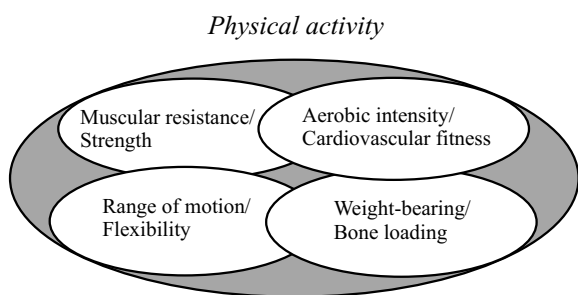


Figure 5.2 Health-related dimensions of physical activity

qualitative differences in physical activity may have implications for the prevention of specific diseases. For example, 100 calories burned swimming may be particularly beneficial to cardiovascular health and the prevention of related diseases but 100 calories expended weight-training may have a more favorable effect on bone mass or osteoporosis risk. Similarly, 100 calories expended in range of motion or flexibility training may be important for maintenance of physical function or avoidance of disability in older populations.

HOW HAS PHYSICAL ACTIVITY BEEN MEASURED?

Physical activity assessment tools have been used to measure many dimensions and attributes of physical activity, with most focusing on the amount of energy expended. These tools can be categorized

into objective and subjective approaches and include but are not limited to:

Objective approaches:

- Direct measures of energy expenditure such as the doubly-labeled water technique, or the respiratory chamber.
- Movement counters which initially measured frequency of movement and have progressively modified to detect differences in speed and direction of movement.
- Physiological measures of physical activity including heart rate monitoring and fitness testing.
- Behavioral observation systems.

Subjective measures:

- An array of questionnaires and surveys which require the individual to recall their past activity behavior. These tools vary in their ability to quantify the type, frequency, duration, and intensity of various occupational, transportation, leisure, and household activities over a variety of time-frames.
- Activity logs and diaries for recording of specific activities.

Each approach has both advantages and disadvantages that can vary based upon the population being studied and the research objectives. In epidemiology, subjective measures have typically been used for the practical assessment of physical activity in populations, and objective measures

have been utilized to validate the subjective activity measures.

Description of Some of the Popular Objective Approaches

Doubly-labeled Water

The doubly-labeled water (DLW) technique is the best estimate of free-living, total energy expenditure and is regarded as a gold standard of energy expenditure in validation studies. It involves the ingestion of isotopically labeled water, from which the amount of labeled hydrogen and oxygen eliminated can be measured over a set period of time, usually one to two weeks. The difference in hydrogen and oxygen turnover rates allows an estimate of carbon dioxide production and thus an estimate of total energy expenditure (24,22). By subtracting the resting energy expenditure, which is determined using standard laboratory procedures of indirect or direct calorimetry, an estimate of energy expended during physical activity is obtained. This estimate is typically expressed in kilocalories expended per day or per week.

Doubly-labeled water allows the measurement of physical activity in free-living populations, with no influence on behavior and no constraints on the time or setting of physical activity. The fact that it is non-reactive, or does not cause an alteration of the participants' behavior, is an important advantage over some other measures of physical activity such as diaries and movement monitors. However, the high cost makes it impractical for many epidemiologic studies. DLW is also only relevant for studying total energy expended in physical activities and provides no information about the intensity or the specific type of activity performed during the sample time frame. Furthermore, it is not applicable for the evaluation of physical activity for more than a 1–2 week period of time unless repeat assessments are made.

Activity Monitors

These have been used to assess physical activity and, more often, to help validate subjective

measures of activity. Examples of these tools include pedometers, activity movement monitors and accelerometers. Pedometers, worn in the shoe or on the hip, estimate movement by responding to vertical movement of the body. Recent enhancements include the ability to adjust for stride length and body weight, for a prediction of kilocalories expended (25). The Large Scale Integrated (LSI) activity monitor (GMM Electronics, Verona PA) contains a cylinder with a ball of mercury that detects movement each time the cylinder is displaced at least 3 degrees from the horizontal plane. Accelerometers such as the Caltrac and more recently developed Tritrac accelerometers detect not only the frequency of movement, but also the acceleration and deceleration of movement in a single (Caltrac) and double plane (Tritrac). The size of these instruments ranges from slightly larger than a wristwatch to that of a cigarette package and they are typically worn on the hip. Physical activity assessed by pedometers and the LSI are typically expressed in counts or steps per day or week. For research purposes, activity assessed by accelerometers can be evaluated in terms of absolute frequency, or weighted by acceleration for an estimate of energy expenditure.

Activity monitors have been used in both children and adults and have been shown to be significantly correlated with physical activity estimates obtained from questionnaires (26–28). Activity monitors cannot detect the difference between level ground and inclines or increases in muscular resistance, however, reducing accuracy for the measurement of varied types of physical activity (29). Since activity monitors were originally designed to quantify walking and running activity, they become less accurate in the measurement of activities that are not similar to walking or running. They can also be affected by passive movement such as car or bus rides on bumpy roads.

Heart Rate Monitoring

This has been used in a variety of clinical and research settings. Since heart rate is directly related to oxygen consumption, it can be used to differentiate activity levels among individuals. Unfortunately, the relationship between heart rate

and oxygen consumption is considerably weaker at the low levels of physical activity which are typical of much of the population. Heart rate is also vulnerable to many non-exercise-related stimuli such as psychological stress, dietary intake, and temperature (30). The potential variability caused by these factors makes it less useful for comparison of relatively inactive individuals. Like doubly-labeled water, heart rate monitoring is usually limited to a short time-frame. In addition, there is the potential for heart rate monitoring to be cumbersome, causing an alteration in activity behavior.

Physical Fitness

Cardiorespiratory fitness defined by measurement of oxygen consumption at a submaximal or maximal workload on a graded treadmill or bicycle ergometry, has been used extensively to validate physical activity assessment tools (31–33). The rationale for using fitness as a validation method for physical activity extends from the consistent findings that aerobic activity improves cardiorespiratory fitness (34). When well-defined laboratory criteria are used, physical fitness testing can be highly reproducible and avoids some of the subjective pitfalls of questionnaires. Fitness provides an objective way of comparing individuals in the population and of evaluating progress in exercise interventions. Like physical activity, physical fitness has been shown to be protective against cardiovascular disease and all-cause mortality (35–37) and may be one mechanism whereby physical activity prevents disease (38). However, physical fitness has a strong genetic component (39). Because of the potential confounding by genetics and the fact that physical activity and physical fitness are often not strongly related, physical fitness testing probably has a more important role as an independent measure of disease risk than as an estimate of physical activity (30).

Subjective Measures

Physical activity questionnaires and diaries have emerged as the tool of choice for physical activity assessment primarily because of practical consid-

erations but also because they can estimate subcomponents of physical activity such as frequency, duration, and intensity. Physical activity surveys do not directly alter the individual's behavior, but are subject to recall biases. These tools vary considerably in their complexity, from self-administered single questions to comprehensive interviewer-administered surveys of lifetime physical activity. Single question questionnaires have been used which ask an individual whether or not they are more active than others of their age and sex or whether they exercise long enough to break into a sweat. More complex questionnaires attempt to survey a wide range of popular activities over a selected time-frame.

Time-frame

Physical activity questionnaires are further distinguished by the time-frame that they cover. Diaries and logs may require the participant to record activities over 1 day, 3 days or the past week. Past-week recall surveys may query the frequency and duration of participation of activities performed over the past week. Examples of past-week recall surveys include the Harvard Alumni Questionnaire, and the 7-day Physical Activity Recall Questionnaire (5, 40, 41). Surveys with a past-week time-frame are less vulnerable to recall bias and are more practical to validate with objective tools than are questionnaires of a longer time-frame. However, since physical activity may vary with season, or as a result of an acute illness or time commitment assessment over a short time period is less likely to reflect 'usual' behavior.

Questionnaires of a longer time-frame, such as 1 year, may be more likely to represent usual activity patterns and have been used extensively in epidemiologic studies. Past-year physical activity has been assessed by questionnaires such as the Minnesota Leisure-time Physical Activity Questionnaire (MLTPQ), the Modifiable Physical Activity Questionnaire (modified version of the Pima activity questionnaire) and the Harvard alumni questionnaire. All of these questionnaires result in a summary estimate of physical activity expended per week averaged over the past year (42, 43, 5). The potential for recall bias is greater when measuring long-term activity patterns although these assess-

ments are less likely to be influenced by acute changes in activity levels than questionnaires with a shorter time-frame. To account for these issues, some questionnaires include assessment over both a short and a long time period in order to obtain the best overall estimate of an individual's typical activity levels (43).

Lifetime Physical Activity

Few studies have attempted to assess a lifetime of physical activity. Since chronic diseases such as osteoporosis and cancer tend to have a long developmental period, it is potentially the long-term chronic exposure to physical inactivity that increases risk for disease. In addition, historical physical activity assessment has the advantage of being feasible to use in case-control studies of rare diseases and avoiding the expense and time of longitudinal studies.

Early measures of historical physical activity categorized people according to employment history (44–46). This approach makes assumptions about the activity level associated with specific job titles and ignores any contribution of leisure physical activity. Other lifetime assessments have grouped subjects according to participation in high school or inter-collegiate athletics (47–50). This approach ignores the contribution of physical activity outside of organized sports.

Historical physical activity has also been assessed using physical activity surveys in a more comprehensive manner, evaluating the extent to which leisure-time physical activities were performed during specific age periods (26, 44, 51). Studies utilizing these historical physical activity questionnaires have demonstrated that people who participated in less leisure-time physical activity over their lifetime had lower bone mass, more hip fractures and are more likely to develop non-insulin-dependent diabetes mellitus (26, 52–54). Historical physical activity assessment is obviously limited by problems with recall and the difficulty in validation. While an ideal study design would examine lifetime physical activity prospectively, the use of historical physical activity questionnaires as described above has enabled examination of factors that would otherwise require many years of study, thousands of participants, and high expense to conduct.

Types of Physical Activity Assessed

Physical activity questionnaires vary according to whether they assess leisure, transportation, occupational or household activities. Early studies in physical activity epidemiology estimated physical activity performed at work. (3,4). Using a classification scheme such as the *US Dictionary of Occupational Titles*, created and published by the Department of Labor (55), individuals were categorized into groups of 'sedentary, light, medium, heavy, or heavy work' (46). Job classification has the advantage of being relatively objective and less vulnerable to recall bias. However, misclassification of individuals is possible due to assumptions about the amount of activity expended in a given occupation and the fact that activity levels of a given occupation can vary across regions. More recent occupational physical activity questionnaires have been developed which query the frequency, duration and intensity of activities within a job rather than simply inquiring about the job title itself (43, 56).

Most contemporary physical activity surveys only assess leisure-time activities that require an energy expenditure above that of daily living. Due to the decline in physical activity levels within occupations in most industrialized countries, it is assumed that assessment of leisure-time physical activity may provide the best representation of population-wise variation in physical activity. Similarly, it is assumed that the activities of daily living such as bathing or feeding are similar among most individuals within the population and that differences in these activities are less likely to contribute substantially to energy expenditure in a population. Leisure time and sporting activities are more distinctive behaviors with more specific starting and ending time, making recall by the participant more precise and definition and quantification easier for the researcher. Because of this focus on leisure activities, it is imperative that the activities queried are both comprehensive and representative of the population and culture being studied.

Although this focus on leisure and sporting physical activity may be valid for younger and healthier populations, some have suggested that differences in activities of daily living or other low-level leisure activities may be the most important determinant of energy expenditure and physical activity in an older or sick population (57).

Therefore, questionnaires have been developed to assess physical activity at the low end of the physical activity spectrum. The Physical Activity Scale for the Elderly (PASE), the Yale Physical Activity Survey (YPAS), and the Modified Baecke questionnaire all query these lower-level leisure activities (27, 28, 58). Because these questionnaires have been developed recently, there has been little evaluation of the relationship between physical activity and disease in older populations. This remains an important area of future research (59).

An Example of a Comprehensive Physical Activity Survey

The most popular survey approaches measure the type, frequency (e.g. number of times per given time-frame), duration (e.g. number of minutes per session), and estimate the intensity (e.g. degree of vigor or metabolic cost) of physical activities performed during a particular time period. It is this comprehensive assessment of physical activity that has allowed for a more sensitive discrimination between individuals of different activity levels and lends itself to subanalyses based on type, duration, and intensity of activity. This approach has served as the basis for much of the epidemiologic research relating physical activity to the prevention of cardiovascular and other diseases.

As described in Figure 5.3, the data obtained from a more extensive questionnaire format give

the researcher options to analyze data at several different levels. Multiplying the number of times per week (or month) of participation by the number of hours (or minutes) per time leads to an estimate of total duration of physical activity within a specific time frame. Comparisons can be made at this step in this process by comparing individuals based on the total time (frequency and duration) spent participating in physical activities (Figure 5.3). If possible, time spent in each activity can then be multiplied by an estimate of the relative intensity of that activity. These estimates are obtained from the literature and correspond to how vigorous the specific activity is thought to be. All of the activities are then summed and expressed in ‘MET-hours per week’ (or kcal/kg per week), which can be converted to kilocalories per week if one knows the body weight of the individuals. However, this involves making an assumption about the weight of the individual throughout the time-frame which is being assessed. As an example of this computation procedure, the Modifiable Activity Questionnaire assigns a specific MET level to each activity based on average levels of energy expenditure determined from the literature (43).

Rather than weighting each specific activity by its relative intensity, some surveys weight groups of relatively similar activities. For example, the Harvard Alumni Questionnaire assigns 5.0 kilocalories per minute to a group of activities deemed to be of low cardiovascular intensity (e.g. gardening, bowling, etc.), 7.5 kilocalories per minute to moderate intensity activities (e.g. dancing) and 10 kilocalories per minute for high-intensity activities (e.g. running) (5).

Regardless of the method of intensity-weighting used, several assumptions are made by the researcher when incorporating intensity into the analysis process: Lists of MET values for most activities are available and provide the basis for calculations in physical activity questionnaires. When obtaining a MET or kcal value from a list, it is assumed to be representative of the manner in which the activity was performed by the individual. Since skill level varies for sporting activities and a wide range of paces may be selected for activities like cycling, walking, jogging, there may be considerable variation in the actual energy expenditure across subjects. Weighting physical activities by intensity also assumes that body-

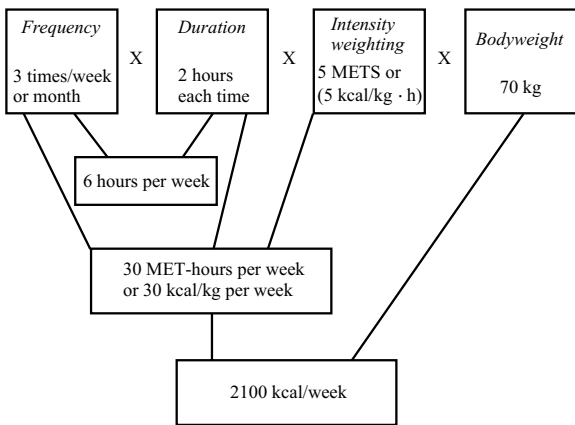


Figure 5.3 Steps in the computation of the summary estimates for the physical activity questionnaire

weight is proportional to resting metabolic rate and that the relative increase in metabolic cost of a specific activity above resting is constant from person to person regardless of bodyweight.

Because of these assumptions made with physical activity questionnaires, estimates of physical activity obtained from them give a relatively limited assessment of absolute energy expenditure. However, since physical activity represents the most variable component of total energy expenditure, they are valuable in relative terms and can be used to rank individuals or groups of subjects within a population from the least to the most active. This relative distribution of individuals based on their reported levels of physical activity can then be examined according to its relationship to physiological parameters and disease outcomes.

THE APPLICATION OF PHYSICAL ACTIVITY ASSESSMENT: POPULATION AND OUTCOME CONSIDERATIONS

Considering the wide variety of approaches for assessing physical activity, the researcher is frequently left in a quandary when designing a specific study. Since physical activity can be defined in several ways, no single standard exists with which to measure physical activity. Time considerations often require the researcher to choose a survey that is a brief but efficient measure of the most common physical activities of a population. Given these imitations, characteristics of the population being studied and the outcome of interest emerge as important factors in the choice of a physical activity assessment tool.

If the objective of the research is to evaluate the relationship between exposure to physical inactivity or activity and a particular disease outcome, it is important that the assessment tool: (1) accurately represents physical activity of the study population and (2) focuses on the component of energy expenditure that encompasses the greatest proportion of total energy expenditure. For these reasons, it is important to consider the culture, gender, and age ranges of the population. In industrialized, developed countries, recent surveys have focused on leisure activity because of the general decline in physical activity in most occupations. The focus on leisure-time physical activity in these countries differentiates active from

inactive people more effectively than would an occupational physical activity questionnaire. However, occupational activity probably remains of greater importance in developing countries where much of the population have physically demanding occupations. Therefore, some questionnaires have included both leisure-time and occupational physical activity assessment.

Physical activity patterns have traditionally differed between men and women. Perhaps due to the historic tendency to conduct epidemiological research on men rather than women, physical activity questionnaires have been more orientated around the types of leisure-time and occupational activities typically performed by men. Women tend to engage in less intense activity and in child care and household activities, all of which are difficult to assess. The use of commonly used questionnaires in women may be less sensitive to differences in activity levels within populations of women. If this occurs, true relationships between physical activity and disease could be obscured. Work is currently being done to more accurately assess physical activity in women.

Since different dimensions of physical activity, such as frequency, duration, intensity, and type, could conceivably have different influences on risk factors for disease and disease outcomes, the choice of a physical activity assessment tool may be determined in part by the disease endpoint being studied. While the majority of health benefits seem to be linked principally to the total amount of activity performed, physical activity assessment could focus on other dimensions, including aerobic intensity, resistance to the muscular system, and weight-bearing, any of which could affect specific diseases or health outcomes.

Whether aerobic intensity can influence risk for disease outcomes independent of energy expenditure is controversial and difficult to determine in population-based studies because subjects who participate in vigorous activities tend to expend more energy in general. Stronger relationships between physical activity and diseases or risk factors for disease have often been observed when physical activity is weighted by intensity. While this could be due to a true relationship between intensity of activity and prevention of disease, it may also be because higher intensity activities are easier to recall and may be more reliably measured

(43). While some studies have shown favorable relationships between more vigorous activity and blood lipids, cardiovascular disease, and mortality (7, 37, 60), others have found that obesity, cardiovascular disease, Type 2 diabetes, and lipid abnormalities may be affected by even low-intensity exercise and thus seem to be largely determined by total energy expenditure (61–63). In other words, these outcomes may be more related to the total time spent doing activities than the intensity of participation in specific activities.

Type 2 Diabetes Mellitus

The evaluation of the relationship between physical activity and Type 2 diabetes risk is complicated by the fact that Type 2 diabetes is a multifaceted disease with a variety of risk factors and disease endpoints, including obesity, insulin resistance and sensitivity, insulin production, glucose intolerance, diabetes incidence, and glycemic control. Evidence exists from experimental, intervention, and/or population-based studies that physical activity may have beneficial effects in most of these steps. (64–69, 52, 63, 70–72). Based upon the findings of many studies, physical activity is most likely to influence glucose tolerance under conditions where insulin resistance is the major cause of the abnormal glucose tolerance (66, 65, 73, 67–69, 74).

Several experimental studies have attempted to determine what characteristics of physical activity are most responsible for positive effects on insulin sensitivity. Some have suggested that physical activity may act through a cumulative effect of frequent exercise (64, 68, 75). This contention is based on the observation that a single exercise episode results in a temporary lowering of blood glucose and an enhancement of insulin sensitivity shortly after the exercise bout. If true, the frequency with which exercise is performed may be important. Research by Holloszy et al. (74) suggests that higher intensity physical activity is more likely to bring about the desired metabolic changes than are lower intensity activities. In contrast, other experimental work by Braun et al. (76) found equivalent effects of lower and higher intensity exercise on insulin sensitivity in females with NIDDM when the exercise was matched for total energy expenditure.

National physical activity recommendations and summary statements suggest that the majority of overall health benefits from physical activity are gained by performing moderate intensity activities. Whether or not this holds for Type 2 diabetes specifically is currently not known. However, in examining some of the prospective data, the largest and most consistent difference in risk of Type 2 diabetes occurs between those individuals who report no activity and those who report some activity. For example, when examining the association between frequency of reported vigorous activity per week in both nurses and physicians, most of the difference in incidence of Type 2 diabetes occurred between those who reported less than once per week of activity compared with those who were active a minimum of once per week (63, 70). In contrast, the protective effect of vigorous physical activity was found to be greater than that of moderate activity in male alumni of the University of Pennsylvania (72), although this may be due to the fact that the recall of higher intensity activities is more reliable (42).

Epidemiologic studies suggest that individuals who are obese and historically sedentary are at the highest risk for Type 2 diabetes and are thus the best targets for physical activity interventions. Since intense exercise is not likely to be feasible or popular in these individuals, interventions will probably be more successful if they focus on lower intensity activities. Unfortunately, lower intensity physical activities are the most difficult to measure. Fortunately, the assessment of physical activity has made considerable progress in the last half century, enhancing the understanding of the relationship between exposure to different levels of physical activity and risk for a wide range of diseases. Because of the contribution of physical activity assessment tools, physical activity is now regarded as one of the fundamental behaviors necessary for a healthy lifestyle. It is likely that any improvement in the accuracy of these tools will only enhance the ability to observe true relationships between physical activity, health, and disease, serving as an incentive and challenge for future researchers.

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Part II



Caucasian Populations

Ascertainment, Prevalence, Incidence and Temporal Trends

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INTRODUCTION

Prevalence and incidence are fundamental concepts in epidemiology. In the study of the epidemiology of diabetes it is usually incidence which features more prominently in the discussion of Type 1 diabetes and prevalence in that for Type 2 diabetes.

It is not difficult to see why this difference has arisen. The onset of Type 1 diabetes is frequently dramatic. It was once believed that these dramatic events signalled the start of the disease process. Now we know differently—that a prodromal period of variable duration is present in many, if not all, cases. For Type 2 diabetes, on the other hand, onset is usually insidious—the disease may remain undetected for a considerable time. The concept of incidence is less satisfactory than for Type 1 diabetes and the frequency with which new cases are diagnosed or discovered is taken to be a more relevant measure of Type 2 diabetes occurrence.

Both the frequency of diagnosis of new cases and prevalence are important items of information about the public health burden of Type 2 diabetes. The first is an indication of the requirement to investigate, diagnose and begin the process of education and behavioural change. The second is an indication of the extent to which health services and society as a whole are required to support individuals with the disease and is an indication of the likely future burden of diabetes complications.

ASCERTAINMENT

The ascertainment of people with Type 2 diabetes (or, more correctly, those with the Type 2 diabetes

process or processes going on) provides the epidemiologist with more areas of difficulty than the ascertainment of Type 1 diabetes. There are a number of interrelated reasons for this. None are insuperable but the means to overcome them are not always available. They are:

- As mentioned above, the fact that the clinical manifestation of Type 2 diabetes is much less dramatic than that of Type 1 diabetes. There must be many people who live and die without it being recognized that they have Type 2 diabetes.
- The identification of people with Type 1 diabetes is greatly facilitated by the fact that they are virtually all treated with insulin. Restriction of the ascertainment to those who were diagnosed at a young age and who have been treated with insulin virtually from the start of their disease effectively means that no other form of diabetes will be identified. The vast majority of those who are receiving oral hypoglycaemic medication have Type 2 diabetes. However, this statement is becoming less valid as other individuals (e.g. those designated as being in the IGT category) are being treated with these drugs. A substantial number of those with Type 2 diabetes will not be identified by the drugs they are prescribed nor by the equipment with which they are supplied. These are the 'diet only' individuals, many of whom do not monitor themselves by means of blood or urine glucose testing. Unfortunately for the epidemiologist therapeutic practices differ in different populations so it is not just a simple matter of multiplying the number of oral hypoglycaemic-treated cases by

a constant to yield the total number of those with Type 2 diabetes.

- The identification of undiagnosed Type 2 diabetes is frequently by means of the oral glucose tolerance test (OGTT). The repeatability of the OGTT, even over short time-spans, is not impressive.
- Partly because of the above, population-based registers for Type 2 diabetes are much less extensively developed than those for Type 1 diabetes.
- Recovery from Type 2 diabetes, though uncommon, is possible (with extensive weight loss, for example) and so cases once identified do not always remain as cases for the remainder of their lives.

The 'capture-recapture' method for estimating the size of populations was developed in zoology, ecology and other subject areas as a means of

estimating the size of free-living populations when it was not possible to identify all individuals within those populations. Its extension to epidemiology has been strongly advocated (1) and it has been used in a number of topic areas, for example the prevalence of mental illness among the homeless (2). It has also been used for estimating the number of publications not identified in systematic reviews of the literature (3). In the last mentioned study, the alternative name of COMMA (comparison of multiple methods of ascertainment) has been advocated. The term 'capture-recapture' is not ideal in the context of epidemiology since no-one is being captured or recaptured in the sense with which these terms were used in ecology or zoology.

COMMA has not been used in the field of Type 2 diabetes epidemiology to anything like the extent of its use in Type 1 diabetes (see elsewhere in this volume) although the advantages of doing so have

Table 6.1 Methods of case ascertainment and their advantages and disadvantages in relation to Type 2 diabetes

Method of ascertainment	Advantages	Disadvantages
(A) Population-based survey (including biochemical testing)	1. Ascertainment of previously undiagnosed cases 2. Diagnostic criteria can be standardized 3. Accurate determination of denominator possible	1. Usually costly 2. Usually a 'one-off'—not a method for continuous monitoring
(B) Population-based survey (excluding biochemical testing)	1. Continuous monitoring of prevalence possible 2. Determination of denominator possible 3. Usually less costly than (A)	1. Ascertainment of previously undiagnosed not possible 2. Standardization of diagnostic criteria usually not possible (e.g. with self-report of diabetes)
(C) Population-based register	1. Continuous monitoring possible 2. Standardization of diagnostic criteria possible	1. Initial stages can be costly
(D) Hospital records	1. Data are usually already being collected for other purposes	1. Some individuals will never be identified 2. Standardization of diagnostic criteria possible but rarely accomplished in practice 3. Not usually possible to identify population denominator
(E) Primary care records	1. Data may be being collected for other purposes 2. Determination of denominator may be possible 3. Most people with diabetes will contact primary care	1. Standardization of diagnostic criteria possible but rarely accomplished in practice
(F) Patients' organization(s)	1. Database will exist for other purposes 2. Members are usually enthusiastic to participate	1. Coverage variable 2. Membership is likely to be biased by age, severity, socio-economic group
(G) Media advertisements	1. Can be a successful way to create interest	1. Response unpredictable 2. Response likely to be biased

been pointed out (4). This is unfortunate since, as has been pointed out by Hook and Regall (5), this method should not be viewed as merely a desirable addition to a study attempting complete ascertainment. It should be an integral part of such studies since it is rarely possible to ascertain 100% of known cases and it behoves all researchers to estimate the number of cases they might have missed. Even though COMMA estimates are vulnerable to bias as a result of association between the individual methods of ascertainment (analogous to less than perfect population mixture between the capture and subsequent recapture in ecological studies), techniques exist for the estimation of these associations (6). When the methods of ascertainment are positively associated (as will frequently be the case in epidemiological studies), the estimated figure for the total population will be an underestimate. At the interface between epidemiology and public health policy we are familiar with working with estimates of disease occurrence that are likely to be underestimates. Provided we are aware of this then techniques such as COMMA, to provide 'ascertainment corrected prevalence rates' (4), are of considerable use. Table 6.1 lists a number of methods of case ascertainment and their advantages and disadvantages in relation to Type 2 diabetes.

PREVALENCE

Kenny, Aubert and Geiss (7) have summarized the current situation with regard to the prevalence of Type 2 diabetes in the United States. They draw attention to the fact that prevalence estimates have increased steadily over the last 40 years. They estimate the current, overall prevalence of diabetes (Type 1 diabetes and Type 2 diabetes) to be 3.1% (in 1993). This represents around 7.8 million people. Over all ages, both sexes and all ethnic groups they report that around 90% of this 3.1% have Type 2 diabetes.

Their Figure 4.7 contrasts prevalence estimates for non-Hispanic whites, non-Hispanic blacks, Mexican Americans and Puerto Rican and Cuban Americans. Unfortunately, this figure and their Table 4.3 which gives the data on which Figure 4.7 is based, is somewhat difficult to interpret in terms of the time periods stated (1976–80 and 1982–84) and the shading in Figure 4.7 of the separate parts

of the bars which represent diagnosed and undiagnosed diabetes and IGT. However, their overall message is clear—that, for each of these three categories, white US citizens have the lowest prevalence of all the groups identified.

In Europe, two of the most recent population surveys in the summary by Pozza et al. (8) are those of Tuomilhto et al. (9) (Finland) and Forrest et al. (10) (United Kingdom). The former found prevalences of between 23% and 32% in people aged 65–84. This survey was based on the modified OGTT and, therefore, detected those with undiagnosed as well as diagnosed diabetes. The proportion of undiagnosed cases was different in the sample from eastern Finland (56%) from that found in western Finland (72%). Forrest et al. (10) used a similar methodology but studied people over the age of 40. Their estimate for the total prevalence of diagnosed and undiagnosed diabetes in this age group was 4.6% of whom 56% were previously undiagnosed. These and other studies quoted by Pozza et al. and by other reviewers suggest that the proportion of previously undiagnosed cases detected in epidemiological studies of Caucasian populations in Europe ranges from just under 50% to around 75%.

INCIDENCE

As suggested at the beginning of this chapter, incidence is not a particularly useful concept in Type 2 diabetes. The time at which the disease process commenced is unknown for most, perhaps all, cases of this disease. The incidence at which new cases are diagnosed is a more valid concept and this has been explored in a number of studies, though very many fewer than have studied prevalence.

In the United States the incidence with which new cases are identified has been studied both in cohort studies such as the Framingham study (11) and in successive cross-sectional studies such as the National Health Interview Survey (12). The latter, it has been noted (7), estimates that around a further 625 000 people with diabetes (both Type 1 diabetes and Type 2 diabetes) are diagnosed each year in the United States. Rates of diagnosis rise with age and, for the United States between 1990 and 1992, are higher in women (2.84 per 1000 population per year) than in men (1.97 per 1000 population per year) (7).

One of the most useful advances in diabetes epidemiology over the last 30 years has been the standardization of biochemical criteria for the diagnosis of diabetes. West, e.g. (13), first raised the issue of differences in the criteria that health professionals used to diagnosed diabetes. Since then, population-based surveys, if they use these standardized criteria, are comparable, provided the conditions for testing and presentation of data are similar. However, studies which are based on self-reported illness are still liable to temporal and cultural differences in the extent to which these are used in clinical practice and the stringency with which individuals are investigated before the disease label is applied. Cross-cultural studies of the use of these criteria by the health professions are required before valid comparisons can be made of self-reported newly diagnosed Type 2 diabetes.

TEMPORAL TRENDS

No Caucasian populations have been described in which rates of diagnosis of diabetes or Type 2 diabetes have fallen over time. Past trends are of some interest, however, it is in the prediction of future trends where descriptive epidemiology makes its most important contribution to health care policy —from the level of the individual practice to the national scale.

Ruwaard (14) has provided detailed descriptions of the calculations required to predict the number of people likely to have diabetes in the population of the Netherlands in the year 2005. For any country, it is a simple matter to take existing estimates of incidence or prevalence and to multiply them by population numbers derived from census projections and thus to predict the numbers of new cases, or the number of people likely to be affected by the disease in future if the risk of acquiring the disease does not change.

Thus, for the United Kingdom, taking prevalence estimates, for people aged 50 and over, from Neil et al. (15), population data for 1991 from the national census and official population projections for 2001 and 2021, estimates of the number of people in this age group likely to have diabetes can easily be made (see Table 6.2). Working on the assumption that there are approximately as many people with undiagnosed diabetes as with diagnosed diabetes, the projections can be enlarged to

Table 6.2 Estimates and projection of the number of adults, aged 50 and over and living in the United Kingdom, who are likely to have diabetes, diagnosed and undiagnosed in the years 1991, 2001 and 2021

	1991	2001	2021
Population	17 972 000	19 442 000	23 380 000
Number (diagnosed diabetes)	501 000	553,000	640,000
Number undiagnosed diabetes)	501 000	553 000	640 000

* Using a prevalence figure of 2.8% for each (see text).

include totals for those likely to have undiagnosed diabetes.

This simple method of forecasting (Ruwaard terms it the ‘static’ model) is limited to the influence that demographic changes will have on prevalence. Any consideration of its implications has to be prefaced by the statement that it assumes no change in the genetic or environmental influences on diabetes prevalence and no change in life expectancy. Also, of course, its predictions are for all diabetes and not Type 2 diabetes.

One of the only things of which we can be fairly confident is that there will be change in the individual risk of acquiring Type 2 diabetes over the next few decades. Population data on obesity, for example, gathered from industrial countries over the last three decades, frequently show an increase in the proportion of those considered obese. One example of this is the situation in the adult population of England. England’s health strategy document—*The Health of the Nation* (16)—included, among its 28 health targets, a reduction, by the year 2005, of the proportion of the adult population regarded as obese by at least 25% for men and at least 33% for women. The first follow up report (17) showed that the proportion of those considered obese (BMI over 30 for both sexes—the same definition as that used in setting the targets) was increasing, from 7 to 13% in men, and from 12 to 15% in women, between 1986/87 and 1991.

Ruwaard’s ‘dynamic’ model (14) uses the ‘prevalence pool’ concept to illustrate the factors influencing the Type 2 diabetes prevalence. Entry into the pool is by incidence (or, more strictly, diagnosis in the case of Type 2 diabetes). Exit is by death or might be by remission (for a few). The latter is considered so small that it is felt it can be

neglected. For the former, future predictions of the influence of diabetes on life expectancy are required.

In the Dutch population the life expectancy of people with Type 2 diabetes, based on past experience, is thought not likely to change a great deal over the time-scale considered. The likelihood of an improved life expectancy for Type 1 diabetes patients will have a limited impact on future predictions of total diabetes since Type 1 diabetes, as in most other Caucasian populations, constitutes at most 20% of the population. Despite this, and because of the ageing of the population over the time period considered (up to the year 2005), the proportion of Type 2 diabetes patients in the population is likely to increase.

The variables which need to be considered in the dynamic model of diabetes prediction (see Table 6.3) may be divided into those which are disadvantageous for the individual and the population, those which are neutral, and those which are advantageous. The first category contains any influence which leads to an increase in the prevalence of risk markers. The rising prevalence of obesity and decrease in physical activity can be included in this category. In the neutral category are the rise in the proportion of the elderly in the population (already included in the static model) and any change in ethnic mix. The advantageous category includes any improved health outcome leading to greater life expectancy and, as variables of unknown but possible influence, improved

Table 6.3 Variables to consider in the 'dynamic' model for predicting future prevalence of Type 2 diabetes*

Category	Variable
<i>'Disadvantageous'</i>	
Increase in prevalence of risk markers	Rising prevalence of obesity Decrease in physical activity
<i>'Neutral'</i>	
Demographic changes	Increasing proportion of elderly** Change in ethnic mix
<i>'Advantageous'</i>	
Improved health outcome	Increased life expectancy
Reduction in prevalence of risk markers	Improvement in conditions of early growth and development
Remission to normal glucose tolerance	Net loss in number of diseased individuals

* Modified from Ruwaard (14), by permission.

** Also taken into account by 'static' model.

Table 6.4 Estimates of the number of people with diagnosed diabetes in the Netherlands in 2005 according to 'static' and 'dynamic' models

Model	1980 (observed)	2005 (predicted)	Increase** (%)
Static**	191 000 (1.35%)	268 000 (1.65% of popn.)	41
Dynamic 1†	191,000	339 000 (2.1% of popn.)	78
Dynamic 2†	191 000	355 000 (2.2% of popn.)	86

* Adapted from Ruwaard (14), by permission.

** Prevalence in 2005 compared with that in 1980.

† For explanation see text.

conditions of early growth and development and any remission from Type 2 diabetes to normal glucose tolerance.

A comparison of the results of Ruwaard's static and dynamic models is given in Table 6.4. Two variants of the dynamic model are used. Version 1 uses a constant incidence over time (i.e. does not assume any change in risk markers and no remission) and takes into account only population changes and changes in life expectancy. The second makes the assumption that incidence rates will rise with time. Further details of the model and these assumptions are given in Hoogenveen et al. (19) and in an appendix to Chapter 5 of Ruwaard (14).

Validation of such models is possible by historic validation (the prediction of past prevalence, using data from the more distant past and their comparison with directly observed data) and sensitivity analyses (the exploration of the effects of varying one or more parameters in the model). The dynamic model is more sensitive to variations in incidence predictions than it is to changes in prevalence estimates of equal magnitude.

CONCLUSION

Although Type 2 diabetes is less common in Caucasian populations than in many others and although, in global terms, the burden of Type 2 diabetes in Caucasian populations makes a modest contribution to the global impact of the disease, the predicted rise in prevalence of Type 2 diabetes in Caucasians makes it an important future public health problem. Despite longstanding knowledge of many of the risk markers for Type 2 diabetes,

population measures for the reduction of the prevalence of these markers and thus the prevalence of Type 2 diabetes have yet to make any substantial impact.

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Type 1 Diabetes: Global Epidemiology

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Type 1 diabetes mellitus is one of the major non-communicable diseases in children aged 14 years or under (1). Although the etiology of Type 1 diabetes is still unknown, it is currently assumed that both genetic (2–5) and environmental factors (6–17) operate together in a process in the pancreatic beta-cells, leading to the onset of diabetes. The role of HLA genetics in the etiology of Type 1 diabetes is well understood, but neither the mode of inheritance nor how environmental factors may initiate/trigger the process which leads to the destruction of the beta-cells and to the onset of diabetes are clear. Recent advances in research into the etiology and natural history of Type 1 diabetes have increased knowledge about different types of diabetes to such an extent that the primary prevention of Type 1 diabetes is becoming a reality. The increasing incidence of Type 1 diabetes, the severity of its complications and the increasing socio-economic costs favor immediate preventive action. Unfortunately, the means for the primary prevention are not yet available.

REGISTRATION OF TYPE 1 DIABETES WORLDWIDE

During the 1970s published reports suggested wide geographical differences in incidence of Type 1 diabetes (18–24), but the lack of standardized data made it difficult to determine the true magnitude of the worldwide variation in Type 1 diabetes morbidity. Standardized collection and analysis of epidemiological data of Type 1 diabetes started in the 1980s and since the mid-1980s Type 1 diabetes registries have been established in many parts of the world. The Diabetes Epidemiology Research

International Group (DERI) (25) played the key role in collecting standardized Type 1 diabetes incidence data between the late 1970s and the mid-1980s, rendering possible the direct comparison of data between countries. The DERI group reported the incidence from 15 countries between 1978 and 1989 (25, 26). The findings indicated a large global variation with the difference between the highest and lowest rates being about 60-fold. The highest incidence rate was found in Finland, followed by the other Nordic countries Sweden and Norway, and the lowest rate was seen in Japan and in Mexico. The authors proposed a strong correlation between the age-adjusted incidence rates and the average yearly temperature and also the existing north–south gradient of incidence rates; possibly indicating the potential of environmental factors in the etiology of disease.

By the end of the 1980s a considerable number of Type 1 diabetes registries had published incidence data worldwide. Most of the information on Type 1 diabetes incidence comes from the geographical regions with a high or intermediate level of incidence, e.g. Europe and North America, where a large number of Type 1 diabetes registries have been established since the mid-1980s. Although several standardized registries have recently been established, data on Type 1 diabetes incidence from Asia and Africa are still sparse. The published data facilitate the descriptive comparison of Type 1 diabetes incidence and the variation of the occurrence of disease roughly throughout most of the northern hemisphere.

The collaborative research project EURODIAB was also established in the late 1980s (27) to gather information about Type 1 diabetes in Europe. The World Health Organization Project, the Multi-

Table 7A.1 WHO DIAMOND centers by continents

Africa 8 centers: Algeria (Oran) Mauritius Nigeria (Lagos) Sudan (Gezira province) Tunisia (Beja, Gafsa, Kairouan, Monastir)	Europe 42 centers: Austria Belgium (Antwerpen region) Bulgaria (East-Bulgaria, West-Bulgaria) Croatia Denmark (3 counties) Estonia Finland France (4 regions) Greece (Attica Region) Hungary (18 counties) Italy (Catania province, Chieti and Pescara, Lazio region, Lombardia region, Pavia province, Region Marche, Sardinia, Torino, Turin province) Latvia Lithuania Luxembourg Netherlands (5 regions) Norway (8 counties) Poland (Cracow, Wielkopolska region) Portugal (Algarve region, Coimbra, Portalegre) Romania (Bucharest region) Slovakia Slovenia Spain (Barcelona, Madrid) Sweden UK (Aberdeen, Leicestershire, Northern Ireland, Oxford region)	North America 9 centers: Canada (Alberta, Prince Edward Island) USA (Allegheny county, Chicago, Colorado, Jefferson county, Memphis, Philadelphia, Washington)
Asia 30 centers: China (Beijing, ChangChun, Dalian, Harbin, Heilongjiang province, Henan province, Huhuhot, Jiangxi province, Jilin province, Oiaokou District, Shanghai, Shenyang, Tie Ling, Urumgi, Zi Gong, Zunyi City) Hong Kong India (New Delhi, New Delhi 2) Israel Japan (Chiba, Hokkaido, Okinawa) Korea (Seoul) Kuwait (Safat) Pakistan (Karachi) Philippines (Quezon City) Russia (Novosibirsk) Taiwan (Taipei)		Central America and West Indies 9 centers: Barbados Dominican Republic Cuba Mexico (Veracruz) British Virgin Islands UK Virgin Islands USA
Oceania 3 centers: Australia (New South Wales) New Zealand (Auckland, Canterbury)		South America 14 centers: Argentina (Avellaneda, Berazatequi, Cordoba, Corrientes, Rosario, Salta) Brazil (Sao Paulo state) Chile (Santiago) Colombia (Barranquilla, Santafe de Bogota DC) Paraguay Peru (Lima) Uruguay (Montevideo) Venezuela (Caracas 2)

Adapted from (28) by permission.

national Project for Childhood Diabetes (DIAMOND) was started in 1990 (28) (Table 7A.1 and Figure 7A.1). Other collaborative groups were also formed, such as the DIABALT group in the Baltic Sea region (29), the Iberian Heritage groups to study the epidemiology of Type 1 diabetes in the Iberian peninsula and in the Americas (30), the Italian Heritage group (31) and the Arab Heritage group (32). All of these have employed standardized protocols so that the incidence data around the world can now be compared.

ASCERTAINMENT OF TYPE 1 DIABETES CASES

The ascertainment of Type 1 diabetes cases has not always been complete in many epidemiological

studies for several reasons. Type 1 diabetes represents only 4–6% of all cases of diabetes and thus we are dealing with small numbers of affected subjects. Type 1 diabetes may have been misdiagnosed or misclassified in some circumstances. Health policy and the lack of regional or national registries has been a serious disadvantage for accurate case ascertainment.

Until the beginning of the 1980s different methods were applied to Type 1 diabetes ascertainment. Classical Type 1 diabetes rarely poses a diagnostic problem. However, most studies of the incidence and prevalence of diabetes in young people have not clearly discriminated between Type 1 diabetes and Type 2 diabetes cases. Almost all studies of Type 1 diabetes limit themselves to cases diagnosed before 30 years of age, although Type 1 diabetes can also occur after the age of 30

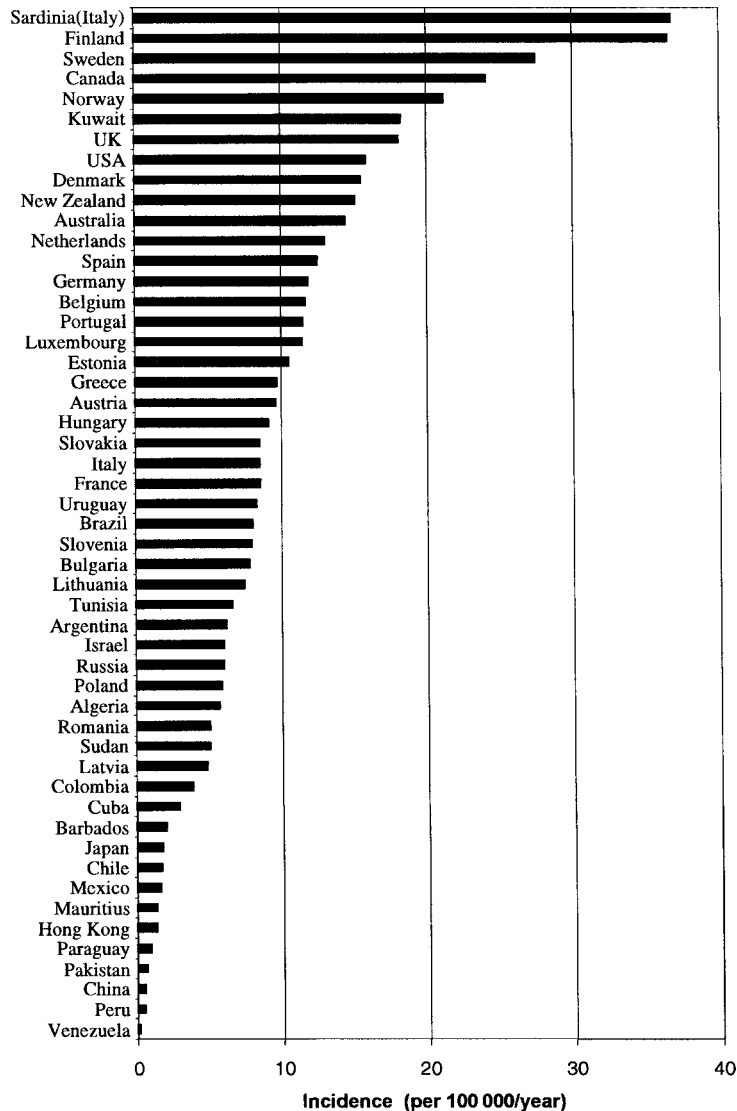


Figure 7A.1 Age-specific incidence (per 100 000 population) of Type 1 diabetes in children aged 14 years or under. Data for boys and girls have been pooled. The populations are arranged in ascending order according to the incidence. Data from Diamond Centers 1990–1994. Adapted from (28) by permission.

years. In ideal circumstances, the necessary conditions for epidemiological studies and a high level of case ascertainment are uniformity of population, lack of migration and an established high rate of cooperation of health care personnel. Effective public health care systems, the existence of computer systems for recording diagnoses, national registries, the involvement of a central person registry or any other means of tracing

individuals throughout the country are remarkable tools that will help the epidemiologist perform a good prevalence or incidence study. Type 1 diabetes is a relatively infrequent disorder that needs a large population sample for its study to avoid under- or overestimation of incidence or prevalence, consequently the true incidence or prevalence rates cannot be established by population-based studies. Different methods were applied

to Type 1 diabetes ascertainment until the beginning of the 1980s. Traditional methods for monitoring Type 1 diabetes have been too expensive or too inaccurate for broad accurate national programs. It has been therefore rather difficult to compare results from different surveys carried out before the early 1980s.

Capture-Recapture Method

The methodological improvement to counting Type 1 diabetes is the capture-recapture approach published by LaPorte and coworkers (33) at the beginning of the 1990s. Although the capture-recapture method does not give an estimate of incidence and prevalence where the point estimate is the absolute truth, it comes closer to the truth than the fairly inadequate systems used earlier. When an attempt is made to identify new cases of Type 1 diabetes multiple sources are used. People with diabetes are identified from hospitals, pediatricians, schools, chemists and so on. To determine the numerator (e.g. the number of new cases), the researchers typically aggregate the sources, sorting out duplicates. That total is used for determining the incidence rates (34–38). This incidence rate should be considered as a crude rate, because it assumes that the aggregate of the lists represents all of the cases in the population. It assumes that the number of missing cases is zero and undercounting is ignored. In the capture-recapture method attention is paid to the duplicates, because they provide important information about the degree to which cases may have been missed. These cases represent recaptured people who have diabetes and the degree of undercounting is estimated and the rates of Type 1 diabetes are corrected accordingly, thus yielding a corrected ascertainment rate.

TYPE 1 DIABETES INCIDENCE WORLDWIDE

Incidence rates reported over a period of 20 years, from the late 1970s to the early 1990s (Table 7A.2) (17,25,27,39–84) show the vast geographical variation in Type 1 diabetes incidence. This large variation worldwide was also seen in small 'pockets' of countries, e.g. around the Baltic Sea.

Between continents the variation in incidence showed that the lowest incidences were found in Asia, followed by Oceania (Australia and New Zealand), South and North America, and the highest rates were found in Europe. The greatest within-continent variation in incidence appeared in Europe, varying from the highest (36 per 100 000) in Finland (43) to the lowest (3 per 100 000) in Macedonia (45). Incidence in Northern Europe was in general higher than the rates observed elsewhere in Europe, excluding Sardinia where the incidence 34 per 100 000 was the second highest in the world after Finland (74). Between 1970 and 1976 the incidence in Denmark was about one-half of that in Sweden, but by the end of the 1980s Denmark (22/100 000) had reached the incidence rates of Sweden (24/100 000) and Norway (21/100 000) and had joined the high-risk Nordic countries (17,27,71). The lowest rate among the Nordic countries was in Iceland (9/100 000) (70), the northern-most country in Europe.

In North America the range of the intracontinental variation in Type 1 diabetes incidence was also large ranging from <1 per 100 000 in Mexico to 24 per 100 000 on Prince Edward Island and incidence overall seemed to be higher in the northern than the southern part of the continent (25). The incidence data from South America (57–59) and Oceania (25, 64, 65) were sparse and sporadic. According to the available data, Type 1 diabetes incidence in the southern hemisphere, in Oceania and South America, seemed to be low and there was no noticeable variation in incidence. Also in Asia the within-continent variation was smaller than in Europe and North America and the incidence did not correlate to the latitude (25, 65). Very few data were available for Africa. Although the data from low-incidence countries are sparse and interpretations of numbers should be made with caution, it appears that neither the global nor the regional pattern of Type 1 diabetes in the 1980s fully supported the earlier proposed correlation between incidence and latitude or the correlation to the average yearly temperature (26).

It seems that there are other environmental differences and particularly genetic differences which seem to play a major role in the pathogenesis of Type 1 diabetes, contributing to the differences in incidence.

Table 7A.2 Age-specific incidence of Type 1 diabetes in children aged 14 years or under (per 100 000 population)

Region	Study period	Estimate of ascertainment	Incidence			M/F Ratio	M/F Excess ***	Number of cases
Country and area		(%)	M	F	T			
Africa								
Algeria								
Oran [46]	1980–1989	?			8.1			505
Libya								
Benghazi [47]	1981–1990	100	6.3	7.8	7.0	0.81	−0.24	165
Mauritius [48]	1986–1990	>95	1.8	2.4	2.1	0.75	−0.39	32
Sudan								
Khartoum [49]	1987–1990	95			10.1			
Tanzania								
Dar es Salaam [42]	1982–1991	?	0.8	0.9	0.8	0.89	−0.13	86
North America								
Canada [25]								
Prince Edward Isl.	1975–1986	99	27.0	20.8	23.9	1.30	0.30	92
Montreal	1971–1985	94	9.6	10.0	9.8	0.96	−0.04	919
United States								
North Dakota [25]	1980–1986	?	21.6	16.2	18.9	1.33	0.33	204
Wisconsin (part) [25]*	1970–1979	>90	20.2	16.2	18.2	1.25	0.25	166
Allegheny County [50]	1965–1989	>90						
White			15.1	13.2	14.2	1.14	0.14	1414
Non-White			8.5	12.1	10.3	0.70	−0.42	146
Rochester [25]	1965–1979	100	15.8	18.4	17.1	0.86	−0.17	38
Colorado [51]*	1978–1988	93						
Non–Hispanics			16.4	14.5	15.5	1.13	0.13	1048
Hispanics			7.1	10.5	8.7	0.68	−0.48	117
Jefferson County [52]	1979–1985	96	9.9	14.9	12.4	0.66	−0.51	128
White			15.1	16.2	15.6	0.93	−0.07	134
Black			3.4	10.6	7.0	0.32	−2.12	41
Philadelphia [53]	1985–1989	93	11.3	14.8	13.4	0.76	−0.31	215
White			12.7	13.6	13.3	0.93	−0.07	109
Black			9.1	13.3	11.0	0.68	−0.46	86
Hispanic			10.6	19.5	15.2	0.54	−0.84	17
San Diego [25]	1978–1981	?	9.6	9.1	9.4	1.05	0.06	48
Central America and the West Indies								
Barbados [54]	1982–1991	94			5.0			37
Cuba [25]	1978–1980	?	2.5	2.8	2.7	0.89	−0.12	267
Mexico								
Mexico City [25]	1984–1986	?	0.4	0.7	0.6	0.57	−0.75	100
Puerto Rico (USA) [55]	1985–1989	?			10.0			
Virgin Islands (GB)[56]	1979–1988	92						27
Black			6.9	4.8	5.9	1.44	0.44	17
South America								
Argentina								
Avellaneda [57]	1985–1990				6.7			30
Brazil								
State of São Paulo [58]	1987–1991	>90	5.8	9.5	7.6	0.61	−0.64	52
Chile [59]	1990–1991	100	2.2	2.8	2.5	0.79	−0.27	78
Peru								
Lima [41]	1985–1991	85			0.4			
Asia								
China								
Shanghai [40]	1980–1991		0.6	0.7	0.6	0.82	−0.22	75
Hongkong [60]	1986–1990	94	1.5	2.4	2.0	0.63	−0.60	22
Israel [27]	1975–1980	100	4.4	6.7	5.5	0.66	−0.52	296
Japan								
Hokkaido [25]	1974–1986	100	1.3	2.1	1.7	0.62	−0.62	283
Kagoshima [61]	1980–1989	100			1.8			
Tokyo [61]	1980–1989	100			1.7			
Kuwait [62]	1992–1993	92	16.6	14.1	15.4	1.18	0.18	86
Republic of Korea								
Seoul [39]	1985–1988	?	0.6	0.8	0.7	0.74	−0.35	71
Russia								
Novosibirsk [63]	1983–1989	96	4.6	4.9	4.7	0.94	−0.07	205

(continued)

Table 7A.2 (continued)

Region	Study period	Estimate of ascertainment	Incidence			M/F Ratio	M/F Excess***	Number of cases
Country and area		(%)	M	F	T			
Oceania								
Australia								
New South Wales [64]	1991	99	14.1	16.1	15.0	0.88	-0.14	188
Western part [65]	1985-1992	100	19.0	25.6	22.2	0.74	-0.35	84
New Zealand [25]								
Auckland	1978-1985	?	9.0	10.5	9.8	0.86	-0.17	233
Canterbury	1981-1986	100	10.2	12.9	11.6	0.79	-0.27	39
Europe								
Austria [27]	1989-1990	94	7.9	7.5	7.7	1.05	0.05	205
Belgium								
Antwerpen [27]	1989-1990	100	9.2	10.4	9.8	0.88	-0.13	31
Bulgaria								
Sofia [66]	1987-1991	?			6.7			
Croatia								
Zagreb [67]	1988-1992	>90	7.7	6.7	7.2	1.15	0.15	72
Denmark								
3 counties [27]	1989-1990	99	21.5	21.4	21.5	1.00	0.01	66
Estonia [68]	1983-1988	95	10.6	9.9	10.3	1.07	0.07	208
Finland [43]	1987-1992	100	37.6	33.5	35.7	1.12	0.12	2062
France								
4 regions [27]	1989-1990	100	7.8	7.8	7.8	1.00	0.00	261
Greece [69]	1992		6.7	6.5	6.6	1.04	0.04	137
Hungary [27]	1989-1990	99	7.7	7.5	7.6	1.03	0.03	256
Iceland [70]	1970-1989	100	9.9	8.8	9.4	1.13	0.13	120
Italy								
Lazio [27]	1989-1990	100	7.2	5.8	6.5	1.24	0.24	117
Liguria [73]	1987-1991	99	11.5	12.0	11.7	0.95	-0.05	117
Lombardia [27]	1989-1990	100	7.6	5.9	6.8	1.29	0.29	193
Marche [72]	1990-1992	100	7.9	8.3	8.1	0.95	-0.05	50
Pavia [76]	1988-1992	100	11.4	9.9	10.7	1.15	0.15	31
Piedmond [77]	1989-1990	91			9.4			
Sardinia [74]	1989-1990	93	34.1	27.2	30.7	1.25	0.25	219
Eastern Sicily [27]	1989-1990	100	11.2	9.0	10.1	1.24	0.24	52
Turin [75]	1984-1988	99	8.8	7.6	8.2	1.15	0.15	148
Latvia [68]	1983-1988	100	6.2	6.8	6.5	0.91	-0.10	215
Lithuania [68]	1983-1988	100	6.5	7.0	6.8	0.93	-0.08	336
Luxembourg [27]	1977-1986	90-100	12.1	12.6	12.4	0.96	-0.04	16
Macedonia [45]	1985-1991	97	2.4	2.5	2.5	0.95	-0.05	112
Malta [78]	1980-1987	?	12.7	14.6	13.6	0.87	-0.15	66
Netherlands [27]	1989-1990	99	12.3	12.4	12.4	1.00	0.00	58
Norway								
8 counties [27]	1989-1990	100	22.3	19.3	20.8	1.16	0.16	158
Poland								
3 cities [27]	1989-1990	100	5.7	6.0	5.8	0.95	-0.05	102
9 western prov. [27]	1989-1990	100	5.3	5.8	5.5	0.91	-0.09	164
Rzeszow [79]	1980-1992	99	5.4	4.8	5.1	1.14	0.14	122
Portugal								
3 regions [27]	1989-1990	91	10.1	4.9	7.5	2.06	1.06	25
Romania								
Bucharest [27]	1989-1990	100	4.6	5.7	5.1	0.81	-0.24	47
Slovakia [80]	1992	95	8.0	9.9	8.9	0.80	-0.25	112
Slovenia [27]	1988-1990	100	5.2	7.7	6.5	0.68	-0.48	56
Spain								
Catalonia [27]	1989-1990	95	10.5	10.6	10.6	0.99	-0.01	297
Madrid [81]	1985-1988	90	11.3	10.5	10.9	1.08	0.08	501
Sweden [100]	1978-1987	99	25.0	23.8	24.4	1.05	0.05	3836
United Kingdom [82]	1988	89	13.8	13.3	13.5	1.04	0.04	1600
Leicestershire [25]	1965-1981	>90	8.7	8.6	8.7	1.01	0.01	272
Northern Ireland [27]	1989-1990	95	17.8	15.4	16.6	1.16	0.16	130
Oxford [27]	1989-1990	98	17.8	14.9	16.4	1.19	0.20	161
Scotland [25]	1976-1983	100	20.0	19.4	19.7	1.03	0.03	1856
Tayside [25]	1980-1983	100	19.7	22.1	20.0	0.89	-0.12	64
Yorkshire [83]	1978-1990	98			13.6			1490
Yuugoslavia								
Belgrad [84]	1982-1992	90	7.6	8.6	8.1	0.88	-0.13	259

M, male; F, female; T, total

*Age of 20 years or under.

**Age of 17 years or under.

***Negative value indicates a female excess and positive value a male excess in the incidence of Type 1 diabetes.

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TEMPORAL TRENDS IN TYPE 1 DIABETES INCIDENCE

Most of the Type 1 diabetes registries have been using consistent case definitions and registration practices for a relatively short time, and only a few registries have been active for a longer period, e.g. 20 years or more. Therefore temporal trends in Type 1 diabetes incidence have been difficult to study in detail. In some countries temporal changes in Type 1 diabetes incidence have been reported (Table 7A.3). Several registries (17, 27, 43, 56, 62, 71, 86–93, 101–103) have reported a change in Type 1 diabetes incidence in North America, Europe and Oceania during various periods between 1966 and 1992. During these years an increase in Type 1 diabetes incidence has been observed in several European countries, whereas in the North American continent occasional peaks

have been reported but no clear increasing trend has been documented.

The greatest temporal increase was found in Europe, especially in the northern part of the continent. For instance, in Finland the increase in Type 1 diabetes incidence has been almost linear for 30 years. The regression-based change in incidence was about 2.8% per year from 1965 to 1992 (43). During the 1970s the increase was steepest in 5–9 year olds and since the mid-1980s in those younger than 5 years old at diagnosis (43). In Sweden, an other Scandinavian country with a high Type 1 diabetes incidence, the increasing trend in incidence was seen during 1977 to 1983, mainly among children younger than 10 years of age. Since then the increase has been leveled off (17). The increase in incidence is not restricted to northern Europe, since increasing long-term trends were also reported for Sardinia (74) and Austria (92).

The increasing trend in Type 1 diabetes cannot be explained by the change in ascertainment rates, because most of the data have been collected or confirmed, or both, according to the requirements established by the DERI group (25). Whether the increase in incidence can be explained by change in genetic susceptibility in the population, or by increasing penetrance of the susceptibility genes in the population, or by an increase in the pool of genetically susceptible individuals is not known. The incidence of Type 1 diabetes has been rising most rapidly in northern Europe where populations have been relatively stable and homogeneous in many countries and where perinatal and infant mortality has drastically decreased during the last few decades. It is very likely that some changes in environmental determinants of Type 1 diabetes have significantly contributed to the rising incidence, but their role has not as yet been determined.

The epidemic-like temporal fluctuation in incidence was reported in several countries (29, 46, 50, 52, 56, 85, 94–99). Although the data are few it appears that in the 1980s in North America the years of the highest Type 1 diabetes incidence were between 1981 and 1984 (50, 52, 56, 95, 99) and in Asia and Oceania most of the peak years were found almost at the same time in 1983 and 1985 (94, 96). In Europe the peak years were between 1983 and 1988, particularly in 1985 and 1986 (29, 50, 75, 94, 100), and in Africa the peak year was 1988 (82). The

Table 7A.3 Reported increase in Type 1 diabetes incidence from 1960 to 1996

Temporal increase reported	Study period	Reference
Europe		
Austria	1966–1986	92
Finland	1965–1984	43
France	1965–1984	89
Denmark	1970–1989	27
Germany	1949–1984	87
Hungary	1976–1985	90
Norway	1973–1982	71
Netherlands	1980–83, 1990–92	91
Poland	1970–1985	50
Sardinia	1958–1987	229
Slovakia	1985–1991	80
Sweden	1977–1983	17
United Kingdom		
Leicestershire	1966–1981	93
Scotland	1966–1986	101
Asia		
Japan		
Hokkaido	1966–1986	102
Israel	1975–80, 1980–89	103
Kuwait	1983, 1992–93	62
Oceania		
New Zealand (White)	1966–1986	88
Australia	1985–1992	65
North America		
United States		
Allegheny county	1965–1989	50
Virgin Islands	1979–1988	56

fluctuation of the high-incidence years from one continent to another may indicate the possibility of pandemics of an infectious disease functioning at least as a triggering factor for the onset of the Type 1 diabetes. Other local environmental exposures may also play a role.

AGE AND SEX DISTRIBUTION OF TYPE 1 DIABETES INCIDENCE

During childhood the incidence of Type 1 diabetes increases with age, and in both sexes the peak in incidence is seen in puberty. This peak seems to occur somewhat earlier in females than in males. Most of the individual studies have been based on a relatively small number of cases and therefore the overall picture with regard to a possible sex-associated effect has remained unclear. Nevertheless, only 20–50% of all patients with Type 1 diabetes are diagnosed during childhood, although most of the cases are diagnosed before the age of 30 years (104, 105).

Age-specific Incidence of Type 1 Diabetes

Age- and sex-specific incidence in children aged 14 years or under has been evaluated in 76 populations worldwide. Age-specific Type 1 diabetes incidence has been reported in 5-year age groups (0–4, 5–9 and 10–14 years) in several countries, summarized in Tables 7A.2 and 7A.4. The variation in the level of incidence between populations became wider with increasing age. Among children aged 14 years or under the incidence of Type 1 diabetes varied from 0.4 to 35.7/100 000 worldwide. Among the youngest children, aged 4 years or under, the incidence varied from 0.3 to 27.6/100 000 and in children aged 5–9 years the range of variation was from 0.4/100 000 to 38.9/100 000, being widest in children aged 10–14 years from 0.6/100 000 to 40.4/100 000.

Sex Ratio in Type 1 Diabetes Incidence

The male/female excess in the incidence of Type 1 diabetes is shown in Table 7A.4 and Figures 7A.2 and 7A.3. Depending on the sex-

specific incidence the sex ratio was calculated in the following way:

- A. The incidence is higher in males than in females: $(I_M/I_F)-1$
- B. The incidence is higher in females than in males: $-(I_F/I_M)-1$

To distinguish the female excess from the male excess in incidence, the rate ratio is expressed as negative in case of female excess in incidence.

The female excess in the incidence of Type 1 diabetes was found in 59% of these populations worldwide (Table 7A.5). The largest female excess in Type 1 diabetes incidence (ratio -2.12) was found in the Black population in Jefferson County, Alabama USA, while the largest male excess (ratio 1.06) in incidence was found in Portugal. However, the number of reported cases in these two populations representing the extremes was small (41 and 25 respectively) and thus the result should be interpreted with caution.

The association between the sex ratio in incidence and the level of incidence of Type 1 diabetes is shown in Figure 7A.4. This association was not linear (the Spearman rank-order correlation between male-to-female ratio and the level of incidence of Type 1 diabetes among 76 population, was 0.37, $p = 0.001$) indicating that the number of the populations with a male excess in the incidence of Type 1 diabetes was higher at higher levels of incidence. The same phenomenon was seen when the level of incidence was divided into quartiles and the populations were grouped into three groups: 25% of the populations were regarded as having a low incidence, 50% an intermediate incidence, and 25% a high incidence. A female excess in incidence was found in 88% of the low-incidence populations ($<6.5/100\ 000$) and in 60% of the populations with an intermediate incidence (6.5–15.0/100 000), while among populations with a high Type 1 diabetes incidence ($>15.0/100\ 000$) a clear male excess in incidence was found in 68% (Table 7A.5).

Sex Ratio by Age Group

The incidence data in 5-year age groups were available for both sexes for 62 populations (Table 7A.4 and 7A.5). Among children aged 4 years or under the male excess in incidence was

Table 7A.4 Age-specific incidence of Type 1 diabetes in children aged 14 years or under (per 100 000 population)

Region	Incidence								
Country and area	Males			Females			Male or female excess**		
	0–4 y	5–9 y	10–14 y	0–5 y	5–9 y	10–14 y	0–4 y	5–9 y	10–14 y
Africa									
Libya									
Benghazi [47]	2.0	5.8	13.9	2.3	8.6	15.6	–0.15	–0.48	–0.12
North America									
Canada [25]									
Prince Edward Isl.	28.6	31.3	32.2	8.5	25.1	38.5	2.37	0.25	–0.20
Montreal	7.7	11.6	14.1	5.8	11.9	11.4	0.33	–0.05	0.16
United States									
North Dakota [25]	11.6	23.9	29.0	9.1	18.5	20.8	0.28	0.29	0.35
Wisconsin (part) [25]	9.9	17.1	33.1	8.2	17.0	23.3	0.21	0.01	0.42
Rochester [25]	13.5	12.2	21.3	8.7	15.4	30.6	0.55	–0.26	–0.44
Colorado [51]*									
Non-Hispanics	10.1	18.8	22.5	7.3	17.6	22.4	0.38	0.07	0.00
Hispanics	4.9	4.4	12.0	3.4	11.7	18.3	0.44	–1.66	–0.53
Jefferson county [52]									
White	10.0	21.5	20.0	6.2	24.3	26.0	0.61	–0.13	–0.30
Black	1.4	2.9	1.4	8.3	14.9	8.3	–4.93	–4.14	–4.93
San Diego [25]	7.0	7.0	14.6	3.6	11.3	12.6	0.94	–0.61	0.16
Central America and the West Indies									
Cuba [25]	1.5	3.4	2.5	1.9	3.0	3.5	–0.27	0.13	–0.40
South America									
Brazil [58]									
State of São Paulo	2.4	5.3	10.1	7.6	12.7	8.5	–2.17	–1.40	0.19
Asia									
China									
Shanghai [40]	0.3	0.3	0.6	0.3	1.5	0.6	–0.08	–4.80	–0.05
Israel [27]	2.2	4.5	6.5	2.7	9.1	8.2	–0.23	–1.02	–0.26
Japan									
Hokkaido [25]	0.5	0.8	2.2	1.5	2.6	4.2	–2.00	–2.25	–0.91
Republic of Korea									
Seoul [39]	0.4	0.2	1.0	0.4	0.5	0.9	0.00	–1.50	0.11
Kuwait [62]	14.9	16.7	18.7	10.7	14.8	17.9	0.40	0.13	0.05
Russia									
Novosibirsk [63]	2.3	2.8	8.7	1.9	4.9	7.8	0.21	–0.75	0.12
Oceania									
Australia									
New South Wales [64]	7.1	14.0	21.0	8.5	17.6	22.1	–0.20	–0.26	0.05
New Zealand									
Canterbury [25]	4.2	5.2	20.9	10.8	7.2	20.1	–1.57	–0.39	0.04
Europe									
Austria [27]	5.1	8.2	10.3	4.5	8.3	9.9	0.13	–0.01	0.04
Belgium									
Antwerp [27]	3.7	12.5	11.6	5.8	11.2	14.1	–0.57	0.12	–0.22
Croatia									
Zagreb [67]	2.2	9.1	12.3	3.4	4.8	12.6	–0.55	0.90	–0.02
Denmark									
3 counties [27]	16.5	12.4	35.6	8.5	26.2	29.6	0.94	–1.11	0.20
Estonia [48]	3.1	11.0	18.1	3.2	13.5	13.3	–0.03	–0.23	0.36
Finland [43]	28.0	39.6	45.3	27.1	38.1	35.5	0.03	0.04	0.28

(continued)

Table 7A.4 (continued)

Region Country and area	Incidence								
	Males			Females			Male or female excess**		
	0–4 y	5–9 y	10–14 y	0–5 y	5–9 y	10–14 y	0–4 y	5–9 y	10–14 y
France									
4 regions [27]	5.4	8.6	9.5	3.8	6.9	12.7	0.42	0.25	–0.34
Greece [69]	2.8	4.7	10.5	2.2	5.9	10.1	0.27	–0.19	0.04
Hungary [27]	4.5	8.2	10.4	4.3	7.6	10.8	0.05	0.08	–0.04
Italy									
Marche [72]	4.3	10.9	8.1	4.5	11.4	8.5	–0.05	–0.05	–0.05
Lazio [27]	4.7	10.1	6.7	5.3	6.6	5.6	–0.13	0.53	0.20
Liguria [73]	8.5	13.2	13.1	8.3	15.9	12.3	0.02	–0.21	0.07
Lombardia [27]	4.8	9.7	8.4	4.8	5.3	7.6	0.00	0.83	0.11
Sardinia [74]	22.4	40.1	36.9	19.6	32.0	28.4	0.14	0.25	0.30
Eastern Sicily [27]	12.7	10.1	10.9	2.6	14.1	10.1	3.89	–0.40	0.08
Pavia [76]	7.0	8.6	16.7	2.4	11.2	14.2	1.85	–0.30	0.18
Turin [75]	5.0	7.8	11.8	4.8	6.8	9.9	0.03	0.16	0.19
Latvia [68]	3.2	5.4	10.5	3.7	6.9	10.0	–0.16	–0.28	0.05
Lithuania [68]	4.1	6.9	8.6	2.9	8.6	9.6	0.41	–0.25	–0.12
Macedonia [44]	1.6	2.2	3.5	1.2	3.4	3.1	0.38	–0.56	0.14
Malta [78]	6.1	12.0	20.2	9.1	15.6	19.5	–0.49	–0.30	0.04
Netherlands [27]	6.8	11.7	18.5	6.1	13.3	17.7	0.12	–0.14	0.05
Norway [27]									
8 counties	13.4	26.3	27.3	7.9	26.2	23.8	0.70	0.00	0.15
Poland									
3 cities [27]	1.7	7.1	8.3	3.6	6.1	8.3	–1.12	0.16	0.00
9 western prov. [55]	2.7	5.6	7.5	1.5	5.9	10.0	0.80	–0.05	–0.33
Rzeszow [79]	3.7	5.6	7.2	2.9	4.9	6.7	0.27	0.15	0.08
Portugal									
3 regions [27]	9.4	8.8	11.9	2.0	5.5	7.1	3.70	0.60	0.68
Romania									
Bucharest [27]	0.7	2.5	10.5	5.1	6.0	5.9	–6.29	–1.40	0.78
Slovakia [80]	6.9	9.9	7.0	6.2	11.4	11.9	0.12	–0.15	–0.70
Slovenia [27]	3.1	3.5	9.0	2.5	6.5	14.3	0.40	–1.10	–0.60
Spain									
Catalonia [27]	4.7	9.8	17.0	3.4	10.9	17.7	0.38	–0.11	–0.04
Sweden [100]	16.8	25.4	31.6	14.5	26.3	29.4	0.16	–0.04	0.08
United Kingdom [82]	10.0	12.9	18.8	9.7	13.6	16.7	0.03	–0.05	0.13
Leicestershire [25]	5.1	8.5	12.3	3.4	8.2	14.1	0.50	0.04	–0.15
Northern Ireland [27]	11.4	15.5	26.5	13.6	13.8	18.7	–0.19	0.12	0.42
Oxford [27]	15.2	14.3	23.9	11.3	13.4	20.0	0.35	0.07	0.20
Scotland [25]	13.7	20.4	25.9	12.2	19.9	25.8	0.12	0.03	0.00
Tayside [25]	17.0	17.7	29.9	15.6	20.7	18.2	0.09	–0.17	0.64
Yorkshire [25]	9.8	13.1	18.2	9.6	13.4	16.9	0.02	–0.02	0.08
Yugoslavia									
Belgrade [84]	4.6	7.6	10.5	3.3	10.3	11.9	0.39	–0.36	–0.13

M, male; F, female; T, total

*Age 17 years or under.

**Negative value indicates a female excess and positive value a male excess in the incidence of Type 1 diabetes.

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found in 66% of the populations, whereas in the age group of 5–9 years there was a female excess in 63% of the populations. In the age group 10–14 years there was again a male excess in incidence in the majority, 60% of the populations.

A female excess in Type 1 diabetes incidence among children aged 4 years or under was found in 64% of the low incidence (<6.5/100 000) populations. However, a male excess increased with a growing incidence. Thus, in 62% of the populations

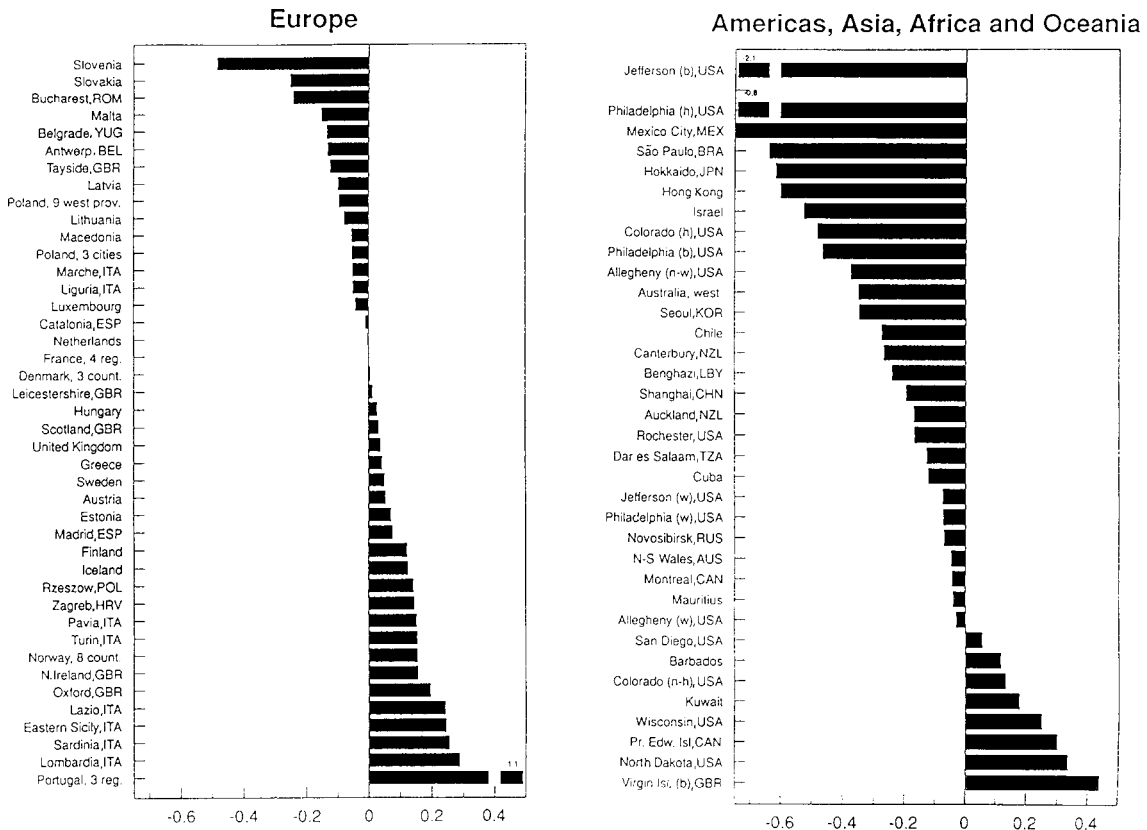


Figure 7A.2 A male to female excess in the age-specific incidence (per 100 000 population) of Type 1 diabetes in children aged 14 years or under. Negative value indicates a female excess and positive value a male excess in the incidence of Type 1 diabetes.

AUS, Australia; BEL, Belgium; BRA, Brazil; BUL, Bulgaria; CAN, Canada; CHN, China; GBR, Great Britain; GRE, Greece; Croatia, HRV; ITA, Italy; JPN, Japan; KOR, Korea; LBY, Libya; MEX, Mexico; NZL, New Zealand; POL, Poland; POR, Portugal; RUS, Russia; ESP, Spain; TZA, Tanzania; USA, United States of America; w, White; n-w, non-White; b, Black; h, Hispanic; n-h, non-Hispanic

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with an intermediate (6.5–15.0/100 000) incidence and in 88% of the populations with a high (>15.0/100 000) incidence a male excess in incidence was found. In children aged 5–9 years a female excess in incidence was found in the populations with a low and an intermediate incidence, whereas 71% of the populations with a high incidence had a male excess. In the oldest age group (10–14 years old) a male excess in incidence was also found in children aged 10–14 years, in 56% of the populations with an intermediate and in 77% of the populations with high incidence, whereas of the populations with a low incidence 55% had a female excess in incidence.

The sex ratio in Type 1 diabetes incidence diverged between continents (Table 7A.6). Europe

was the only continent where the slight male excess in incidence was seen: 55% of the populations had a male excess in the incidence of Type 1 diabetes. The sex ratio within Europe varied from a female excess in Slovenia (ratio –0.48) to the male excess in Portugal (ratio 2.06). In the North American continent a female excess in incidence was found in 67% of the populations and the greatest female excess (ratio –2.12) was in the Black population of Jefferson County, Alabama, USA. The male excess in incidence was found mainly in the northern part of the continent, in Colorado, Wisconsin and North Dakota in the USA and on Prince Edward Island, Canada. The number of populations from other continents is relatively small. Among populations from Asia, Central

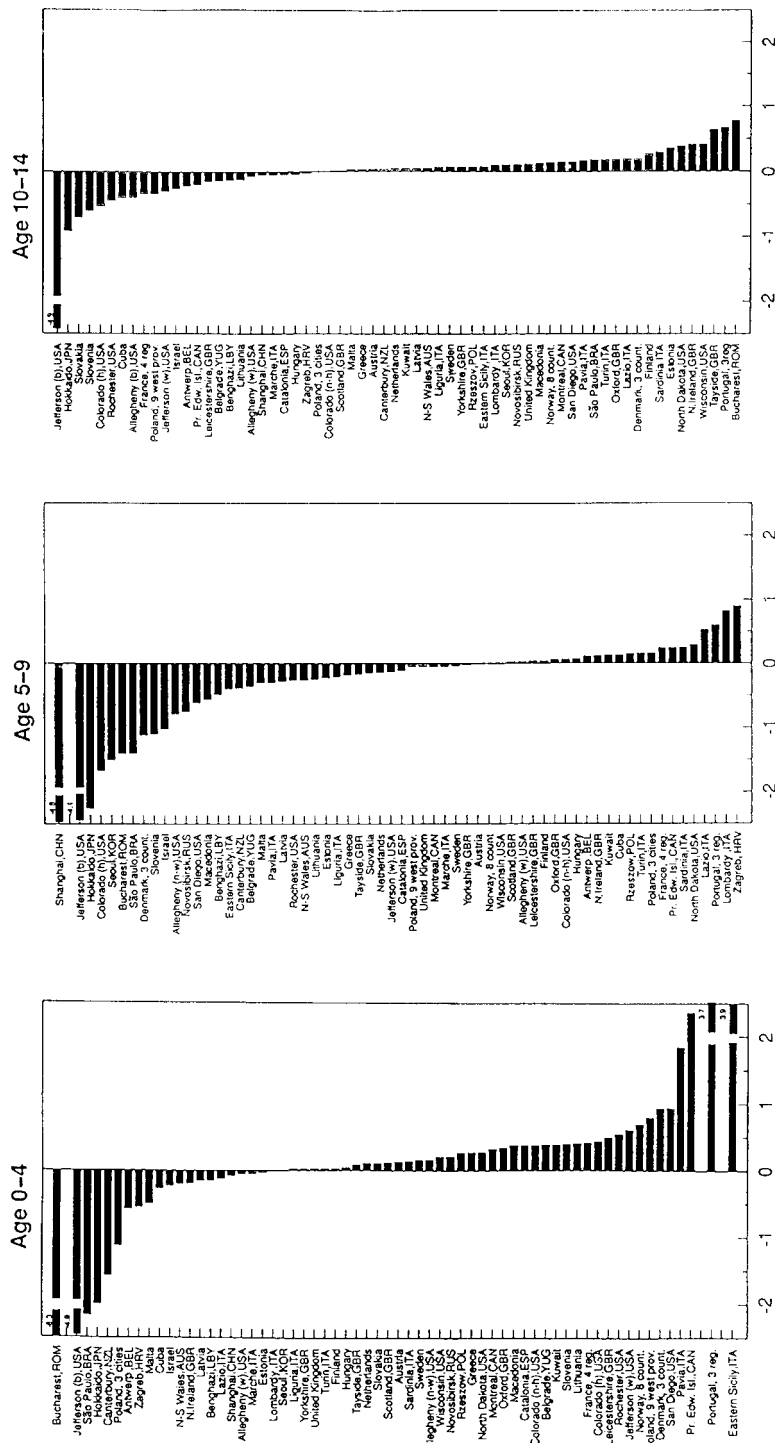


Figure 7A.3 A male to female excess in the incidence (per 100 000 population) of Type 1 diabetes in children aged 14 years or under for boys and girls in age groups: 0–4 years, 5–9 years and 10–14 years. Negative value indicates a female excess and positive value a male excess in the incidence of Type 1 diabetes.

AUS, Australia; BEL, Belgium; BRA, Brazil; BUL, Bulgaria; CAN, Canada; CHN, China; GBR, Great Britain, GRE, Greece; CRO, Croatia; HRV, ITA, Italy; JPN, Japan; KOR, Korea; LIB, Libya; MEX, Mexico; NZL, New Zealand; POL, Poland; POR, Portugal; RUS, Russia; ESP, Spain; TZA, Tanzania; USA, United States of America; w, White; n-w, non-White; b, Black; h, Hispanic; n-h, non-Hispanic

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America and the West Indies only two out of ten populations had a male excess in incidence, and among populations from South America, Africa and Oceania there was a female excess in incidence

Table 7A.5 Number of populations (%) with a low (<6.5), intermediate (6.5–15.0) or high (>15.0) incidence of Type 1 diabetes (per 100 000/year)*

	Low (<6.5)	Intermediate (6.5–15.0)	High (>15.0)	Total
Age ≤ 14 years¹				
Female excess	15 (88.2)	24 (60.0)	6 (31.6)	45 (59.2)
Male excess	2 (11.8)	16 (40.0)	13 (68.4)	31 (40.8)
Total	17	40	19	76
Age 0–4 years²				
Female excess	7 (63.6)	13 (38.2)	2 (11.8)	21 (33.9)
Male excess	4 (36.4)	21 (61.8)	15 (88.2)	41 (66.1)
Total	11	34	17	62
Age 5–9 years³				
Female excess	8 (72.7)	25 (73.5)	5 (29.4)	39 (62.9)
Male excess	3 (27.3)	9 (26.5)	12 (70.6)	23 (37.1)
Total	11	34	17	62
Age 10–14 years⁴				
Female excess	6 (54.6)	15 (44.1)	4 (23.5)	25 (40.3)
Male excess	5 (45.5)	19 (55.9)	13 (76.5)	37 (59.7)
Total	11	34	17	62

*The populations have been divided into three groups according to the incidence (per 100 000/year) percentile point: 25%, 50% and 75% corresponding to the incidence levels (<6.5, 6.5–15.0, >15.0).

¹Chi-Square 11.858, df 2, $p = 0.003$. ²Chi-Square 8.099 df 2, $p = 0.017$.

³Chi-Square 10.035, df 2, $p = 0.007$. ⁴Chi-Square 3.121, df 2, $p = 0.210$.

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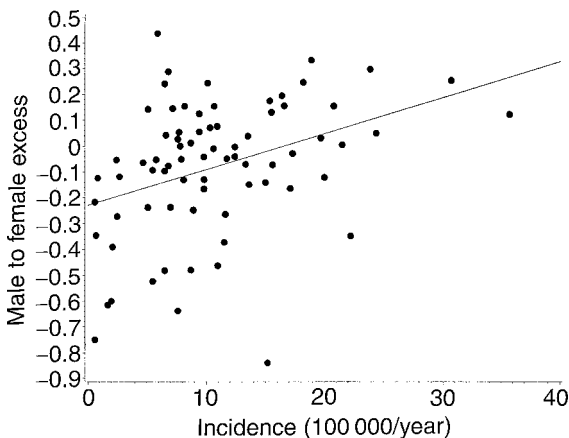


Figure 7A.4 An association between male to female excess in the age specific incidence of Type 1 diabetes in children aged 14 years or under in 74 population worldwide (Jefferson, USA Black-population (2.1) and Portugal (1.1) have been excluded). Reproduced from Karvonen et al. (1997) *Diabetes/Metabolism Reviews*. 13(4): 275–91, by permission.

Table 7A.6 The global distribution of the populations with a male or female excess in the incidence of Type 1 diabetes

Continent	Number of populations with a male or female excess in the incidence of Type 1 diabetes		
	Male excess	Female excess	All
Europe	23	19*	42
North America	5	10	15
Central America and the West Indies	1	2	3
South America	0	2	3
Asia	1	6	7
Oceania	0	4	4
Africa	0	3	3
All	30	46	76

*Includes three populations with equal incidence in males and females. Reproduced from Karvonen et al. (1997) *Diabetes/Metabolism Reviews*. 13(4): 275–91, by permission.

among all populations. All populations with an incidence higher than 23.0/100 000 had a male excess in incidence, and all populations with an incidence lower than 4.5/100 000 had a female excess in incidence (Figure 7A.4). The majority (77%) of the populations which had a male excess in incidence were European. Populations with a female excess in incidence were mainly of Black or Asian origin.

SEASONAL VARIATION IN TYPE 1 DIABETES INCIDENCE

Seasonal variation in Type 1 diabetes incidence was already reported in the 1920s when higher rates of ‘acute diabetes’ were found during the late autumn, winter and early spring (1). Peaks in incidence, with one peak in the winter months and the other during the late summer, were detected in northern Sweden among children aged 0–14 registered during 1938 to 1977 (106). Several other epidemiologic studies have described seasonal patterns in the onset (or better at diagnosis) of new cases of insulin-dependent diabetes in children (17, 22, 49, 51, 53, 78, 81, 82, 86, 97, 107–111, 113). Most studies have reported higher occurrence of insulin-dependent diabetes during the cold autumn and winter months than during the warmer spring and summer months, but these findings are difficult to compare because of differences in

methodology. Overall the seasonal variation in the month of diagnosis of the disease has been reported in regions where seasons are well-defined summer or winter.

The months/seasons of highest incidence have varied across populations; however, the low incidence during the warm months has been consistent. There were some exceptions in the seasonal pattern; in Europe in France (89) and in Western Siberia (94) there were no seasonal differences in diabetes incidence. In the US Virgin Islands (56) there was a noticeable peak in incidence in June, but the number of cases was small and the difference in the yearly temperature is minimal at this latitude. In Finland, where the incidence of Type 1 diabetes in children is the highest in the world and steeply rising over the last four decades, a statistically significant seasonal pattern could be confirmed for males but not for females. During a calendar year, one cycle with a decreased incidence of insulin-dependent diabetes in June was found among younger boys. Among older boys there were two distinct cycles with a decreased incidence, the first in June and the second during November–December. The most visible seasonal pattern was a lower number of cases diagnosed in June, while during the rest of the year the incidence remained relatively stable and high (114).

TYPE 1 DIABETES AND POSSIBLE ASSOCIATION WITH VIRAL INFECTIONS

Seasonal variation in the diagnosis of Type 1 diabetes has been considered as indirect evidence for environmental exposure in the development of Type 1 diabetes. Recent studies have provided more indirect evidence for an association between viral infections and the pathogenesis of insulin-dependent diabetes, but the final evidence for viruses causing insulin-dependent diabetes is still missing (114). Some communicable diseases occur more frequently during the cold winter months in areas where the climate changes during the year. Therefore infectious diseases could play a role, at least as a triggering factor in the onset of clinical symptoms of insulin-dependent diabetes.

Although a large number of common viruses, e.g. mumps, rubella and the Coxsackie B group, have been implicated as having a role in the

development of Type 1 diabetes, this disease is not a common consequence of viral infection. Even though it was suggested in the last century that there might be a connection between mumps and Type 1 diabetes (115), the part that viruses play in Type 1 diabetes is still not clear. Many reports have shown a temporal relationship between certain viral infections and Type 1 diabetes, but whether viruses are directly responsible for damage to the pancreatic β -cells in humans or whether they can cause diabetes by triggering an autoimmune response is unknown (116). *In vitro*, mumps virus, Coxsackie B3 and B4 virus, and reovirus type 3 can infect human pancreatic β -cells and destroy them. In mice the encephalomyocarditis virus, the meningovirus and the Coxsackie B4 virus are able to destroy pancreatic β -cells when inoculated, and in cattle a form of diabetes developed after an outbreak of foot-and-mouth disease (117). The number of well-documented case reports involving Coxsackie B viruses is small. However, they show that virus infections can trigger or be the final cause in the development of Type 1 diabetes, at least in some cases (118). An increased prevalence of Type 1 diabetes has been found in patients with congenital rubella (119–121) and it has been shown that rubella virus can multiply in the pancreas and cause lesions. Rubella used to be a very common cause of infection in many populations, but it has now been eradicated from many parts of world, e.g. from Northern Europe. However, at the same time an increasing trend in incidence does not support the potential role of rubella infection as a causal or triggering factor for onset of Type 1 diabetes.

Viruses are unlikely to be the major precipitating factors in Type 1 diabetes, otherwise the incidence of Type 1 diabetes should have fallen during the first decade of immunization against measles, rubella, mumps and poliomyelitis in the USA (122). In Finland, the country with the highest incidence of Type 1 diabetes in the world, the immunization programme against mumps and rubella was started in 1982. The incidence of Type 1 diabetes is still increasing in Finland (123), and the increase in incidence has been steepest among the youngest children since the mid-1980s.

Recent data from Sweden (124) and Finland (125) suggest that mothers whose children subsequently became diabetic had higher group-specific enterovirus antibodies during this particular

pregnancy than mothers whose children remained non-diabetic. The mechanism of possible perinatal virus exposure remains unknown. A sequence similarity between Cocksackie B and glutamic acid decarboxylase (GAD) has been described (126), leading to speculations of possible molecular mimicry, but this hypothesis is unproven.

It must be borne in mind that many virus variants are grouped together under one name: for instance, the term 'Cocksackie virus B4' signifies at least 13 variants. It may be that only a rare variant of the Cocksackie virus B group is diabetogenic and that vaccination against this variant might be possible in the future.

It has been reported that diabetic patients had reduced titers of antibodies to reoviruses and reduced titers of IgG and IgM antibodies to mumps, compared with healthy controls, whereas mumps-specific IgA antibodies were found more frequently (128). These results suggest that the immunologic response to certain viruses is different in Type 1 diabetes patients compared with healthy people and may indicate that Type 1 diabetes patients have selective defects in their humoral response to certain viral antigens. This is clearly an area for further research with respect to prevention of Type 1 diabetes.

Although recent observations suggest that exposures to enterovirus infections both *in utero* and in childhood may be able to induce and promote β -cell damage and thus lead to Type 1 diabetes, we do not have enough evidence to say that such infections are truly causing Type 1 diabetes. Many people hope that it will be possible to develop a vaccine to prevent Type 1 diabetes, but much more information is needed before it will be possible to provide sufficient evidence to justify such an approach. Vaccination may not simply remove a disease like Type 1 diabetes. Interestingly, it was noticed that the penetrance of diabetes in female NOD mice reared in a pathogen-free environment approaches 100% (126). After exposure to mouse hepatitis virus, only 35% of mice became diabetic.

TYPE 1 DIABETES AND NON-VIRAL ENVIRONMENTAL FACTORS

Some nutritional factors have been implicated in the etiology of Type 1 diabetes but no firm data linking diet to incidence of the disease exist in

humans. There has not yet been any prospective study to obtain accurate dietary information on a representative sample of genetically susceptible first-degree relatives of Type 1 diabetes patients with follow-up to determine Type 1 diabetes incidence.

Breastfeeding and Cow's Milk Protein

Borch-Johnsen et al. (130) proposed an inverse correlation between the frequency and duration of breastfeeding and the frequency of Type 1 diabetes in Norway, Sweden and Denmark. They postulated that breast milk provides protection against environmental factors that lead to the selective destruction of pancreatic β -cells in genetically susceptible children. It could also be that commercially available milk substitutes or baby foods contain chemicals toxic to the pancreatic β -cells or that cow's milk contains certain proteins that could be harmful to islet β -cells. If it could also be shown in other countries that the duration of breastfeeding is relevant to the incidence of diabetes, then education campaigns for prolonged breastfeeding could be started. This might also have other beneficial health aspects besides Type 1 diabetes prevention.

In the BB rat it was possible to reduce the incidence of diabetes by feeding the weanling rats a semisynthetic diet in which the proteins were replaced by L-amino acids (131). In this study, the presence of intact protein in the diet was necessary for the development of diabetes, and even small amounts of dietary protein increased the incidence in the BB rat. It was suggested that people with a low-protein diet might also have a low incidence of Type 1 diabetes. A more recent study showed that diet has a dramatic effect on the immune system in the BB rat (132): thymus weight and total white cell count were increased through a more pure diet, insulinitis decreased, and the ratio of T-helper to T-suppressor cells was doubled.

The available ecological studies show that the risk of Type 1 diabetes may be related to neonatal feeding practices and cow's milk consumption (133, 134). Ecological correlations as high as 74–94% have been reported. These studies do not, however, prove that the association observed represents a genuine causal relationship between infant feeding and Type 1 diabetes. Moreover, in

Sardinia, where the incidence of Type 1 diabetes is the second highest in the world after Finland, cow's milk consumption is not particularly high and is far lower than in Finland (135).

The case-control study design provides a better way to determine whether the exposure and the disease are directly linked. The reviews of published results from studies where potential biases have been minimized have suggested that there could be an approximately 1.5-fold increased risk of Type 1 diabetes with a short duration of breastfeeding (<3 months) and an early introduction of cow's milk in the diet (136, 137). On the other hand, the estimated population attributable risk for early cow's milk exposure is only approximately 10–15%, i.e. only this proportion of Type 1 diabetes cases may be prevented by removing the cow's milk exposure. Moreover, the recent trend data from Finland clearly show that the dramatic increase in the frequency and duration of breastfeeding in the 1980s has not been associated with any decrease in Type 1 diabetes incidence, but rather that the incidence has steadily increased, as during the last 40 years (43).

The theory that cow's milk proteins may be involved in the β -cell destructive process is supported by the findings of increased levels of antibodies to cow's milk protein and to bovine serum albumin in the sera of diabetic children compared with non-diabetic controls (138–141). Unfortunately, the emphasis has been placed so heavily on the cow's milk hypothesis that alternative hypotheses have been largely ignored and many studies of infant diet and the risk of Type 1 diabetes have been overly simplistic. Therefore, the data we have at present on infant diet exposures are still not precise and accurate enough to allow us to develop specific interventions that would test the cow's milk hypothesis or to propose alternative hypotheses (139). The experimental data in humans incriminating cow's milk have been challenged, as has the finding that antibodies to bovine serum albumin are linked to Type 1 diabetes (133, 136, 137). Nevertheless, a feeding intervention trial in newborns, randomizing them to receive formula with or without suspected cow's milk protein, is being planned. Pending better and more precise information, it is prudent and safe to recommend a long duration of breastfeeding, not only for possible prevention of diabetes but also for

many other reasons. Until more definitive data are available on the timing, duration of exposure, exact identity of the diabetogenic foods and how they may induce or promote diabetes, current infant feeding patterns should not be changed because of worry about possible Type 1 diabetes in some children.

Nitrosamines

Other studies have also shown that dietary factors could precipitate the expression of diabetes. In Iceland the traditional high intake of smoked and cured mutton during Christmas and New Year was correlated with an excess of boys under the age of 15 years born in October who developed Type 1 diabetes (142); N-nitroso compounds were found in the smoked and cured mutton, and it was postulated that nitrosamines (which are known to cause cancer) are also capable of damaging the pancreatic β -cells before or shortly after conception. This hypothesis was tested in pregnant Swiss mice, with suggestive results (143). Nitrosamines are toxic substances that are related to the rodenticide Vacor, which has also been shown to cause diabetes in humans after ingestion (144). Nitrosamines are also related to streptozotocin, an agent used to induce experimental diabetes in mice. Analytical case-control studies in Sweden (11) and in Finland (145) have confirmed that the frequent intake of nitrosamine-rich foods increases the risk of childhood Type 1 diabetes. These findings were further supported by an ecological study showing a correlation between the incidence of Type 1 diabetes and the content of nitrate in drinking water in Colorado (146). It would be extremely interesting to study the content of nitrosamines in the diet and in the drinking water of countries with a high or a low incidence of Type 1 diabetes, as this may also have important implications for prevention of Type 1 diabetes.

GENETIC BACKGROUND OF TYPE 1 DIABETES

Familial Clustering

Although the susceptibility to Type 1 diabetes is inherited, the main problem in prevention of Type 1

diabetes using the high-risk approach is that only 12–15% of Type 1 diabetes occurs in families with first degree relatives with Type 1 diabetes. The majority of Type 1 diabetes—about 85%—occurs in a sporadic fashion and is therefore unaccounted for in most studies aimed at estimating risk and predictive value of certain markers. One has to bear in mind not only that about one-third of the nuclear families where Type 1 diabetes is ‘sporadic’ are single-child families, but that in a proportion of the sporadic families second- and third-degree family members with Type 1 diabetes can be found in the extended families. Some of the sporadic families are therefore potentially multiplex families.

It was already noted over 2000 years ago that Type 1 diabetes shows familial clustering, i.e. is passed on from one generation to the next ‘in the seed’ (147). It is now clear that the risk in family members is not equally strong for all first-degree family members. HLA-identical siblings of a child with Type 1 diabetes have the highest risk (20%), whereas HLA haploidentical family members (siblings, parents and offspring) have a lower risk (5%, 3–6% and 2–5%, respectively). The mode of inheritance of Type 1 diabetes does not follow a simple autosomal dominant, recessive or intermediate trait, nor a two-locus model. It is best explained by a complex model (polygenic or mixed model) where a set of genes have an additive or interactive effect. Type 1 diabetes is a multifactorial disease with a complex sex-associated effect.

Data from Finland (148), Sweden (149) and the USA (150) show that at the time of diagnosis of Type 1 diabetes in a child, more fathers (5–6%) than mothers (2–3%) also have Type 1 diabetes. One way to describe the strength of familial clustering is the risk to siblings of Type 1 diabetes children (RRs compared with the population prevalence). By the age of 15 approximately 5–6% of siblings have developed Type 1 diabetes in Northern European populations, and when the population prevalence (cumulative incidence) is 0.4–0.6%, i.e. the risk in siblings is 12–15 times greater than that in the general population. From this risk difference between all siblings regardless of their HLA status and the general population Risch concluded in 1987 that HLA genes contribute only 25% to the genetic background of Type 1 diabetes (151), which is obviously an underestimate due to ignoring HLA status.

The Type 1 diabetes disease genotype has a low penetrance, i.e. not all HLA-identical siblings of a Type 1 diabetes proband will develop the disease. The risk for an HLA-identical sibling (who by definition shares both parental haplotypes with the diabetic proband) of developing diabetes is approximately 20%. This is 35–50 times greater than the risk in the general population. The risk for an HLA haploidentical sibling who has one parental haplotype in common with the proband is about 5%, and the risk for an HLA non-identical sibling who has no parental haplotype in common with the proband is less than 1% (152).

The attributable risk of genetic factors determining the susceptibility to Type 1 diabetes is much less than 100%, as only 20–30% of monozygotic twins (MZ) become concordant for Type 1 diabetes (153, 154). In population-based twin and family studies from Finland the risk in MZ twins (19%) seems to be similar to the risk in HLA-identical siblings (19%), which can be taken as evidence for a major role of genes in the HLA region. On the other hand, the estimate of the genetic effect in the population-based Finnish twin study was about 70% (153). Furthermore, animal data also suggest incomplete penetrance of genes predisposing to diabetes, as not all inbred non-obese diabetic (NOD) mice and only 60% of Bio-Breeding (BB) rats develop diabetes.

The HLA System

The major susceptibility to developing Type 1 diabetes is conferred by genes in the HLA region which is located on the short arm of chromosome 6 in the distal portion of the 6p. 21.3 band. The HLA region represents about one-thousandth of the total human genome and is about 4 million base pairs long (4 centimorgans) and contains more than 100 genes, including the gene or genes that confer susceptibility to Type 1 diabetes. Many genes and pseudogenes are known to exist in the highly polymorphic HLA system located in the phylogenetically conserved MHC (major histocompatibility complex) region on chromosome 6 (155) (see also Chapter 6). The genes of the HLA-A, C and B loci at the telomeric end of the HLA region code for the α -chain of the class I antigens. (The invariable β -chain of the class I antigens is β_2 -microglobulin coded on chromosome 15.) In the

class III region, between class I and class II, are genes coding for the complement factors C2, C4A, C4B and Bf and genes coding for heat shock protein (HSP)70 and tumor necrosis factors (TNF α and TNF β) which segregate codominantly with HLA haplotypes consisting of class I and II alleles (whole, entire or extended HLA haplotypes) (156). TNF α has been implicated in the development of septic shock and its gene was coincident with *idd-1* in a genome-wide search for Type 1 diabetes susceptibility genes using microsatellite markers (157). It gave a maximum LOD score (MLS) of 7.3 showing strong linkage disequilibrium in all three data sets of affected sibpair families.

The class II loci at the centromeric end of the HLA region consist of the HLA-DR, DQ and DP regions. In the DR region DRB1 is the most important gene coding for the β I-chain determining the specificities DR1 to DR18. The DRA gene codes for the DR α -chain, and DRB3, DRB4 and DRB5 genes for other DR β -chains. Of the DR specificities, DR4 (DRB1*0401) plays a very important role and DR3 (DRB1*03011) a somewhat lesser role in Type 1 diabetes. The DQ specificities—of which DQ8 (DQA1*0301,DQB1*0302) shows an even stronger association with Type 1 diabetes than DR4—are determined by two polymorphic genes: DQA1 coding for the DQ α -chain and DQB1 coding for the DQ β -chain. No recombination has been found between the DR and the DQ genes. In contrast, linkage disequilibrium is not maintained between the DR,DQ and the DP genes (DPA1 coding for the DP α -chain and DPB1 coding for the DP β -chain). There is a recombination hotspot in this region. Between DQ and DP a group of important functional genes have been discovered (158), of which the putative peptide transporter genes TAP1 (previously RING4) and TAP2 (previously RING11) might be relevant to Type 1 diabetes. TAP is the acronym for transporters for antigen processing, and the TAP genes encode proteins which deliver cytosolic peptides to the class I molecules which they need for export to the plasma membrane and for conformational correctness of the molecule. TAP2 has been shown to be in linkage disequilibrium with the class II alleles also in Type 1 diabetes (159). Many more genes not directly relevant to Type 1 diabetes exist in the MHC region, including the genes for hemochromatosis, 21-hydroxylase deficiency (CYP21),

valyl-t synthetase, HLA-E, F, G,DQA2, DQB2, DQB3, DOB, DMA (RING6) and DMB (RING7), the proteasome-like genes LMP2 (RING12) and LMP7 (RING10), and a collagen gene. A very high proportion of Type 1 diabetes patients (about 95%) possess either HLA-DR3 or DR4, whereas the frequencies of DR2 and DR5 are decreased in Type 1 diabetes patients. There is no increase in the recombination frequency in families with Type 1 diabetes. A very important feature is the epistatic effect of B8 and B62, and especially of DR3 and DR4: this could indicate that both parents contribute genetically to their offspring's susceptibility to Type 1 diabetes. The excess of DR3/DR4 heterozygotes in Type 1 diabetes is well documented, and the coexistence of DR3 and DR4 also seems to influence the concordance rate in identical twins (160–163).

Looking back, one has to interpret these results with caution as all data on DR3/DR4 heterozygosity (ranging from 30 to 51% in the various studies in Europids) were derived from studies where the patients had been selected either from a hospital or clinic, or for a specific reason, as in the first prospective family study ever done, the Bart's Windsor Family Study (BWFS)(160, 164, 165). In the first population-based Type 1 diabetes study (DiMe Study) (166, 167) in Finland, the country with the highest incidence of Type 1 diabetes in the world, the frequency of DR3,DQ2/DR4,DQ8 was only 21% in the Type 1 diabetes probands diagnosed under the age of 15 years. It was also only 21% in the Type 1 diabetes fathers and Type 1 diabetes mothers. The striking feature in the DiMe Study was that the frequency of DR3/DR4 was significantly different in 632 probands belonging to simplex and 103 to multiplex families (20.1% vs. 31.4%, $p = 0.012$). This explains the results of the BWFS, where the Type 1 diabetes families were especially selected for being potentially multiplex and, as a consequence, 51% of the probands were DR3/DR4 heterozygous. It has been generally accepted that the HLA genetic characteristics of Type 1 diabetes are the same for sporadic and familial cases. A Danish study comparing 55 familial with 57 sporadic cases found no significant differences within the MHC region using HLA-A, B, DR, DQ, TNF and HSP70, although they observed a difference at the manganese superoxide dismutase (MnSOD) locus on chromosome 6q (168).

Most HLA studies in Type 1 diabetes have compared the HLA frequencies found in unrelated Type 1 diabetes patients with those found in healthy control subjects. Studies in unrelated patients can only reveal associations between HLA antigens and Type 1 diabetes. In contrast, family studies are a much more powerful tool to establish linkage between the HLA genes and Type 1 diabetes. Family studies are rarer because they are more difficult to carry out; not enough attention is therefore given to the fact that only particular HLA haplotypes are increased in Type 1 diabetes (166, 169, 170). For instance, the well-documented increase in DR4 is due to a selective increase of specific haplotypes. These extended haplotypes are more precise markers for Type 1 diabetes than the antigens of any single locus, whether it be the B, the DR or the DQ locus. Calculating the risk for an HLA antigen of a single locus, for instance for DR4, might lead to the conclusion that the majority of DR4-positive people in the population may never develop diabetes; such a conclusion is misleading. A more meaningful approach would be to see how often particular DR4-positive haplotypes, which are made up of certain antigens coded for by the HLA region from A to DQ which are in linkage disequilibrium, occur in the general population and then to calculate how often people have specific DR4 haplotypes. For instance the A2, Cw3, B62, TNFa2, C2*1, BF*S, C4A*Q0, C4B*3, DR4 (DRB1*0401), DR53, Dw4, DQ8 haplotype or the A2, Cw1, B56, TNFa6, BF*S, C4A*3, C4B*Q0, DR4 (DRB1*0401), DR53, Dw4, DQ8 (166) haplotype (which is unique for Type 1 diabetes in the Finnish population), never develop Type 1 diabetes. It is possible that a number of different genetic interactions between the various HLA loci might confer susceptibility. Unfortunately, there are no methods available that can make use of multiple polymorphic markers coded for at different but closely linked loci which might interact in increasing the liability to develop Type 1 diabetes. Linkage disequilibrium between the HLA alleles makes these calculations very difficult and therefore the use of entire HLA haplotypes—defined through segregation in families and spanning 3.5 kb of the HLA region from A to DQ—as markers for Type 1 diabetes susceptibility is the best way to overcome this problem. In the genetically relatively homogeneous

Finnish population, 41 different HLA haplotypes have been found to be associated with Type 1 diabetes (171). All have been seen transmitted from Type 1 diabetes parent to a Type 1 diabetes child in a population-based study. The presence of one of these 41 haplotypes explains over 85% of Type 1 diabetes in Finland: 29 carry the class II alleles DR4, DQ8, 7 carry DR3, DQ2 and 5 carry other DR, DQ combinations. Their haplotype-specific absolute risk varies, the highest risks being over 200 when the average risk in the population is 35/100 000/year (172). This variation depends primarily on HLA class I (A, C, B) alleles (173).

Molecular genetics has made it possible to reach the HLA genes themselves, and a new and exciting era has begun (174–176). It is now quite clear that there are no mutant genes involved in Type 1 diabetes and that no unique disease alleles exist in Type 1 diabetes. In the beginning only sequence variations outside the functional genes were found. Most hypervariable sites are not in the coding regions but in the flanking sequences and are correlated only because of linkage disequilibrium (177).

The amino acid sequences of the HLA-DQ β -chain derived from healthy people and from Type 1 diabetes patients have also been determined (178). All haplotypes that were negatively associated or not associated with Type 1 diabetes had the amino acid aspartic acid in position 57 of the α 2 helix of the DQ β -chain. Todd and co-workers concluded that Asp57 provides dominant resistance as it influences the antigen-binding properties by forming a salt bridge and as codon 57 occupies a key position in the peptide-binding site. A hypothesis that the DQB1 polymorphism explains the worldwide pattern of Type 1 diabetes incidence was put forward (179) but shown to be too simplistic (180) and not applicable to Type 1 diabetes in Orientals. Of Chinese Type 1 diabetes patients 22% were homozygous for Asp57, and in Japan both haplotypes that confer susceptibility to Type 1 diabetes (the DRB1*0405, DDQA1*0301, DQB1*0401 and the DRB1*0901, DQA1*0301, DQB1*0303 haplotype) have aspartic acid at position 57 of DQB1 (181). An association of the DR3-related DQ α -chain with the DR4-related DQ β -chains in DR3/DR4 heterozygous individuals was demonstrated (182). In 1990 a hypothesis was put forward by Khalil et al. based on the formation not only of the usual *cis* but also of

trans-associated heterodimers between DQB1 and DDQA1 (SS heterodimers) (183) with arginine in position 52 of DDQA1 correlating with susceptibility to Type 1 diabetes. This hypothesis could not explain why Finland has the highest incidence of Type 1 diabetes in the world. In addition, assuming the theory of *trans*-complementation is correct, 60% of population-based Finnish controls were capable of forming SS heterodimers and should therefore have an underlying susceptibility to Type 1 diabetes (164).

HLA-DQ remains the best single marker for the genetic susceptibility to Type 1 diabetes as long as both loci DQA1 and DQB1 are used and not single amino acids only. However, it is now quite clear that the DRB1 locus also has an independent influence on susceptibility (184, 185) and that entire HLA haplotypes (including loci from A to DQ) are the most specific markers for Type 1 diabetes. They offer a means of grading susceptibility to Type 1 diabetes accurately. Using empirical Bayes methods and Gibbs sampling, a pure haplotype effect could be demonstrated (186). These methods confirmed that the A2, Cw1, B56, DR4, DQ8 haplotype confers an unusually high risk for Type 1 diabetes in the Finnish population for which it seems to be specific. This haplotype has not been found in Type 1 diabetes in any other population. It partly explains why Finland has the highest incidence in the world and why the incidence is still increasing (171).

Sequence determination, sequence-specific oligonucleotide hybridization, and restriction fragment length mapping are not superior to HLA serology for defining the risk of developing Type 1 diabetes. All differences detected by DNA typing so far are just more markers for the extended HLA haplotypes that are increased or decreased in Type 1 diabetes. No different patterns have been found between healthy and diabetic HLA-identical siblings using any of the molecular markers. So far molecular methods have not helped to solve the puzzle why the majority of HLA genetically susceptible individuals do not develop Type 1 diabetes. Studying the HLA system at the DNA level does not give additional clues about sporadic cases in the population.

Even though the determination of the HLA genes themselves is a major breakthrough for our understanding of Type 1 diabetes, this may not directly contribute a great deal to the prevention of

Type 1 diabetes. It seems unlikely that gene manipulation and gene therapy in humans will be possible for Type 1 diabetes in the near future. One day genetic counselling might become a reality in families with a history of Type 1 diabetes. Assuming that both parents had been HLA genotyped prior to planning a family, and that one of the four parental haplotypes turned out to be a proven very high-risk Type 1 diabetes susceptibility haplotype (for instance, the A2, Cw1, B56, DR4, DQ8 haplotype in Finland) co-segregating with Type 1 diabetes in this family, then only one of four children is likely to inherit this predisposing haplotype. Three of four children will have the same risk for developing Type 1 diabetes as the background population. Should the parents have this choice if they wanted it? Genetic counselling would only work using entire haplotypes—not single alleles or single amino acid differences—so that recombination (crossing over) could be detected. This approach has, of course, nothing to do with population screening for Type 1 diabetes-susceptible individuals.

Non-HLA Genetic Markers

Non-HLA genetic markers have been shown to be important in the NOD mouse which spontaneously develops Type 1 diabetes characterized by autoimmune insulinitis, lymphocytic infiltration in and around the islets, and autoantibodies to islet cell antigens. Genetic linkage to the murine MHC (major histocompatibility locus) on chromosome 17 was shown using experimental crosses between NOD and other diabetes-resistant mouse strains (187). *Idd-1* is located in the H-2 region in the mouse, which is homologous to the human HLA region. A genome map was constructed in the mouse using PCR (polymerase chain reaction)-based microsatellite length variants, and initially three non-MHC loci were identified: *Idd-3* on chromosome 3, which controls insulinitis; *Idd-4* on chromosome 11, which influences the age of onset; and *Idd-5* on chromosome 1 (188). None of these genes was obligatory for the development of diabetes in the NOD mouse. Further studies suggested that a minimum of nine genes are involved in Type 1 diabetes—seven confer susceptibility and two (*Idd-7* and *Idd-8*) confer protection from diabetes in the NOD mouse

(189). A polygenic basis for susceptibility to diabetes exists in the NOD mouse.

In humans, non-HLA genes have been studied in Type 1 diabetes for many years, spurred on by Risch's postulation that only 25% of the overall genetic susceptibility to Type 1 diabetes is accounted for by HLA genes (148). The results of the search for non-HLA genes were inconclusive (190). The fast acetylator phenotype (191, 192), the Lewis-negative phenotype (193) and the phenotype GLOI-I (red cell glyoxalase I coded on chromosome 6) (194) were found to be increased in Type 1 diabetes. The Kidd blood group (chromosome 18) (195) and, the Gm (14q32.3) and Km (2p12) immunoglobulin allotypes have been studied in Type 1 diabetes patients (196), as have the 5' flanking region of the insulin gene (11p5.5) (197, 198), the tyrosine hydroxylase gene (chromosome 11), the manganese superoxide dismutase (MnSOD) gene (chromosome 6q) (165), the insulin receptor (chromosome 19) (199), the T cell receptor (chromosome 7) (200) and several interleukin-1 related genes on chromosome 2q (201).

In 1994, results from a genome-wide search for genes predisposing to Type 1 diabetes using 289 microsatellite markers in affected sibling pairs were published (157). Although many chromosomal regions showed weak positive evidence of linkage to Type 1 diabetes, it was clear that there were no genes with large effects apart from the HLA region on chromosome 6. The microsatellite marker locus TNFa in the HLA class III region gave a total maximum LOD score (MLS) of 19.3 in all three data sets (*IDDM* 1). Marker loci up to 20 centimorgans from TNFa still gave MLS values over 1.0, which was taken as the threshold in this search. Evidence for linkage, with MLS values ranging from 2.1 to 1.1, was found for the insulin gene (*IDDM* 2) region (11p15), for the regions 15q26 (*IDDM* 3), 11q13 (*IDDM* 4), 6q24–27 (*IDDM* 5), 18q11–12 (*IDDM* 6), 2q31–33 (*IDDM* 7) and on several other chromosomes including 7q (CFTR) but not in all three data sets. In a study using 35 microsatellite markers on mostly the same family data sets (from the Warren Repository in the UK and the Human Biological Data Interchange in the USA) linkage between Type 1 diabetes susceptibility and a marker near the glucokinase gene on chromosome 7p was also found (202).

It seems that non-HLA genes, e.g. the insulin gene (11p. 15.5) may play a role in cases where the

HLA haplotypes carry a relatively low absolute risk (203, 204), even though a HLA-DR-dependent effect of the insulin-IGF2 region was found originally (205). When all the genes that possibly confer susceptibility to Type 1 diabetes are observed together, we can see a graded susceptibility starting from the high-risk HLA haplotypes, which alone are sufficient to predispose to the disease, to the polygenic cases where one or more non-HLA genes have to act together to reach the threshold of genetic susceptibility. Incomplete penetrance is known to exist in Type 1 diabetes and can be partly explained by the non-expression of a gene that ordinarily produces a particular phenotype. The screening of the entire genome has revealed that the majority of familial clustering of Type 1 diabetes is probably due to shared genetic factors at many different loci, and not primarily due to shared environmental factors. This is in agreement with the results from the Finnish twin study (153). Nevertheless, environmental factors are also important since they may influence the penetrance of the Type 1 diabetes susceptibility genes (206). The true estimates for the contribution of HLA and non-HLA genes to the overall genetic susceptibility to Type 1 diabetes need to be obtained from unbiased data in the future. While the Type 1 diabetes susceptibility genes are usually necessary for Type 1 diabetes, they alone are not sufficient to produce the disease. How the susceptibility genes interact with the postulated environmental factors (which have so far remained fairly elusive) during the process leading to overt Type 1 diabetes is not known. The proposed molecular mimicry between Type 1 diabetes susceptibility genes and certain putative environmental risk factors, like Epstein–Barr virus and position 49–60 on the DQ8 β -chain, is an interesting phenomenon, but it remains to be proven how relevant it really is for preventing Type 1 diabetes.

PROSPECTS FOR THE PREVENTION OF TYPE 1 DIABETES

Genetic Screening

Modification of Environmental Factors

When a screening test is applied it is necessary to know not only the levels of sensitivity and

specificity of the test, but also the predictive value of a positive test. This is the likelihood that a person with a positive test will develop the disease. It is important to note that predictive values, and hence the actual performance of the test, depend on the prevalence of disease in the target population or group. As an example, a screening test with 90% sensitivity and specificity (both of which being fairly good) will have a predictive value of 8.3% only when the cumulative incidence is 1% (which is the case for Type 1 diabetes in many populations). Even if the cumulative incidence is higher, say 5% (as in first-degree relatives of Type 1 diabetes patients), the predictive value would be only 32%. Thus, genetic screening for Type 1 diabetes in the population (determining for instance high-risk HLA alleles like DQB1*0302 and DQB1*0201 in all newborns of a hospital [227]) would necessarily yield numerous false positive results, because the occurrence of the disease is low. Even with 95% sensitivity and specificity the predictive power would never reach even 50%, i.e. more than half of the positive results would be false positives. For instance, in the Finnish population, the frequency of DR3, DQ2 and/or DR4, DQ8 is approximately 40%, producing a huge number of false positives if these alleles were used as screening tools. On the other hand, aiming at a more specific test (e.g. using DR3, DQ2/DR4, DQ8 heterozygosity as the marker in order to avoid the problem of false positives) we would find 4% of the Finnish population positive for DR3, DQ2/DR4, DQ8. This would lead to a serious loss in sensitivity since only 21% of children with Type 1 diabetes in Finland are led to a serious loss in sensitivity since only 21% of children with Type 1 diabetes in Finland are DR3, DQ2/DR4, DQ8 heterozygous. Screening with such a low sensitivity and predictive power can be considered rather useless and probably unethical as we can only estimate the genetic predisposition. It might be possible one day to develop a more sensitive test using HLA haplotypes defined very precisely by amino acid sequencing, and to apply these in a high-risk group such as the offspring of Type 1 diabetes patients in whom the risk for developing Type 1 diabetes is over 10%.

Dahlquist has suggested that for interpreting the role of risk-identifying determinants and their possible causal relationship to the etiology of Type 1 diabetes, it is important to separate non-genetic

exposures that may (1) initiate the natural history of the disease; (2) promote or accelerate this process; or (3) precipitate the clinical onset of Type 1 diabetes (207). Some of the putative risk factors for Type 1 diabetes may act at several stages in the natural history of the disease. Since we know that the induction time from the first initiating event to the onset of clinical manifestation can be long, it is possible that the exposures which can be called initiators have acted very early in life and perhaps already during the fetal and neonatal period. Potential non-genetic exposures which might be associated with the development of the disease are listed in Table 7A.7.

It is likely that these factors will only have an effect leading to Type 1 diabetes in genetically susceptible individuals, and then only in a proportion of them. Twin and family studies have shown that the concordance for Type 1 diabetes in both identical twins and HLA-identical siblings is 20–25% (153, 154). Identical twins share the same environment during fetal life (though not always) and in early childhood. Thus, it remains unclear why many (75–80%) of the genetically susceptible individuals do not get the disease even though they are exposed to environmental risk factors. This also needs to be taken into account when intervention studies are planned and the preventable fraction and statistical power calculated. Finally, it is unknown what proportion of individuals who

Table 7A.7 Non-genetic factors possibly associated with the development of Type 1 diabetes

Initiators:
Maternal–child blood group incompatibility
Viral infections
Nitrosamines
Intrauterine malnutrition:
lack of proteins or of certain amino acids; toxic agents;
caffeine
Toxic chemicals
Vaccines
Vitamin D
Cow's milk proteins or protein fragments
Promoters:
Frequent intake of food rich in simple carbohydrates or
proteins
Viral infections
Precipitator:
Infections
High growth rate
Stressful life events
Toxic chemicals

are genetically susceptible to Type 1 diabetes will develop Type 2 diabetes in later life. There are data suggesting a shared HLA genetic background to both Type 1 diabetes and Type 2 diabetes; both forms of diabetes are associated with certain HLA haplotypes (208) or HLA alleles such as DR4 (209, 210).

At present, the only practical advantage of determining HLA genotypes and other predictive markers for Type 1 diabetes in relatives of Type 1 diabetes patients is that those with a high risk of developing the disease can be observed for hyperglycemic symptoms so that ketoacidosis at the onset of overt diabetes can perhaps be avoided. According to a survey in Japan in the 1960s and 1970s, 1 in 200 children with newly diagnosed Type 1 diabetes died of ketoacidosis at the clinical onset of, or during the first years of, the disease (211).

It is to be hoped that the high-risk approach will be of more use in the future when a better understanding of the pathophysiologic mechanism of the disease has been achieved and the environmental factors have been clarified. As not all siblings or offspring defined to be at high risk by HLA genotyping and with the existing immunologic and clinical markers develop diabetes, it is unethical to attempt immunotherapy in these still healthy children (212, 213).

Even though it is possible to define HLA antigens on fetal cells obtained through amniocentesis to ascertain the HLA status prenatally, this does not help in Type 1 diabetes as yet. An even more difficult approach is to try to prevent Type 1 diabetes in the entire population. The environmental factors that precipitate Type 1 diabetes are not well understood and more research in this area is definitely needed. Even though rapid methods of screening for HLA antigens exist, the costs of such screening would outweigh the potential benefit. HLA screening programs will be useful and ethical only when the environmental determinants of Type 1 diabetes are better understood.

Once clinical symptoms are detectable, the majority of islet β -cells have already been destroyed. Nevertheless, trials with cyclosporin A (214, 215) and a combination of azathioprine and prednisolone (217–219) have shown some positive results in newly diagnosed Type 1 diabetes patients, indicating that it might be possible to protect the residual β -cell function. The well-known ‘honeymoon period’, i.e. improved β -cell

function after the initiation of insulin therapy, also indicates that secondary prevention may have some effect but only for a short period of time. Nicotinamide has been tested in newly diagnosed Type 1 diabetes patients with conflicting results (219–222).

Intervention at the time of clinical onset cannot be expected to normalize insulin secretion. All studies have indicated that patients with the largest β -cell reserves responded best to various therapeutic strategies. For effective secondary prevention, interventions in the disease process before clinical symptoms appear are more likely to be successful in maintaining endogenous insulin secretion. It has been shown that nowadays the diagnosis of Type 1 diabetes is often made when appreciable β -cell mass is still preserved (223). Thus, it has been proposed that in the future immunological prevention attempts should first be tested in newly diagnosed Type 1 diabetes patients before they are applied in larger trials for prevention in prediabetic, asymptomatic subjects who may be at high risk of developing Type 1 diabetes. Because the evolution of Type 1 diabetes is immunologically mediated, there have been attempts to intercept this process by immune intervention (224). A large number of immune intervention trials carried out thus far have failed to show a clinically beneficial response (225).

In 1990, the US National Institutes of Health convened a workshop to discuss the prevention of Type 1 diabetes. The position statement which was corrected in 1994 declared (226):

1. Sufficient data exist to warrant studies for the prevention of Type 1 diabetes.
2. Intervention for the prevention of Type 1 diabetes should be attempted only in the context of defined clinical studies with Institutional Review Board oversight.
3. Intervention studies for the prevention of Type 1 diabetes are best accomplished by randomized controlled studies.
4. A registry of intervention studies should be maintained, and all planned studies should be reported to a coordinating body.

In addition, it was mentioned in the statement that screening of any population is discouraged outside the context of defined research studies. Two major issues have to be considered if screening of a

population is contemplated: (1) the performance of the proposed test, and (2) the prevalence (cumulative incidence) of the disease.

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Type 1 Diabetes: Prediction Based on the Genetic-Epidemiological Facts in the 90s

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The possibility of preventing Type 1 diabetes has gained increasing attention over the last decade. Prevention of the disease, however, requires effective and safe methods of intervention as well as reliable ways to predict the development of the disease at individual level. We here review the genetic-epidemiological aspects related to the prediction of Type 1 diabetes, with a view to the current appreciation of the aetiology of the disease.

THE AETIOLOGY OF TYPE 1 DIABETES: EVIDENCE OF A GENETIC CONTRIBUTION

The importance of genetic susceptibility to Type 1 diabetes is clearly demonstrated by twin and family studies. It has been suggested that the concordance rate of Type 1 diabetes in identical (monozygotic) twin pairs is 25–60% against 10–15% in non-identical (dizygotic) twin pairs (1,2,3). Several family studies have found rather consistent estimates of recurrence risks of Type 1 diabetes at about 5–10% among siblings and children of Type 1 diabetes patients (4,5).

In Caucasian populations strong associations with Type 1 diabetes are found for the HLA markers DR3 and DR4 and their DNA analogues at the HLA-DQ locus (6), particularly when present in the heterozygous state DR3/DR4. HLA-DR2, and maybe DR5, seems to confer protection against Type 1 diabetes. The degree of haplotype sharing in siblings from Type 1 diabetes families influences the recurrence risk considerably, with an estimated recurrence risk of about 15–20% for HLA-identical siblings, a risk of about 6% for haploidentical sibs and close to 0% for non-identical sibs (7). It is important to note that the estimated risk for HLA-identical siblings

seems to be considerably lower as compared with the concordance rate in monozygotic twins. On the other hand, the risk for HLA-identical siblings is considerably higher than the risk among unrelated individuals that carry high-risk HLA-markers (i.e. the HLA-DR3/DR4 heterozygous category).

The influence from genetic factors outside the HLA-region has been suggested for some years (8). Humane genome mapping has made it clear that the genetic susceptibility to Type 1 diabetes may be linked to several loci (9), including the insulin gene region on chromosome 11 (10,11) and other loci (10). In addition, non HLA-linked susceptibility to Type 1 diabetes agrees with the higher concordance rate among monozygous twins as compared with HLA-identical siblings although a higher degree of sharing of environment in twins may also contribute to this difference.

Although no definite models of the genetic susceptibility in Type 1 diabetes have been obtained, it seems that simple dominance is unlikely, and that the frequency of the disease susceptibility gene(s) is rather high with a low penetrance (12,13,14). Thus, the largest contribution to the pool of susceptibility genes originate from non-affected individuals. This agrees well with the fact that 80–90% of newly diagnosed children represent single case families, i.e. without prior known cases of Type 1 diabetes among close relatives (5).

THE AETIOLOGY OF TYPE 1 DIABETES: EVIDENCE OF A NON-GENETIC CONTRIBUTION

The most striking evidence of a non-genetic contribution to Type 1 diabetes relates to the fact

that the concordance rate in monozygotic twins is far below unity (1,2,3). Since monozygotic twin partners have identical genes, this difference can only be attributed to the influence of non-genetic exposures. Two additional lines of evidence provide support for the non-genetic contribution. First, the huge variation in the incidence of Type 1 diabetes between Caucasian populations (16) cannot be explained by the geographical distribution of susceptibility genes. Second, the rising incidence of Type 1 diabetes, as observed in many European populations (17), cannot possibly be explained by increased size of the pool of susceptibility genes (18) and must be attributed to increased susceptibility in individuals at genetic risk and/or the introduction of environmental causative agents in these populations.

The search for non-genetic determinants of Type 1 diabetes has been intensified over the last decade and has focused on viral infections, nutritional factors, stressful life events, and socio-economic status (19,20) and recently also on the intrauterine environment (21).

Virus infections have for a long time been implicated in the causation of Type 1 diabetes (22). It has been demonstrated that congenital rubella infection is associated with a high risk of subsequent development of Type 1 diabetes (23). The development of Type 1 diabetes has also been associated with cytomegalovirus infection, mumps and Coxsackie B infections (24). The mechanisms by which infectious agents cause β -cell destruction by immune-mediated mechanisms are largely unknown although various hypotheses have been presented recently (25,26). It may also be possible that viral infections are associated with clinical precipitation of Type 1 diabetes in subjects suffering from ongoing β -cell destruction.

Following the results from animal studies that dietary changes influence the incidence of diabetes (27), several studies in humans have focused on the possible role of dietary factors in Type 1 diabetes.

A study from Iceland suggested that exposure to nitrosamines in women at the time of conception may increase the risk of Type 1 diabetes in the male offspring (28). Some support to this concept has come from the case-control studies in Sweden (29,30) and Finland (31), but the finding needs confirmation and does not explain the high Type 1 diabetes incidence level in populations where exposure to nitrosamines is less common than in Iceland.

The association between Type 1 diabetes and breastfeeding has been extensively studied since a Danish study (32) found that reduced length of breastfeeding during infancy seems to be associated with increased risk of developing Type 1 diabetes. The literature on cow's milk exposure and Type 1 diabetes has been reviewed extensively (33,34). In general, the associations described have been weak and, if causal, can explain the development of diabetes in only a limited number of cases. Also, changes in breast feeding habits over time as well as recall biases are potential confounders that are difficult to control.

The possible association between reduced breastfeeding and Type 1 diabetes risk may reflect an aetiological role of cow's milk protein, as indicated by a much higher occurrence of antibodies to cow's milk protein in newly onset diabetic children as compared with control subjects (35,36). This possible association is in accordance with migrant studies from New Zealand, demonstrating that Samoan children in New Zealand, following introduction to milk formula, increased their risk of Type 1 diabetes as compared with children in Samoa (37). Accordingly, the increased Type 1 diabetes risk among children with lack of or with reduced duration of breastfeeding might be explained by early introduction to a protein that acts as a trigger for the immunological destruction of the β -cells, possibly by cross-reaction with a membrane protein(s) of the β -cell (38).

A few studies have addressed the possible aetiological role of psychological factors and stressful life events in the period preceding clinical onset of disease. Although with rather weak associations, several reports have provided consistent evidence of such possible influences (39,40,41). It is possible that stressful life events and psychological dysfunction, through elevated stress hormone levels, increase the demand for endogenous insulin production and thereby accelerate clinical precipitation of Type 1 diabetes in individuals with ongoing β -cell destruction.

Conflicting results have been reported regarding the associations between socio-economic status and Type 1 diabetes. A Danish study (42), in the Copenhagen area, found higher incidence of Type 1 diabetes in regions with relatively low average income level, whereas a study in North America found an opposite trend (43). In both

studies, the associations were rather modest only. In a Swedish case-control study (19) a positive, but rather weak association between Type 1 diabetes and low educational and income level was found. Such associations are probably explained by unknown events and factors in lifestyle that may influence the risk of developing Type 1 diabetes as well as the socio-economic status (19).

Low weight at birth or weight at one year of age are associated with increased risk of subsequent development of impaired glucose tolerance and Type 2 diabetes, maybe because intrauterine malnutrition during critical periods of fetal life and infancy will lead to a suboptimal development of the endocrine pancreas. This could theoretically have implications for the pathogenesis of Type 1 diabetes as well. However, the small number of studies performed have not found evidence of an association between low birthweight and Type 1 diabetes (44). On the contrary, a Swedish case-control study (21) found that the risk of developing Type 1 diabetes was lowest in children small for gestational age and highest in children large for gestational age. In our own twin study there was no association between birthweight and Type 1 diabetes, and variables related to birthweight and length could not explain why some pairs are concordant while other remain discordant (44).

THE AETIOLOGY OF TYPE 1 DIABETES: SUMMARY

With all currently available information considered together, there seems to be no doubt that Type 1 diabetes develops as the consequence of interaction(s) between genetic factors and non-genetic determinants, leading to an immune-mediated process of β -cell destruction which may be ongoing for several years before Type 1 diabetes presents clinically. This is schematically illustrated in Figure 7B.1. Many details of the aetiological determinants remain to be established, particularly how genetic factors interact with non-genetic determinants in the activation of the immune system. Possibly, each of several distinct combinations of genetic markers may, when exposure to relevant environmental factors takes place, induce the disease process that represents the unique pathogenetic feature of Type 1 diabetes. Possibly, other factors (?stress, ?infections)

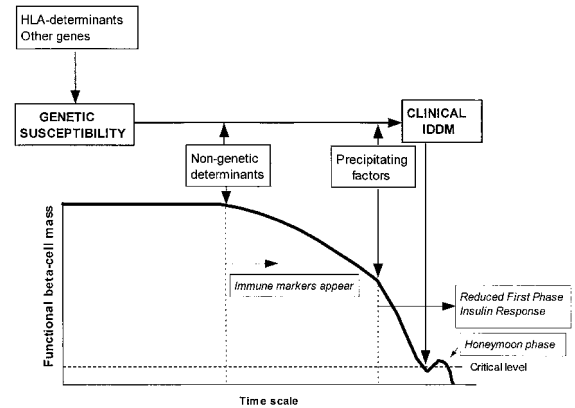


Figure 7B.1 Graphic illustration of the disease process and development of Type 1 diabetes

may accelerate the process to the precipitation of clinical disease. If so, this aetiological heterogeneity implies severe difficulties in finding a unified approach to prediction and prevention of Type 1 diabetes which may apply to all subjects at risk in different populations.

PREDICTION OF TYPE 1 DIABETES: YES OR NO?

The main reason for predicting Type 1 diabetes is the provision of possible intervention before clinical disease develops (45, 46, 47, 48). Current strategies for the prevention of Type 1 diabetes include cow's milk exclusion, treatment with nicotinamide and prophylactic treatment with insulin (48). A rational basis for establishing intervention for preventive purposes in the general population has not yet been developed and the current preventive strategies are restricted to controlled clinical trials among subjects considered at high risk of developing Type 1 diabetes (48). Even though such subjects represent only a minority of the general population, the outcomes of ongoing trials will most likely offer a better understanding of the natural history and causation of Type 1 diabetes, in addition to providing quantitative assessments of the performance of the available strategies.

The potentially adverse effects of predicting a disease like Type 1 diabetes include anxiety in individuals who are classified as being at high risk

without well-established hopes for prevention. This is of particular concern in subjects who are found to be falsely positive by means of some test measure. Type 1 diabetes develops predominantly in children, adolescents and young adults and this underlines the need to consider seriously all the ethical aspects related to predicting Type 1 diabetes.

PREDICTION OF TYPE 1 DIABETES: AVAILABLE MARKERS

The current appreciation of the aetiology and pathogenesis of Type 1 diabetes has important implications for prediction of the disease. Until immune markers appear in the circulation, the only available and reasonably well-established markers of Type 1 diabetes are represented by genetic determinants (Figure 7B.1). The appearance of immune markers signifies an activation of the immune system which to a high degree correlates with an ongoing destruction of the β -cells of the pancreas. When a sufficiently large part of the cells has been destroyed metabolic decompensation develops, with clinical presentation of Type 1 diabetes as the consequence. This may be preceded by the demonstration of reduced response in insulin secretion to a glucose challenge. The scenario provides for the establishment of several types of markers in predicting Type 1 diabetes.

As mentioned above, Type 1 diabetes tends to cluster in families due to sharing of genetic susceptibility factors. A positive family history of Type 1 diabetes, e.g. the presence of Type 1 diabetes among first-degree relatives of a given subject, is therefore *per se* a marker for predicting Type 1 diabetes. This is most strongly illustrated from estimation of probandwise concordance rates in twin studies, implying a long-term risk of Type 1 diabetes mounting to 60% or even higher for monozygotic (identical) twin partners in some studies (3). However, for first-degree relatives other than twins the long-term recurrence risks are considerably lower and even further reduced when moving to more remote categories of relatives (4). In spite of the genetic susceptibility to Type 1 diabetes, by far the majority of newly diagnosed patients will have a negative family history (15). Overall, when considering family history as the only marker the ability to predict Type 1 diabetes seems rather modest. Nevertheless, a positive

family history may serve as an important instrument for selecting and recruiting subjects for preventive trials in which additional types of markers are employed (see below).

Since associations between Type 1 diabetes and genetic markers from the HLA system were described more than 25 years ago, an increasing number of genetic susceptibility factors has been characterized. Prediction of Type 1 diabetes on the basis of the presence of genetic markers may thus supplement and enhance information from family history. However, currently defined genetic markers of Type 1 diabetes occur frequently in unaffected subjects, and it can be calculated (as illustrated below) that the absolute cumulative lifetime risk in unrelated subjects carrying high-risk markers probably does not exceed 5–10%. This condition, combined with ethical and logistic problems, restricts the utilization of genetic markers for predictive purposes to individuals already classified as being at increased risk from a positive family history.

The presence of immune markers in the circulation, even years before clinical presentation of Type 1 diabetes, is believed to signify an ongoing immune-mediated destruction of the β -cells (49). Currently defined immune markers of Type 1 diabetes include islet cell antibodies (ICA) (50), insulin autoantibodies (IAA) (51) and autoantibodies to glutamic acid decarboxylase (GAD) (52, 53). The utilization of immune marker assays, particularly when combined, has become particularly important over recent years as an instrument for identifying candidates for enrolment in intervention trials as extensively developed in England (54, 55). The prevalence of high-titer immune markers is relatively low in the general population (56), thereby restricting their application to clinically unaffected relatives of patients with Type 1 diabetes (55).

Assessment of β -cell function provides for the establishment of the class of metabolic markers of Type 1 diabetes. Impaired secretion of C-peptide, with or without preceding glucagon-stimulation, indicates severely impaired ability to produce insulin or to respond to increased demands of insulin. Reduced first phase insulin response to an intravenous glucose challenge strongly predicts subsequent development of clinical Type 1 diabetes and need of insulin treatment (57). Probably, both markers become positive very late in the

prodromal (preclinical) phase (Figure 7B.1) at a time where it may be too late to use them for intervention purposes.

PREDICTION OF TYPE 1 DIABETES: METHODOLOGICAL CONSIDERATIONS

Prediction of a chronic disease like Type 1 diabetes involves a quantitative assessment of the risk of developing the disease. At the most basic level, ignoring specific markers, the disease risk may be estimated from the population incidence by the relationship

$$R_{t=1,2} \approx 1 - \exp\{- (INC \cdot (t_2 - t_1))\}$$

where $R_{t=1,2}$ represents the cumulative risk of developing Type 1 diabetes over the period (usually in years) from $t = 1$ to $t = 2$ in the general population, and INC represents the population incidence (expressed as number of new cases per person-year at risk) applicable to this period and assumed constant. For a relatively rare disease like Type 1 diabetes the quantity $INC \cdot (t_2 - t_1)$ is usually small (<0.05); under these circumstances, the relation approximates the more simple expression

$$R_{t=1,2} \approx INC \cdot (t_2 - t_1).$$

Thus, if the population incidence of Type 1 diabetes among children aged 0–14 years is 16 per 100 000 person-years, the cumulative risk of developing Type 1 diabetes over a period of five years may be estimated to 0.08% ($=0.00016 \text{ year}^{-1} \cdot 5 \text{ years}$). Since no markers are involved, the estimated disease risk is applicable to all subjects at risk in the population concerned under the implicit assumption of equal risk for all such subjects.

Access to information of markers associated with the disease enhances risk assessment and prediction. Now, the population can be divided according to marker status and subsequent disease development. Table 7B.1A illustrates this for a cohort approach in which a out of $a + b$ marker-positive subjects develop disease within a given follow-up period, and c out of $c + d$ marker-negative subjects develop disease. The population risk, R , is $(a + c)/(a + b + c + d) = (a + c)/N$.

From the entries and totals of Table 7B.1A, the relevant measures of test performance can be derived immediately. These measures include the predictive value of a positive test (PPV), the predictive value of a negative test, sensitivity (SENS) and specificity (SPEC), see Table 7B.1B, left and centre columns. Whereas SENS and SPEC may be estimated from random samples of patients and unaffected subjects, respectively, the direct estimation of the predictive values from the entries of Table 7B.1A requires that patients and unaffected subjects are represented in numbers proportionate with the distribution in the general population. Formally, this is expressed in the following important relation, derived from combining and rearranging the estimates of the individual measures:

$$PPV = (SENS \cdot R) / \{(SENS \cdot R) + [(1 - SPEC) \cdot (1 - R)]\}.$$

This expression permits the estimation of PPV on the basis of the marker distributions in random samples of patients and unaffected subjects (Table 7B.1A and B), if an estimate of the general population risk is available. The expression also illustrates the complicated relationship between, on one side, the positive predictive value and, on the other side, the general population risk, sensitivity and specificity. The positive predictive value will differ from population to population by differences in population risk, even should both sensitivity and specificity be identical across populations. Accordingly, assessments of the performance of a given marker assay for predictive purposes are specific for a given population and cannot without due consideration to this fact be generalized to other populations.

The measures of test performance may be expressed in epidemiological terms as shown in

Table 7B.1A The 2×2 table illustrating the population distribution by marker status and disease

	+Type 1 diabetes	–Type 1 diabetes	Total
Marker +	a	b	$a + b$
Marker –	c	d	$c + d$
Total	$a + c$	$b + d$	$N = a + b + c + d$

General population risk, R : $(a + c)/N$.

Table 7B.1B. Measures of test performance, their estimation and epidemiological correlates

Measure of test performance	Estimation	Corresponding epidemiological measure
Positive predictive value, PPV	$a/(a + b)$	Disease risk among marker-positive subjects, R_E
Predictive value of negative test	$d/(c + d)$	Disease-free survival in marker-negative subjects, $1 - R_0$
Sensitivity, SENS	$a/(a + c)$	Proportion of marker-positive patients
Specificity, SPEC	$d/(b + d)$	Proportion of marker-negative subjects remaining disease-free

Table 7B.1B, right-hand column. For example, the positive predictive value (PPV) corresponds with the absolute disease risk among marker-positive subjects. This appreciation is important because the association between a disease and a marker is often summarized as the so-called relative risk from which the absolute risk among marker-positive subjects (=PPV) may be estimated if knowledge of the population risk, R , is available. The relative risk, RR , contrasts in a ratio the disease risk in marker-positive subjects with that in marker-negative subjects, i.e.

$$RR = R_E/R_0.$$

With the definitions in Table 7B.1A, R_E (=PPV) is estimated from $a/(a + b)$, and R_0 from $c/(c + d)$. For a relatively rare disease like Type 1 diabetes, the ratio R_E/R_0 approximates $(a \cdot d)/(b \cdot c)$ which is also known as the cross-product ratio or odds ratio of the 2×2 table, well known from association studies.

Now, the population risk, R , represents the weighted average of R_E and R_0 , the weights being provided by the population prevalence, P_M , of the marker:

$$R = (P_M \cdot R_E) + \{(1 - P_M) \cdot R_0\}.$$

When using the relationship $RR = R_E/R_0$, this expressing can be rearranged to estimate R_E :

$$R_E = (RR \cdot R) / \{1 + P_M \cdot (RR - 1)\}.$$

Let us assume that the population risk of Type 1 diabetes over a period of 5 years is 0.08% (as before), and that a case-control study has found a relative risk of 50 for a marker with a population prevalence of 0.20. These data yield an estimated value of R_E (and therefore also PPV) at 0.37%. In the same population, a marker conferring a relative risk of 50 but with a population marker

prevalence as low as 0.01 would lead to an estimated value of R_E at 2.68%. For populations with lower general disease risk, the estimates would be correspondingly reduced.

As a contrast, let us consider a high-risk population, for example unaffected first-degree relatives of Type 1 diabetes patients. The incidence, and hence risk, may be assumed to be about 5–10 times higher than the risk in the general population; this corresponds with a cumulative risk over 3 years at, say, 0.5%. Let us further assume that the relative risk of the marker remains at 50, but that the marker has a prevalence of 0.30 in this group of subjects. Now, the estimated R_E comes out at 1.59%. This figure may seem surprisingly low, but nevertheless the marker data have made it possible to classify the 70% marker-negative subjects in this prior defined high-risk group as having a negligible risk ($= R_E/RR = 1.59/50 = 0.03\%$).

The numerical data used in these examples are fairly representative for currently defined genetic and immune markers in societies at medium-to-high population risk of Type 1 diabetes. The exercise demonstrates clearly that prediction of Type 1 diabetes on the basis of any single marker leads to low positive predictive values. Even in subjects classified as being at a high risk from a positive family history of Type 1 diabetes, the performance, when assessed by estimated values of PPV, is rather modest. The main challenge in this respect involves the utilization of combined marker information as the basis of improved prediction of Type 1 diabetes.

PREDICTION OF TYPE 1 DIABETES: A HYPOTHETICAL EXAMPLE

Numerous recent studies have illustrated how combined marker information enhances the prediction of Type 1 diabetes (58), particularly in connection with preventive trials (48). The approach is

most conveniently illustrated by a numerical example. In this section we use a positive family history of Type 1 diabetes (FH) as the first step marker which is combined with the presence of a genetic susceptibility marker (GM) as the second step marker. We apply hypothetical data which we, however, consider to be fairly representative for a country such as England with well-established traditions in epidemiological and clinical diabetology (48, 54, 55, 56, 58).

First of all, we consider a population of unaffected children aged 0–14 years. For convenience, the population size will be fixed at 1 000 000 subjects which we assume to follow during a period of 5 years. The incidence of Type 1 diabetes (ignoring marker status) may be set at 0.00016 per person-year at risk, corresponding with an absolute disease risk at 0.08% over 5 years. Secondly, we assume that 1.0% of the subjects in this population has a positive family history (FH) and that subjects with positive FH have a risk of 0.88%; this is plausible considering the population incidence level. A given genetic susceptibility marker (GM) has a population prevalence of 0.02 (2.0%), which is of the order of magnitude of the frequency of one of the currently defined genotypes conferring high risk of Type 1 diabetes. However, within the FH-positive subjects the prevalence of GM is assumed to be 25% due to the prior probability of sharing any given genotypes with a sibling. The presence of GM is assumed to confer an absolute risk of 1.0% over 5 years in FH-negative subjects; this agrees with estimated absolute risks at 5–10% over an extended period for unrelated subjects with a high-risk genetic marker of Type 1 diabetes (as mentioned before). However, in FH-positive subjects it is assumed that the disease risk over 5 years is 2% due to the effects of sharing additional risk factors with affected relatives. Under these assumptions the population distribution according to this dual marker system will be realized as shown in Figure 7B.2. The absolute risks as obtained from assumptions and implications are also shown, together with the corresponding estimated number of new cases of Type 1 diabetes over a period of 5 years.

The most important measures of test performance are presented in Table 7B.2. The positive predictive values (and, thus, the marker-specific absolute risks of developing Type 1 diabetes) are given by assumptions or implications in this

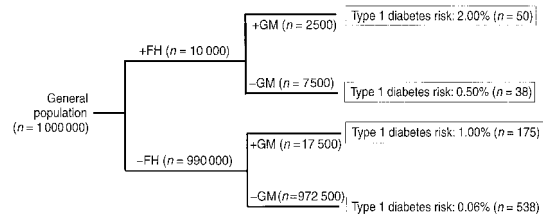


Figure 7B.2 Distribution according to positive family history (FH) and presence of a genetic marker (GM) in a population of 1 000 000 children. Assumptions: see text

example, but are realistic for reasons given before. Their low level, even for the combined marker-positive category, indicates that the large majority of marker-positive subjects will remain disease-free for a substantial period of time. Nevertheless, these subjects represent the target group for potential prevention of Type 1 diabetes. Most importantly, this dual screening strategy, which in the first step is based on anamnestic information only, has allowed for the classification of more than 97% of the whole population as belonging to a very low-risk category. In spite of this, the estimated values of sensitivity (SENS) in Table 7B.2 indicate that the majority of new cases of Type 1 diabetes will not be predicted by these markers, neither when applied as single markers nor when combined.

It must be stressed that hypothetical examples like the one above are very sensitive to changes in the underlying assumptions which, for reasons mentioned earlier, most likely will differ from population to population. Until more precise population-based assessments of various strategies

Table 7B.2 Positive predictive value (PPV), sensitivity (SENS), specificity (SPEC) and relative risks (RR) for markers in the prediction of Type 1 diabetes

Marker	PPV (%)	SENS (%)	SPEC (%)	RR
Single markers:				
FH alone	0.88*	10.94	99.01	12.16
GM alone	1.13*	28.13	98.02	19.17
Markers combined:				
FH and GM	2.00*	6.25	99.75	36.19**

FH: Positive family history GM: Genetic marker Hypothetical data.

* Assumed values, expressed as estimated cumulative risk of Type 1 diabetes over 5 years.

** Expressed relative to being negative for both markers.

in the prediction of Type 1 diabetes are available, different sets of assumptions should be explored in corresponding scenarios. The principles and methods illustrated above may be useful for such purposes. The methods may be further refined by stratification within a marker category, e.g. distinguishing between subjects at low versus high ICA-titer.

CONCLUDING REMARKS

Until now, prediction of Type 1 diabetes has relied on family history and the presence of genetic and immune markers. By combination with metabolic markers of impaired β -cell function, prediction may be considerably enhanced, but may be of limited practical value because of advanced β -cell destruction at the time these markers become positive. In the future we will most likely witness a refinement in laboratory methods to establish more specific immune markers, and further details on the genetic factors conferring susceptibility to Type 1 diabetes will be revealed. For the time being, the utilization of prediction in preventive trials is currently restricted to the relatively few subjects who, by means of a positive family history of Type 1 diabetes, may be considered as having a high disease risk. With our existing knowledge of the causation and pathogenesis of Type 1 diabetes, the ability to predict the disease is characterized by a rather modest level of performance, as clearly indicated by low predictive power and relatively low sensitivity, and will not assist in reducing the public health burden of Type 1 diabetes to any significant extent. Yet, quantitative prediction of Type 1 diabetes has a role to play as an instrument in the efforts to separate unaffected subjects in a small group at relatively high disease risk from the vast majority of subjects at very low risk. This is of particular importance if/when measures to prevent Type 1 diabetes can be applied to the population at large. In this context, it must be kept in mind that the impact at population level of predicting and preventing Type 1 diabetes varies between societies because the performance of predictive markers is closely related with levels of disease risk and distribution of markers within a given population. Therefore, generalization of results and estimates from one population to another must be done with due consideration to these

aspects. To improve this situation it is necessary to incorporate the influence of non-genetic aetiological factors in the future methods of predicting Type 1 diabetes and to develop strategies that apply to specific populations. This requires much more knowledge about the geographical variability, nature and mechanisms of aetiological factors, particularly concerning their relationship with immune and genetic markers. Further research along these lines is promising since non-genetic determinants, in contrast to genetic factors, are potentially modifiable for preventive purposes. Predictive strategies that incorporate non-genetic factors may therefore lead to new avenues in the prevention of Type 1 diabetes.

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Type 1 Diabetes: Atypical Diabetes in Young People Across the World

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INTRODUCTION

For about two decades there have been reports of atypical diabetic syndromes among young people of Asian, African, and Latin American origin (1–5). Type 2 diabetes is increasingly being recognized as a disease of children in the US, as well. These patients are typically diagnosed at first with Type 1, insulin-dependent diabetes mellitus. Their subsequent clinical course shares many characteristics of Type 2, non-insulin-dependent diabetes mellitus, so that the syndrome is often described as an intermediate form of diabetes. They exhibit many of the classic symptoms of Type 1 diabetes at onset (i.e. weight loss, polyphagia, polydipsia, polyuria, ketonuria or ketoacidosis), but the need for insulin therapy diminishes markedly after several months or years. More recently, children and adolescents with classic insulin-resistant Type 2 diabetes (Early 2) have been more frequently reported in case-series and clinic-based reports. These reports have rekindled interest in defining more clearly the spectrum of diabetes mellitus among children and adolescents (Figure 7C.1). Speculation continues regarding the etiology of insulin-resistance and Type 2 diabetes in children, focusing on both genetic factors (e.g., admixture) and environmental causes (e.g., obesity). The scientific literature is currently so sparse that any single comprehensive theory cannot be supported. Nonetheless, work on the descriptive epidemiology as well as the metabolic disturbances associated with Early 2 has begun.

Key research questions in this area focus on how best to describe early-onset Type 2 diabetes along the continuum of glucose tolerance in young

people in terms of descriptive epidemiology (i.e. prevalence and incidence rates) as well as etiology (i.e. metabolic, behavioral, genetic and immunologic risk factors). Identifying risk factors distinguishing Type 1 diabetes from Early 2 is of particular clinical relevance in order to optimize treatment regimens. Certainly, major improvements in quality of life and compliance can be projected if young patients can be treated with oral hypoglycemic agents rather than insulin. The onset of Type 2 diabetes compounds the normal stresses and strains of maturation in adolescents who have a condition requiring regular blood glucose monitoring, multiple pills and/or injections, and strict attention to diet and exercise. Nonetheless, the payoff is important: the risk of diabetic retinopathy and kidney disease can be substantially reduced if strict blood glucose control is maintained over an extended period of time (6). As noted four decades ago (7),

‘Management of the adolescent who has any one of the chronic or handicapping diseases presents difficulty, but that of the adolescent who has diabetes would seem to be the most challenging and demanding, for here the damage is not already done—as is unfortunately true with many other conditions—but may, if the handling is much less than ideal, become irreparable’.

Longitudinal data show that Type 1 diabetes duration before puberty does not add to the risk of developing chronic complications. Individuals diagnosed during puberty have an increased risk of death, compared to those who were diagnosed in childhood (8). Clinicians often report that self-management of diabetes deteriorates at puberty, even among previously well-motivated, adherent

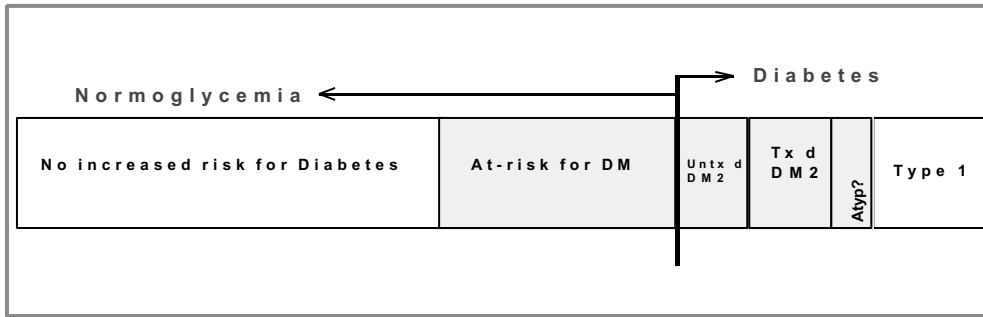


Figure 7C.1. The continuum of glucose tolerance in young people

individuals. Developing reliable criteria for distinguishing Type 1 diabetes from non-insulin-requiring diabetes early in the course of the disease has the potential to markedly enhance the treatment adherence of adolescents with Early 2 and thereby improve their quality of life over many years.

THE RANGE OF DIABETES IN YOUTH

Surveys for diabetes among children and young adults from many geographic locations reveal a spectrum of clinical characteristics. The majority of young European-origin patients appear to fit the clinical picture of Type 1 diabetes, while the prevalence of Maturity-onset Diabetes of Youth (MODY) is estimated at 1–3% (9). In other ethnic groups Type 2-like syndromes are reported more frequently among children, although no consensus on defining characteristics has yet emerged. Winter's classic case-series, published in 1987 (1), described 12 of 129 African American patients with an atypical disease course, an absence of the Type 1 diabetes-associated HLA variants and no detectable islet cell antibodies (ICA). C-peptide levels in these patients were intermediate between those of Type 1 diabetes patients and non-diabetic subjects. Additional characteristics resembling Type 2 diabetes were observed, such as obesity and a high prevalence of diabetes among relatives. These patients were ultimately characterized as having 'atypical' disease.

The possibility that an intermediate form of diabetes is etiologically distinct received an enormous boost in 1997, with the addition of 'Type 1b' to the newly revised WHO/ADA classification

scheme for diabetes mellitus as a non-autoimmune, idiopathic form of Type 1 diabetes. In the third NHANES study, conducted between 1988 and 1994, 13 of 2867 subjects aged 12–19 years were considered to have diabetes based on insulin treatment ($n=9$), treatment with oral agents, or elevated fasting glucose levels. The overall prevalence of diabetes in this age group was therefore calculated to be 4.1 per 1000, with an estimate that at least 31% of these subjects had Early 2 (10). The NHANES-3 estimate, while based on an extremely small number of cases, included non-Hispanic whites, African Americans and Mexican Americans in the sampling frame. On the other end of the age range, Zimmet and colleagues defined a syndrome, latent autoimmune diabetes of adults (LADA), to distinguish lean, ketosis-prone individuals with diagnosis of diabetes in adulthood that progressed more or less rapidly to insulin dependence (11). Taken as a whole, these developments undermine the conventional practice of categorizing diabetes as either autoimmune Type 1, or insulin-resistant Type 2. Aizawa and colleagues (12) suggest that a combination of many factors, including susceptibility genes, viral infections, immune attack, aging, variation in the beta-cell mass at birth and glucose toxicity, can operate to cause beta-cell damage and insulin resistance. They advocate a comprehensive view of the etiology of diabetes, taking these many factors into account for all patients.

ETIOLOGIC HYPOTHESES

Speculation regarding the etiology of atypical diabetic syndromes or youth-onset Type 2 diabetes has been ongoing, and has centered on genetic

factors (i.e., admixture) as well as on environmental causes (e.g., obesity). The scientific literature is currently so sparse that any single comprehensive theory cannot be supported.

It may be that, compared with adults, glucose intoxication in young people at the outset of a Type 2-like disease is generally more severe: marked hyperglycemia disrupts both the insulin secretory response and insulin signaling (13). Once initial metabolic decompensation is resolved, beta-cell function returns somewhat, allowing patients to avoid repeated bouts of ketosis despite, in many cases, poor glycemic control. In this scenario, the initial cause of metabolic disruption might be related to obesity, hormonal changes associated with puberty, and/or genetic factors. The prognosis for these patients would then be similar to that of Type 2 diabetes, depending largely on the level of glycemic control and a gradual, long-term deterioration of beta-cell function.

Another possibility could be related to the presence of susceptibility genes for both Type 1 and Type 2 diabetes in the same patients, so-called 'double diabetes' (14). This is a particularly attractive hypothesis when discussing young people from ethnic groups which are at high risk for Type 2 diabetes, such as African Americans and US Hispanics. Presumably, reduced beta-cell activity due to autoimmune processes could precipitate overt diabetes earlier in the course of insulinitis among patients who are already genetically predisposed to insulin-resistance.

EARLY-ONSET TYPE 2 DIABETES: TEMPORAL TRENDS, ETHNICITY AND DISTINCTIVE FEATURES

A number of clinic-based studies in the US demonstrate an increasing rate of diagnosis of Type 2 diabetes among children. At the Cincinnati Children's Hospital, the major pediatric referral hospital in the region, 54 of 1027 diabetic patients age 0–19 (5.3%) met criteria for Type 2 diabetes over a 13-year period. Type 2 diabetes accounted for 2–4% of all diabetes diagnosed before 1992; in 1992–94 the proportion increased to 8–17% of all incident cases. Most patients were diagnosed during a routine physical exam rather than by demonstrating the classic symptoms of diabetes onset. Incidence of Type 2 diabetes was higher in

African Americans and in females; the majority of these patients were obese (mean body mass index [BMI] was 37.7 kg/M²) and had a first- or second-degree relative with diabetes. The investigators pointed to the rising prevalence of obesity among young people as a likely etiologic factor. Interestingly, there was also a concurrent and significant increase in Type 1 diabetes in this population observed over the same period of time (15).

Similar data were reported from Arkansas in a retrospective chart review of 50 cases of childhood Type 2 diabetes diagnosed over 8 years (16). Again, a striking increase in the frequency of the diagnosis was observed, particularly in the last years of the study. Compared with 50 Type 1 diabetes patients from the same hospital, young Type 2 diabetes patients were more likely to be African American (74%), female, and older at diagnosis. In Cincinnati, young African American patients could be distinguished from non-Hispanic white youngsters with similar diagnoses by the severity of presentation: fully 25% were in diabetic ketoacidosis (DKA) at onset, as compared with none of the whites (17). Vargas and colleagues (18) reported on 19 cases of Type 2 diabetes seen in their New York City clinic over a 2-year period; 42% were referred for obesity and had hyperglycemia on screening, while the remainder were referred for polyuria. Minority children were overrepresented (47% Hispanics, 37% African American, 11% non-Hispanic white, 5% Asian) and most (87.5%) had a family history positive for diabetes. All had acanthosis nigricans, and there was equal representation of boys and girls.

Pediatricians from Southern California, reporting on a series of 18 children aged 5–17 at diagnosis of Type 2 diabetes, observed that these patients were more obese (mean BMI 27.4 vs. 16.6 kg/M²), more likely to be of Mexican origin (67% vs. 20%), and had more diabetic first-degree relatives, than 174 classical Type 1 diabetes patients attending hospital-based endocrine clinics (19). Another clinical group in Los Angeles reported that 31 of 55 diabetic Mexican American children had Type 2 diabetes (20); all subjects were obese and islet cell antibodies were absent. The Early 2 patients were aged 10–17 at diagnosis, and all those with family history data had diabetic relatives. In July 1999, in a report to the Diabetes Mellitus Interagency Coordinating Committee of NIH, Daniel Hale of San Antonio, Texas, reported

a substantial increase in the proportion of Type 2 diabetics among his pediatric patients. Over nine years, 1991–1999, 123 of 669 young diabetes patients (18%) were diagnosed as Type 2 while 5% were unclassifiable; no data were presented on treatment modalities. Dr Hale observed that the number of Mexican American patients rose from an average of 2 per year in the early 1990s to about 20 per year recently. A similar increase occurred for African Americans, while among non-Hispanic white young people the increase in recognition of Type 2 diabetes has occurred only in the last few years. Between 1997 and 1999, about 40% of all new cases of childhood diabetes in Dr Hale's practice were classified as Type 2 diabetes.

Some of the most valuable data on the epidemiology of Type 2 diabetes come from the longitudinal study of the Pima Indians. An analysis of 30 years of data in this extremely high-risk population demonstrated increasing rates of Early 2 among children (21). The prevalence of diabetes was determined in 5274 Pima Indian children using oral glucose tolerance tests for three 10-year intervals between 1967 and 1996; increases over time were seen in both boys and girls. For boys aged 10–14, prevalence rose from 0% in 1967–76 to 1.4% in 1987–96, and from 2.4% to 3.8% for those 15–19 years old. In girls the rate increased from 0.7% in 1967–76 to 2.9% in 1987–96 in the 10–14-year-old age group, and from 2.7% to 5.3% for ages 15–19 years. The investigators noted a corresponding increase in bodyweight among young Pimas, as well as an increase in the frequency of exposure to diabetes *in utero*, and found that these variables accounted for most of the increase in diabetes prevalence over the 30 years.

Heather Dean, a pediatric endocrinologist practicing in Manitoba, Canada, reported a substantial increase in the number of Native American children aged 6–17 referred for Type 2 diabetes treatment (22). The first case was referred in 1985; by 1994–98 there were on average 12 cases being diagnosed per year. She estimated minimum annual incidence and prevalence rates based on her patient load alone at 41/100 000 incident and 1.7/1000 prevalent cases among Native American children aged 5–19. Finally, an analysis of the US Indian Health Service outpatient database revealed a 45% increase in the prevalence of diabetes between 1988 and 1996 for persons aged

15–24, from 4.8 to 7.0/1000 per year (23). During the same period, the rate for those <15 years old remained stable and relatively low at 1.3/1000. In both of these reports at least some of the increase in risk of Early 2 over time is likely due to increased diagnostic awareness of the disease in the very young.

The small amount of data available on non-European populations worldwide demonstrate that for many years Early 2 may have comprised a large proportion of youth-onset diabetes. Kitagawa et al. (24) screened Tokyo schoolchildren for glycosuria each year between 1974 and 1981. Using glucose- and tolbutamide-tolerance tests in combination with data from other sources, they estimated that the yearly incidence of Type 2 diabetes among elementary and junior high school students was $3.2/10^5$ per year compared with about $1.5/10^5$ for Type 1 diabetes. In an extension of this study through 1995, these investigators reported that Early 2 incidence increased, particularly among older children, to $2/0/10^5$ for elementary, and $13.9/10^5$ for junior high school students in 1991–95 (25). The increase was more marked among older schoolchildren and females, although 24.3% of female patients were not obese as defined by the investigators (greater than 20% above ideal bodyweight), compared with just 6.4% of male patients who were not obese. A majority of patients reported diagnosed diabetes in a first- or second-degree relative, even though the absolute prevalence of diabetes in the Japanese population is much lower than in other industrialized nations.

Japanese investigators in Osaka estimated the prevalence of Early 2 in elementary and junior high school students during 1997 by combining data from a school screening program, hospital records, and a government-supported medical benefits database (26). Using the capture-mark-recapture method, they reported a prevalence rate of $21.1/10^5$, much higher than had been previously reported. They speculated that since the school urine screening program in Osaka accounted for only about 20% of the cases, studies based primarily on this method of case-finding may be severely underascertained.

Type 2 diabetes may comprise the bulk of diabetes among young Asian Indian patients in South Africa as well: Asmal et al. (3) reported that 86% of Indian patients under 40 years of age

attending a diabetes clinic had Type 2 diabetes; the prevalence for African diabetics under the age of 35 at the same clinic was 16%. Mohan et al. (4) described 219 patients from a total clinic population of >4500 in southern India (prevalence ~5%), who were ketosis resistant, had onset <25 years of age, and were controlled without insulin treatment for at least 5 years.

In summary then, we see that among nonwhites, the occurrence of Early 2 may not have been as rare as supposed prior to the last 5 years. In the US, insulin is still the only government-approved treatment for diabetes in childhood, so ascertainment based on treatment with insulin most certainly would lead to at least some degree of misclassification. We conclude from the available literature that an important component of the current 'epidemic' of Type 2 diabetes in children can be attributed to misclassification of early Type 2 as Type 1 diabetes, particularly among nonwhites. However, real increases in incidence are likely to be occurring as well. A brief overview of the epidemiology of the various recognized diabetic syndromes and their risk factors may help to clarify the current situation regarding Early 2 and atypical diabetes in youth.

MATURITY-ONSET DIABETES OF THE YOUNG (MODY)

Compared with Type 1 diabetes, MODY exhibits a milder course. Onset is often asymptomatic, and DKA usually does not develop even in the presence of chronic hyperglycemia. The majority of studies on MODY have focused on European-origin patients, and almost all of the specific genetic associations which have been reported are restricted to whites. The term MODY, then, may be most properly used only with reference to European-origin patients. A case definition for MODY offered by Tattersall and Fajans (27) was that of a patient with diagnosis before age 25 in whom fasting glycemia could be normalized for at least 2 years without the use of insulin. Obesity has been described in some reports of MODY patients but not in others, and the female:male ratio may or may not exceed unity depending on which clinic series is being described. Evidence for autoimmunity is not generally reported, and most

investigators agree that islet cell antibodies (ICA) are not found in these patients (28).

Youth-onset Type 2 diabetes patients are consistently reported to have more affected family members than patients with Type 1 diabetes (28). Inheritance in European-origin MODY families usually follows that of an autosomal dominant pattern, with vertical transmission of disease from one generation to the next, and approximately 50% of siblings affected. Reports of early onset Type 2 diabetes in non-European ethnic groups show vertical transmission in only a subset of such families (4). Recent work in Europeans and US whites has concentrated on the association of MODY with mutations near the glucokinase gene (29), while the HLA-DR and -DQ alleles linked to Type 1 diabetes have not been demonstrated in youth-onset Type 2 diabetes patients.

EPIDEMIOLOGY OF 'TYPICAL' TYPE 1 DIABETES IN VARIOUS POPULATIONS

While the body of published epidemiologic research on Type 1 diabetes among US minorities remains small, the picture in general conforms to that of Type 1 diabetes when it occurs in other ethnic groups. There is substantial variation in Type 1 diabetes risk among populations worldwide (30). Although recent studies have generally reported lower risks among African-origin, Asian, and Hispanic groups compared with non-Hispanic whites (30–39), wide geographic differences are seen within each ethnic group. Table 7C.1 demonstrates a 4-fold risk gradient among African-origin groups in the Western Hemisphere, and an 8-fold difference across Hispanic populations. Genetic studies have shown the importance of HLA region polymorphisms in determining these differences (40), but there is also good evidence of an environmental component in Type 1 diabetes etiology. Epidemics have been reported in association with viral outbreaks, and migrant studies have shown short-term geographic differences in risk among children of the same ethnic background (41).

Clearly, one possible explanation for the incidence differences shown in Table 7C.1 is that there are variations in the numbers of Type 2 diabetes or atypical patients classified as Type 1. This could result from real differences in incidence

Table 7C.1. Incidence of Type I diabetes among various ethnic groups

Location	No. patients	Rate/100,000	Age range	Years	Ref.
<i>African-origin Groups:</i>					
US: Chicago	299	13.2	0–17	1985–90	31
US: Allegheny County	146	10.3	0–19	1965–89	32
US: Alabama	69	8.1	0–17	1979–88	33
Barbados	59	5.0	0–14	1982–91	34
<i>Hispanic Groups:</i>					
Puerto Rico	1033	15.4	0–15	1985–90	35
Spain: Madrid	501	11.3	0–14	1985–88	36
US: Chicago	114	10.8	0–17	1985–90	31
Brazil: São Paolo	52	7.6	0–15	1987–91	37
Cuba	267	1.8	0–14	1980–88	38
<i>Non-Hispanic White Groups:</i>					
Finland	1014	35.3	0–14	1987–89	30
US: Allegheny County	1414	14.2	0–19	1965–89	32
Estonia	208	10.3	0–14	1983–88	30
Western Poland	164	5.5	0–14	1989–90	30
<i>Asian-origin Groups:</i>					
Hong Kong	22	2.0	0–14	1986–90	39
Japan: Hokkaido	283	1.7	0–14	1974–86	30
Korea	35	0.6	0–14	1985–86	30

across the world. However, it also might reflect a range of professional practice regarding the use of insulin with pediatric patients, since most epidemiologic studies define Type 1 diabetes by the use of insulin therapy. In the latter situation, different proportions of Early 2 subjects might be included in epidemiologic studies of type 1 diabetes, according to whether local standards permit oral hypoglycemic agents to be used in diabetic children. For example, several groups have found early Type 2 diabetes to be more frequent among females. Wagenknecht et al. (33) identified three girls with Type 1 diabetes for every boy among African Americans in Jefferson County, Alabama (US), while the sex ratio for whites in the same study was ~ 1.0 . If female sex is truly a risk factor for Early 2, then misclassification would be suspected in the Alabama study. Alternatively, it is certainly possible that real differences in the risk of atypical, non-Type 1 diabetes exist among ethnic groups located in different geographic regions, potentially attributable to differences in genetic admixture, the population frequency of relevant genes and/or environmental determinants of risk.

INTERMEDIATE SYNDROMES: 'DOUBLE DIABETES'

Correctly distinguishing the etiology of childhood diabetes has been an issue for many investigators. An incidence study of diabetes among Swedish youth aged 15–34 demonstrated that even in this relatively homogeneous population with few structural barriers to diagnosis and optimal treatment, confusion as to the clinical type and etiology of diabetes can occur (42). Patients diagnosed in 1983–84 ($n = 281$) were followed for 3 years. Initially, 75% were classified as Type 1, 19% were Type 2, and 6% were unclassifiable or their diabetes was secondary to another disease process. By 3 years duration, 87% of the Type 1 diabetes patients were still classified as Type 1, and 72% of the initial Type 2 diabetes patients were still in that category. Thus, 13% of Type 1 diabetes and 28% of Type 2 patients ($n = 43$ in all) exhibited an atypical clinical course. Of these, six patients were designated Type 1 at onset on the basis of glycemia, ketonuria and other clinical characteristics. At followup, these patients remained lean, but had come off insulin without developing

ketosis, and had C-peptide levels intermediate between those of the 'true' Type 1s and the Type 1 diabetic patients. Thus, even in a carefully defined population, correctly distinguishing Type 1 from atypical or early-onset Type 2 diabetes can be difficult based on clinical data alone.

A few investigators have hypothesized that Type 2 diabetes can coexist with insulin-deficient Type 1 diabetes, where insulin resistance develops with increasing insulin dosage. These 'double diabetes' patients are most often those with Type 2 relatives (43). In their longitudinal study of the natural history of chronic complications ($n = 658$ childhood onset Type 1 diabetes patients), Erbey et al. reported that those with incident coronary artery disease or overt nephropathy had higher levels of insulin resistance and more relatives with Type 2 diabetes (44).

Further confusion arises when certain data on adults with diabetes are considered. Correct definition is an absolute requirement for the epidemiologic investigation of a disease, yet 5–10% of most patients reported in clinic series reports have been unclassifiable into either major category of diabetes. This difficulty has been a topic of discussion for many years (42,45). Fasting and glucagon-stimulated C-peptide levels have been shown to distinguish Type 1 from Type 2 diabetes in all but a handful of European patients (46), although few long-term population-based data are available. Atypical diabetes among non-Europeans may be more akin to Type 2 diabetes with respect to insulin secretion, although at onset most atypical patients are clearly insulinopenic.

In adult blacks, Banerji et al. (47) have described a syndrome they refer to as 'Flatbush' diabetes. The 21 middle-aged African American patients in this report developed DKA, all but 4 of them at the time of diagnosis. Subsequently, however, the clinical course of their disease resembled Type 2 diabetes. At the time of the study, 3–120 months after the episodes of DKA, these patients were lean to mildly obese, and fewer than half were being treated with insulin. Diabetes was reported in a first-degree relative of 14 (67%) of the patients. Assays for ICA and GAD antibodies were negative, but an elevated frequency of the Type 1-related HLA alleles DR3 and DR4 was reported. Compared with non-diabetic adults (13 blacks, 3 whites), these patients had significantly lower insulin and higher glucose areas on 2-hour

oral glucose tolerance testing, yet clamp studies revealed insulin resistance in all but one patient. The investigators concluded that the etiology in these adult patients must be a hybrid of Type 1 and Type 2 diabetes.

Banerji and colleagues conducted additional studies in blacks with Type 2 diabetes contrasting insulin-sensitive vs. insulin-resistant syndromes using the euglycemic clamp technique (48). Differences in visceral fat deposition were reported (49), and varying associations with HLA-DQ polymorphisms were identified among 25 insulin-sensitive, 21 insulin-resistant, and 89 normoglycemic African Americans. The insulin-resistant group had a higher than expected prevalence of the DQw7 allele, and the insulin-sensitive group had a lower frequency of DQw6, when compared with each other and with non-diabetic blacks. No HLA-DR or Class I differences were observed. Joffe et al. (2) reported data from South African black Type 2 diabetes patients suggesting a rapid fall in beta-cell function compared with whites, despite obesity and a relatively mild clinical course. There was no increase in C-peptide after sulfonylurea treatment for hyperglycemia. The beta-cell response to a glucose challenge was reduced in obese non-diabetic blacks when compared with obese non-diabetic whites. The authors cite these data as evidence in support of a primary defect in insulin production rather than in insulin sensitivity, perhaps related to childhood under-nutrition.

ISLET AUTOANTIBODIES

The presence of one or another type of ICA presumably indicates ongoing pancreatic autoimmunity, and therefore ostensibly rules out an insulin-resistant or Type 2 etiology in diabetes. ICA are almost always found in newly diagnosed Type 1 diabetes patients, and they are found in 3–5% of first-degree relatives of patients. They appear in <0.5% of the general population; when detected in non-diabetic individuals the predictive value of ICA for later developing IDDM is quite high: relative risks ranging from 50 to >200 have been reported by investigators from many parts of the world (50,51). This was explored in a large group of relatives of patients by Riley et al. (52), and the risk estimate among blacks was actually

somewhat higher than that among whites. A more recent analysis of islet cell autoimmunity among young insulin-treated patients, testing for ICA on both human and rat pancreas substrates, demonstrated that 11.6% of 43 African American patients compared with just 4.1% of 394 non-Hispanic white patients were negative for all four major kinds of ICA tested. (53)

Specific antibodies to glutamic acid decarboxylase (GAD) have been associated with pancreatic autoimmunity in more recent years (54, 55). Like other kinds of ICA, they are found in 75–80% of newly-diagnosed patients, and very rarely in non-diabetics. The presence of GAD antibodies is predictive of the development of Type 1 diabetes in high-risk groups and population samples (56), and have been reported in subsets of Type 2 diabetic patients as well. Ethnic differences in GAD antibody prevalence have also been demonstrated (57). Among 125 Pima Indian children diagnosed at ages 5–19 with Type 2 diabetes, GAD antibodies were detected (at low levels) in 7 individuals. Antibody screening was conducted at or near the time of diagnosis; the occurrence of GAD antibodies in non-diabetic Pima children was slightly lower. In contrast, 71.7% of non-Hispanic white patients and 55.8% of the African American patients in Allegheny County, aged <19 years at onset, were GAD antibody positive (53). Compared to other kinds of ICA, GAD antibodies persist after the diagnosis of Type 1 diabetes for an extended period: Rowley et al. (58) reported that 59% of Type 2 diabetic adults with duration >3 years were GAD antibody positive, although just 13% were positive for conventional ICA. This is a key advantage in studying autoimmunity among patients with diabetes of variable duration.

RESIDUAL BETA-CELL FUNCTION IN TYPE 1 AND TYPE 2 DIABETES

At the time of diagnosis, there is at least a small number of functioning beta-cells in most patients, irrespective of the type and etiology of diabetes. Regulation of insulin release, as well as insulin signaling, are disturbed in response to prolonged hyperglycemia; this glucose toxicity is resolved by treatment of the newly-diagnosed disease, endogenous insulin secretion and insulin activity resume for at least a short interval in most patients

(59). The ‘honeymoon’ seen in the first few months of overt Type 1 diabetes is a result of this sequence. Eventually, in Type 1 diabetes patients, autoimmune beta-cell destruction resumes until a complete loss of the ability to secrete insulin results. In contrast, Type 2 diabetes patients continue to secrete insulin for a sustained period, although they, too, may eventually lose the capacity to produce insulin as their beta-cells become exhausted. This pattern is seen in both youth-onset Type 2 diabetes and the much more common adult type. Thus, the measurement of C-peptide represents an obvious strategy for distinguishing Type 1 diabetes from Type 2 diabetes in questionable cases. If Type 2 diabetic patients continue to secrete insulin (hence C-peptide) for an indefinite period, then the rate of fall in C-peptide might distinguish them from ‘true’ Type 1 patients.

A number of investigators have addressed this question. Madsbad (60) reviewed the literature in preparation for the Diabetes Control and Complications Trial (DCCT), concluding that persistent secreters tended to be older at onset, but that the degree of metabolic control had no long-term association with C-peptide. He inferred that the evidence for a relationship with ICA was inconsistent across studies, although a few years later Marner et al. reported that those in whom ICA were still present >30 months after diagnosis had a more rapid fall in beta-cell function (61). Recruitment of potential DCCT subjects aged 13–39 provided the opportunity to measure fasting and Sustacal-stimulated C-peptide in large numbers of patients who had been classified as having Type 1 diabetes on clinical grounds (62). Average C-peptide levels declined from 0.2 pmol/ml (fasting) and 0.4 pmol/ml (stimulated) at 1 year to 0.05 pmol/ml (fasting) and <0.1 pmol/ml (stimulated) at 5 years. Importantly, a much more steep decline in residual beta-cell function was observed for adolescents aged 18 than for adults. Snorgaard et al. (63) tracked C-peptide levels from diagnosis to 6 years duration in 124 patients under 30 years of age. Peak C-peptide reached a median level of 0.27 nmol/l at 6 months duration; the median decline from the peak level was 0.08 nmol/l per year (fasting) and 0.03 nmol/l per year (postprandial). Median postprandial C-peptide was 0.06 nmol/l at 5 years duration. These investigators also reported a more gradual decline among

patients whose disease was diagnosed after age 30. Using these data, we might expect our 'true' Type 1 diabetes patients to exhibit fasting C-peptide levels of approximately 0.11 nmol/l at 2 years duration, with a relatively steep decline in beta-cell function based on their young age at onset; those with undetectable C-peptide might also be more likely to continue to be positive for ICA or GAD.

Fasting and glucagon-stimulated C-peptide levels have been shown to distinguish Type 1 from Type 2 patients in all but a few Europeans (46), although few long-term population-based data are available. Umpierrez et al. (64) studied a large series of African American adults for beta-cell function, genetic and immunologic markers, classified as lean with DKA ($n = 54$), obese with DKA ($n = 77$), obese without DKA (51), and obese non-diabetics ($n = 25$). Obese patients presenting with DKA had fasting and stimulated C-peptide levels significantly higher than the lean DKA patients and significantly lower than the obese non-DKA group.

HLA, GLUCOKINASE, AND OTHER GENETIC ASSOCIATIONS WITH DIABETES

Recent advances in the genetic epidemiology of Type 1, Type 2 and MODY may soon make it possible to distinguish them based on genetic markers. Inheritance in European-origin MODY families usually follows that of an autosomal dominant pattern, with vertical transmission of disease from one generation to the next, and approximately 50% of siblings affected (28). Reports of non-Type 1 in other ethnic groups show vertical transmission in only a subset of such families (4). Work in Europeans and US whites has identified several associations of MODY with specific mutations (29); the HLA-DR and -DQ alleles linked to Type 1 diabetes are not found in MODY patients (27, 65). Indeed, some investigators suggest that patients with early-onset Type 2 diabetes can be distinguished from MODY patients on the basis of inheritance patterns (66).

There is widespread consensus that Type 2 diabetes, in contrast to MODY, is a genetically heterogeneous condition (45, 67). Familial aggregation is common, leading numerous investigators to search for relevant genes with limited success.

An array of polymorphisms have been linked to Type 2 diabetes and obesity in single families or ethnic groups, but no generalizable associations have yet emerged (65, 68, 69).

Among African-origin and Hispanic patients with 'typical' Type 1 diabetes, immunogenetic similarities to European-origin Type 1 diabetes patients have been demonstrated with a few notable exceptions. The strong association of Type 1 diabetes with alleles at the HLA-DR and -DQ loci has been confirmed among both African-origin patients and Latinos (40, 70). In a case-control study from Colorado, Mexican American children with Type 1 diabetes were more likely than non-diabetic controls to have HLA-DR3, -DR4, and -DQ alleles which code for an amino acid other than aspartate at position 57 of the B1 subunit (non-Asp-57); similar findings were reported among non-Hispanic whites (71). The associated odds ratios were not significantly different by ethnicity, although fewer Mexican American patients carried DR3. Among blacks, similar strong associations with HLA-DR and -DQ alleles have been reported. Todd et al. (72) reported that the diabetes-associated DR9 haplotype among Afro-Caribbean Type 1 diabetes patients in England carried a non-Asp codon at position 57 of DQB1, in contrast to DR9 among whites, which appears to be protective against IDDM and codes for Asp at DQB1-57 (73).

A positive family history is found in only 10–15% of Type 1 diabetes patients, while among Type 2 and MODY patients many relatives are affected. The frequency of diabetes among relatives of 9 atypical patients from Winter's clinic series was significantly higher than among relatives of 'typical' black ($n = 5$) and white ($n = 11$) Type 1 diabetes patients (74). Diabetes was ascertained in these relatives by patient or family report, and thus may also reflect differences in health care-seeking behaviors or other environmental risks.

A study of African American women reported that HLA-B41 and -DR2 were positively associated with risk of insulin-requiring gestational diabetes mellitus, and with risk of developing Type 2 diabetes in those with previous gestational diabetes (75). This report is interesting in light of the findings that older, ketosis-prone blacks with 'Flatbush' diabetes described by Banerji et al. showed a higher than expected frequency of the Type 1-associated HLA alleles (47). Evidently the

strong association of HLA class II alleles with diabetes is not yet fully understood.

RISK FACTORS: THE EPIDEMIOLOGY OF OBESITY AND HYPERINSULINEMIA IN CHILDREN

It is well accepted that overweight as a child is a risk factor for obesity in adulthood. Using data from the Fels Longitudinal Study, Guo et al. (76) correlated girls' percent ideal body weight aged 10–18 with their percent ideal weight at age 35; all coefficients exceeded 0.6. We know that obesity, impaired glucose tolerance and insulin resistance are important metabolic risk factors for Type 2 diabetes mellitus (77,78), and they are also suspected to be important etiologic components of youth-onset disease.

Defining obesity in growing children and adolescents is more problematic than in adults, and various investigators have relied on skinfolds, body mass index (BMI; defined as weight/height²), ponderosity (weight/height³), and other methods (79). Irrespective of which of these measures is used, most secular analyses indicate that adiposity has increased among US youth since 1960. Comparing data from four US national surveys collected between 1963 and 1980, Gortmaker et al. (80) reported that the prevalence of obesity increased by 54% among children aged 6–11, and 39% in adolescents aged 12–17. These investigators defined obesity as triceps skinfold thickness >85th percentile of the 1963–65 National Health Examination Survey 2 (NHES-2) distribution. Among young African Americans (ages 6–11) the prevalence of obesity doubled from 8.8% in 1963–65 to 16.8% in 1976–80, while among black adolescents the corresponding rates were 10.2% and 18.7%. By 1976–80, fully 25.1% of black females and 12.7% of black males aged 12–17 were obese. However, using BMI in a similar analysis of four national datasets (two of which were the same as Gortmaker's), Harlan et al. (81) found no significant increases in obesity among whites or blacks 12–17 years old. A more recent comparison of the second and third National Health and Nutrition Examination Surveys [NHANES-II (1976–80) and NHANES-III (1988–91)] showed that the prevalence of overweight, defined as BMI >85th percentile from NHES, increased from 15% to 21%

among youth aged 12–19 years (82). Cross-sectional anthropometric surveys of Mexican American children were conducted in Brownsville, Texas in 1972 and again in 1983 (83). Mean BMI and triceps skinfold increased significantly over the 11-year interval except among boys >15 years old. In preparation for an intervention study in 4th grade Mexican American children in Texas, baseline data were collected in 1997–98 on 173 subjects: 21% of boys and 18% of girls were overweight, defined as age- and sex-specific BMI >85th percentile of the 2nd National Health Examination Survey (84). Of these children 60% reported a first- or second-degree relative with diabetes.

Other investigators in the US report similar high levels of overweight along with physical inactivity in children and adolescents in various geographic locations. A survey of 522 schoolgirls aged 10–18 in 1991 recorded overweight (>85th percentile in NHANES-1) in 22% of non-Hispanic white, 37.6% of non-Hispanic black, and 26.7% of Hispanic girls in Lynn, Massachusetts (85). More than 75% of these girls reported watching television >2 hours per day, and only 13% participated in strenuous physical activity >3 times per week. In preparation for an intervention trial among 4th graders in Baltimore, survey data were collected in 1995 from 785 students from primarily African American, low-income schools. They reported, on average, watching >4 hours of television per day (86).

A US national survey of adolescents conducted in 1996 demonstrated large ethnic differences in reported inactivity, but less of a disparity in moderate-vigorous physical activity (87). Average television/video use was 20.4 hours/week for non-Hispanic blacks and 13.1 for non-Hispanic whites. Non-Hispanic black and Asian girls had the lowest levels of physical activity. The increasing prevalence of obesity and physical inactivity among children provides a disconcerting glimpse of future generations, as recent longitudinal studies of the rate of fat accretion in children have revealed that a major determinant is parental fatness (88).

INSULIN RESISTANCE AND HYPERINSULINEMIA IN HEALTHY CHILDREN AND ADOLESCENTS

A reasonably comprehensive literature is emerging on puberty and insulin metabolism. In a study of

normal, European-origin children (14 prepubertal and 19 pubertal), Amiel et al. showed them to exhibit selective insulin resistance which may have served to enhance the anabolic effect of insulin in proteins (89). A much larger study of insulin resistance (357 healthy children, ages 10–14; 73 were African American) demonstrated a significant decrease in insulin sensitivity through puberty, resolving to near prepubertal levels by Tanner stage 5 (90). Girls were more insulin resistant than boys at every pubertal stage; approximately 50% of this difference could be accounted for by adiposity as reflected by skinfold thickness. Non-Hispanic white boys were more insulin resistant than African Americans, and there was no significant ethnic difference among girls, controlled for BMI, adiposity and blood pressure. The authors suggest that the initial reports of greater insulin resistance among black compared to white children could have resulted from the small numbers in these previous studies.

However, black:white differences in insulin resistance and acute insulin response (AIR) were observed in another recent study of 95 prepubertal children that incorporated careful dietary measures (91). Black children had higher vegetable/ fruit and lower dairy intake than whites, and they were more insulin resistant and had higher AIR. Dietary intake did not account for the ethnic differences in AIR, controlled for social class and adiposity.

An elevated fasting insulin concentration is recognized as a risk factor for Type 2 diabetes. The longitudinal Pima Indian study provides information on the predictive value of obesity, family history, and insulinemia in childhood for subsequent development of Type 2 diabetes (92). Overweight was closely correlated with fasting insulin levels and family history of diabetes; in those with a positive family history, obesity was the best predictor of diabetes risk. Compared with non-Hispanic white children, Pima children had consistently higher fasting insulin levels despite similarities in age, height, and fasting glucose concentration (93). Multiple linear regression on (log) insulin demonstrated a significant interaction of race and relative weight; the models included age, age², and fasting glucose, and accounted for 49% of the variance in boys and 52% of the variance in girls.

Using oral glucose tolerance tests, the Bogalusa (Louisiana) group demonstrated significantly

higher 0–60 minute insulin areas in non-diabetic black children compared with whites aged 5–17, controlled for age, weight, height and Tanner stage (94). Fasting and 2-hour insulin concentration in 1975–76 was higher among young Nauruans (ages 8–19) who developed impaired glucose tolerance or Type 2 diabetes over the next 11 years, than among those who remained normoglycemic (95).

These studies corroborate other investigations of metabolic physiology that suggest that there are differences among racial groups in the anatomical and pathophysiological correlates of glucose intolerance (64). In particular, African-American children with equivalent body fatness to white children have less abdominal fat, higher insulin concentrations, and lower insulin sensitivity (91,96). It is not clear whether these differences influence the clinical presentation of glucose intolerance in the different racial groups, but one would expect African-American children to be more vulnerable than white children to alterations in insulin secretion because of their dependence on elevated secretion to compensate for greater insulin resistance. Likewise, they would be more vulnerable than other groups to further decreases in insulin sensitivity, known to emerge during puberty. Whether this has implications for the etiology of Early 2 remains to be seen.

POLYCYSTIC OVARY SYNDROME; ACANTHOSIS NIGRICANS

Polycystic ovary syndrome is typically diagnosed in patients with symptoms of androgen excess, i.e. infertility, hirsutism or oligomenorrhea, and elevated serum androgen levels, and is associated with insulin resistance. The prevalence of polycystic ovary syndrome is ~20% of asymptomatic women in England as detected by ultrasound (97,98). Among 18–40-year-old Asian Indian women in England the prevalence on ultrasound was >50%, and polycystic ovary syndrome was significantly associated with acanthosis nigricans and elevated fasting blood glucose, in addition to the recognized symptoms of hirsutism, infertility and menstrual irregularities (99). Using a short intravenous glucose tolerance test, the presence of polycystic ovary syndrome in these women accounted for a reduction in insulin sensitivity comparable to that seen in women who had

diagnosed Type 2 diabetes without polycystic ovary syndrome (-60 mmol gluc/l-min for polycystic ovary syndrome without diabetes, vs. -68 mmol gluc/l-min for Type 2 diabetes without polycystic ovary syndrome). There was no relationship to blood pressure, insulin sensitivity, or lipids.

INSIGHTS FROM THE CHICAGO CHILDHOOD DIABETES REGISTRY

The population-based Chicago Childhood Diabetes Registry has been ascertaining diabetes with onset $<$ age 18 since 1985 among African American and Hispanic children (100). During the first 10 years of the study, 1985–94, there were 735 incident cases of insulin-treated diabetes among 520 non-Hispanic blacks and 215 Hispanics. Overall, the average annual risk for non-Hispanic blacks, $15.3/10^5$,⁵ was significantly higher than that for Hispanics ($10.8/10^5$). The average yearly incidence among non-Hispanic black males was $13.7/10^5$ persons, while among non-Hispanic black females it was $16.8/10^5$. Among Hispanic males the average annual risk was $10.8/10^5$ and among Hispanic females it was $10.7/10^5$ per year.

Time Trends in Incidence

While overall incidence rates did not change between 1985 and 1994, there was a dramatic rise in diabetes risk for non-Hispanic black females [average annual percent increase 4.7% ($p = 0.03$)], and for Hispanic males [average annual percent increase 6.1% ($p = 0.08$)]. In contrast, rates were

stable for non-Hispanic black males and Hispanic females.

Data-based Classification of Early 2

Using medical records, and, when available, questionnaire responses, we were able to distinguish a group of probable Early 2 subjects from the body of registered cases using criteria as depicted in Figure 7C.2. On the medical records, those with any mention of obesity, ‘possible Type 2’ or ‘atypical’ diabetes, acanthosis nigricans, polycystic ovary syndrome, or those with a BMI >27 Kg/M² at onset, were selected; in addition, those who responded to specific questions during the interview were considered likely to be Type 2. These questions elicit information on cessation of insulin use after the ‘honeymoon’ period, as well as on current treatment with oral agents. Those who do not meet one or more of the above criteria were considered to have type I diabetes. Using these criteria, we were able to begin to address the question of secular increases in Early 2.

Early 2 Incidence

The proportion of currently registered cases classified as Early 2 as defined above is 28.3% among non-Hispanic blacks ($n = 704$), and 21.9% among Hispanics ($n = 315$). Recognizing the obvious biases related to incomplete ascertainment of those with more recent onset, we saw an increase in the number with Early 2 over time (Figure 7C.3). Yet even during the earliest years, the proportion who were likely to have Type 2 diabetes based on

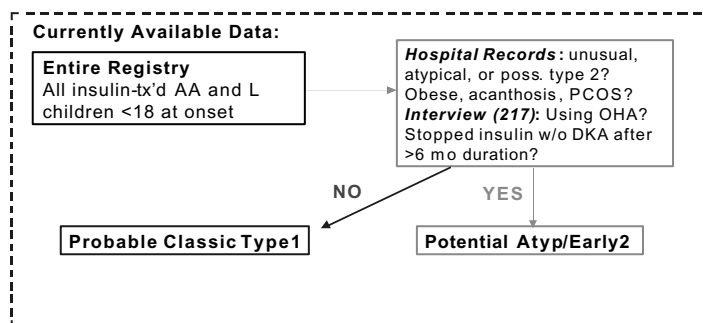


Figure 7C.2. Current algorithm for distinguishing Early 2 based on available Data

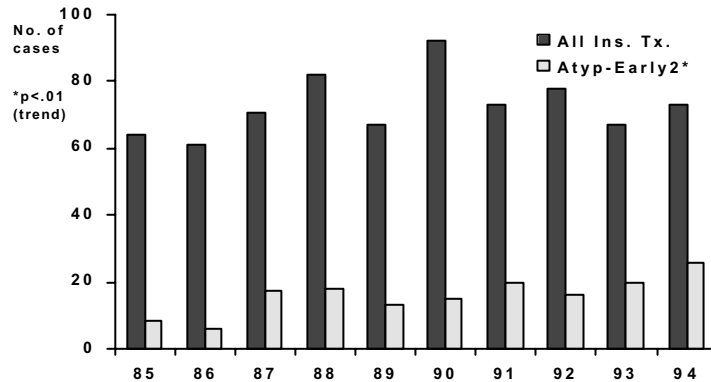


Figure 7C.3. Early Type 2 among all diagnosed cases, Aged 0–17, Chicago, 1985–94

available data was ~18%. This finding raises the possibility that the recently reported ‘epidemic’ of Type 2 diabetes among minority children is, at least in Chicago, partly due to increased willingness on the part of physicians to arrive at a diagnosis of Type 2 diabetes in a young person, compared to a few years ago.

Distinguishing Type 2 from Type 1 Phenotype: Onset Characteristics and Subsequent Clinical Measures

It would be ideal to be able to distinguish Type 1 from Type 2 diabetes at the time of diagnosis or as

soon as possible afterwards, on demographic, behavioral and/or clinical characteristics. Using the available data-based criteria described above, we compared Early 2 with presumed Type 1 patients (Table 7C.2) in the 735 non-Hispanic blacks and Hispanic cases with onset 1985–94. In interpreting this analysis it is important to remember that *none of the typical onset symptoms per se was included in our algorithm* for distinguishing Early 2, however, clinicians noting in the medical record that a child had ‘atypical’ or ‘possible Type 2’ diabetes may well have considered them. Mean age at diagnosis was significantly older among the Early 2s, 13.1 vs. 10.5 years among the Type 1 patients, as was the proportion of females, 62.4 vs. 49.8%, respectively.

Table 7C.2. Onset characteristics and demographics by phenotype, Chicago cases, 1985–94

	All	Type 1	Early 2	P-val
<i>N</i>	735	562	173	
Females, <i>N</i> (%)	388 (52.8)	280 (49.8)	108 (62.4)	0.005
African Americans, <i>N</i> (%)	520 (70.7)	389 (69.2)	131 (75.7)	0.121
Has ≥1 diabetic parent or sibling	226 (30.7)	144 (25.6)	82 (47.4)	<0.001
Interviewed, <i>N</i> (%)	195 (26.5)	152 (27.0)	43 (24.9)	0.637
<i>Onset Characteristics:</i>				
Age, mean (SD)	11.1 (4.4)	10.5 (4.6)	13.1 (3.2)	<0.001
DKA diagnosed, <i>N</i> (%)	246 (67.2)	200 (73.8)	46 (48.4)	<0.001
Weight loss, <i>N</i> (%)	256 (71.3)	198 (74.4)	58 (62.4)	0.037
Polyuria, <i>N</i> (%)	356 (94.9)	265 (97.1)	91 (89.2)	0.005
Polyphagia, <i>N</i> (%)	107 (29.9)	76 (28.9)	31 (32.6)	0.582
Polydipsia, <i>N</i> (%)	343 (92.0)	252 (92.6)	91 (90.1)	0.555
Sign/symptom present, <i>N</i> (%)*	375 (98.2)	279 (99.6)	96 (94.1)	0.002
Blood pH, mean (SD)	7.247 (0.126)	7.234 (0.125)	7.286 (0.121)	0.004
Glucose, mg/dL, mean (SD)	582 (287)	595 (271)	549 (324)	0.174

* At least one of the following noted at onset: DKA, weight loss, polyuria, polydipsia, polyphagia.

There were marginally more non-Hispanic blacks in the Early 2 group. A larger proportion of the Early 2s had a first-degree diabetic relative, and they were more likely to be survivors of both low birthweight (29% of Early 2 vs. 9% of Type 1) and large-for-gestational-age (43% of Early 2 vs. 9% of Type 1). DKA was noted less frequently for the Early 2 patients, but it was diagnosed in almost half of them, and the initial glucose value for Early 2s was not significantly lower than for the Type 1 diabetics; acidosis was somewhat less severe for the Early 2 patients. At least one typical symptom was present in 94% of the Early 2s and virtually all of the presumed Type 1 diabetics. In sum, a majority of youth-onset Type 2 diabetic patients had severe symptoms at the time of diagnosis, including high blood glucose values, yet they differed from the presumed Type 1s on demographics (age, sex) and family history.

PROPOSED DIAGNOSTIC CRITERIA FOR EARLY 2

It is clear from the above discussion that much work remains to be done on the descriptive epidemiology of non-Type 1 diabetes among young people. Optimally, genetic, immunologic and clinical characteristics would be incorporated into a schema for defining youth-onset Type 2 diabetes as a clinical entity. The process of establishing classification criteria has evolved over time, and has been the subject of lengthy debate. A plausible scheme must be both clinically relevant and based in theory. Much recent attention has emerged from the disciplines of psychiatry and psychology, where questions of the validity, reliability and reproducibility of pathologic classes are often extremely difficult. Various models for classifying disease have been proposed, including those based on a hierarchy of traits, those utilizing ideal types with clustering of attributes, those employing matrices, and hybrids incorporating elements of each (101). Irrespective of which structure is adopted, a classification scheme must achieve both internal and external validity. There must be a satisfactory level of agreement between different raters using the same set of criteria, as well as consistent ratings by the same individual over time (102). Both intra- and inter-rater reliability have been studied in a variety of medical

settings, and useful statistical procedures have been devised (103). Skinner (104) argues in favor of integrating classification theory and empirical methods into one general framework. The system of classification must also satisfy external standards: it must be capable of distinguishing differences among groups based on signs and symptoms, clinical outcomes, and/or etiology. This aspect is probably most important from the utilitarian perspective of predicting disease and assessing the effectiveness of treatment.

Several attempts have been made to set diagnostic criteria for Early 2. Ciampi et al. (105) used empirical recursive partitioning methods to distinguish heterogeneity among a group of 111 Type 1 diabetes patients. They defined two clusters of clinical similarities; the three major distinguishing factors were indicators of severity of presentation, disease duration, and a scale of beta-cell function. The two clusters of patients were older vs. younger than age 6 at onset, more females vs. more males, higher vs. lower C-peptide, and had a number of additional distinguishing characteristics. HLA DR antigens did not differ between the two groups of patients.

Clinicians also have begun to address diagnostic criteria for Early 2. Using their clinical experience as well as other clinic-based reports, Arslanian and Danadian characterized 'youth-onset atypical diabetes' as having a preponderance of black children, onset ~13.5 years and in mid-puberty, increased female:male ratio, increased BMI, acanthosis nigricans, and a family history of Type 2 diabetes (96). Heather Dean distinguished 'NIDDM in Youth' from Type 1 diabetes in her Native American patient population using age (> 6 and usually >9 years), obesity (>120% ideal body-weight or BMI>85th percentile), clinical criteria (no recent weight loss or acute hyperglycemic symptoms), and a family history of Type 2 diabetes (106). The American Diabetes Association consensus statement tentatively suggests the criteria of obesity at onset, a positive family history, and acanthosis nigricans. Severe symptoms of hyperglycemia, polycystic ovary syndrome in females, and lipid abnormalities may also be present (107). While all of the schemes have much in common, no one criterion stands out as the definitive marker of Type 2 diabetes, particularly at the onset of the disease, when distinguishing Type 2 from Type 1 in a young person is crucial.

SUMMARY

The current status of research on diabetes in childhood points out the necessity for a comprehensive study of variant types of youth-onset diabetes. Attempts to evaluate incidence or risk factors are frustrated where there is confusion regarding the type of disease; this is a particular difficulty in those ethnic groups where youth-onset Type 2 diabetes may be more prevalent. Until now, prevalence estimates have been based solely on clinic series or case reports; the spectrum of atypical syndromes and their occurrence cannot therefore be accurately described.

In examining the sparse body of relevant knowledge, we conclude that youth-onset Type 2 diabetes may be related to being a member of an ethnic group at high risk for Type 2, and/or to the increasing prevalence of obesity among children. Adolescents and adults with clinical syndromes intermediate between Type 1 and Type 2 diabetes have been described, and may provide etiologic clues. Autoimmunity to GAD can be measured more consistently than other types of ICA, and may be useful in confirming an autoimmune etiology in longstanding diabetes. GAD antibodies are not found in adults with 'typical' Type 2 diabetes, although no data are now available on GAD antibody prevalence in young people with non-Type 1 disease. Several genes have been associated with MODY in small numbers of patients, and are worthy of further scrutiny for their relationship to Early 2 in a well-defined, population-based sample. Sophisticated theoretical and statistical methods for establishing and subsequently evaluating classification criteria are available and are being applied to the question of defining atypical or early-onset Type 2 diabetes.

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Type 2 Diabetes: Aetiology and Environmental Factors

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INTRODUCTION

The first evidence for an environmental factor in the aetiology of Type 2 diabetes was described in the sixth century during the Brahman period of Hindu medicine by the three physicians Charaka, Susruta and Vagbhata. They wrote of diabetes:

It is the disease of the rich and one that is brought about by the gluttonous overindulgence in oil, flour and sugar.

In about 400 BC in China, Neijing described diabetes, its complications and its relationship to overnutrition. One thousand years and more later, dietary factors were implicated as a major factor in the occurrence of Type 2 diabetes by Thomas Willis:

Diabetes was so rare among the ancients that many famous physicians made no mention of it and Galen knew only two sick of it. But in our age given to food fellowship and gushing down chiefly of unalloyed wine, we meet examples and instance enough, I may say daily, of this disease.

In contrast, war-related deprivations have been associated with marked reductions in rates of death from diabetes. An impressive decline in diabetes death rates during the First and Second World Wars has been reported in different places (1). In Berlin, for instance, the diabetes mortality rate declined from 23.1 per 100 000 in 1914 to 10.9 in 1919. The same trends were found in other European countries in populations that were short of food. No changes in diabetes mortality were described in places where there was no food shortage during the First World War such as Japan and North America (2). The probable

influence of caloric consumption on risk of diabetes has been further demonstrated in many places. At a time when food consumption per caput was rising sharply in Japan (3), in Taiwan (4) and, more recently in some Pacific islands (5), there was a sharp rise in the prevalence of diabetes. In 1969, Charles and Medard published an instructive report on the relationship of diabetes to nutrition in Haiti, one of the poorest developing countries in the world (6). Poor people in Haiti consumed 980–1500 kcal person/day compared with more than 3000 kcal consumed by the rich people during the study period. Diabetes rates were about 100 times as great in the rich. Although food consumption and diabetes rates have usually been quite low in rural villages in many developing countries, both urbanization and/or severe under-nutrition (less than 1000 kcal and less than 50 g of protein consumed per day per caput) may enhance rates of diabetes. Traditionally living populations seem more or less 'protected' from diabetes; but severe deprivation of protein and calories may cause diabetes (7). This issue will be discussed in the section on malnutrition-related diabetes mellitus (EDM).

There is now a considerable amount of evidence to suggest that rapid acculturation is associated with increased rates of Type 2 diabetes (8). There are clearly several characteristics of the Western way of life which predispose to the development of obesity. It may simply be that the increase in obesity resulting from an aggregation of these factors (especially physical inactivity and increased intake of energy-dense foods leading to energy intake in excess of requirements) explains the increasing rates of Type 2 diabetes, particularly in individuals or populations with an appropriate

genetic predisposition. The roles of obesity and genetic factors are considered in Chapter 19. Energy intake is impossible to assess adequately in epidemiological studies even when the best instruments presently available for assessing dietary intake are employed, since it has now been clearly demonstrated that overweight and obese individuals underestimate their intake. On the other hand, energy output can be accurately measured (9), but the techniques are not suited for use in large-scale epidemiological studies. This chapter will therefore describe the role of individual nutrients and other possible environmental factors in the aetiology of Type 2 diabetes. It is important to emphasize that there are major difficulties in assessing nutritional aetiologies of any chronic disease. The pros and cons of the various dietary instruments (diet records, 24-hour recalls and food frequency questionnaires) and problems inherent in the various epidemiological approaches are discussed elsewhere (10).

CARBOHYDRATE AND DIETARY FIBRE

The suggestion that refined carbohydrates, and sugars in particular, might be involved in the aetiology of Type 2 diabetes dates back to the writings of early Indian physicians. However, in the 1960s, Yudkin resurrected the suggestion that high intakes of sucrose may be particularly important in the aetiology of Type 2 diabetes when he drew attention to the positive correlation between intakes of sucrose and diabetes prevalence in 22 countries (11). But it has subsequently become clear that the correlations were heavily dependent upon which countries were selected for inclusion and that such geographic correlations do no more than provide clues for further research, they certainly do not imply causality. Over 40 studies have examined the role of sugars in the aetiology of Type 2 diabetes, with about half suggesting a positive association and a comparable number suggesting no association. Some have even suggested an inverse association between diabetes incidence and sucrose intake (12). Poor assessment of dietary intake, inability to disentangle dietary and other confounding factors and overinterpretation of data derived from observational studies characterize many of these studies. Further evidence to suggest that sucrose is not an important

contributing factor in the aetiology of Type 2 diabetes comes from carefully controlled studies in people with Type 2 diabetes (13). Isoenergetic substitution of moderate amounts of sucrose in the diets of individuals participating in a randomized cross-over experiment did not result in deterioration in glycaemic control. Despite the lack of direct evidence incriminating sucrose in the aetiology of Type 2 diabetes it is probably inappropriate to totally exonerate sucrose. A recent epidemiological prospective study in school children has shown a clear relationship between the difference in measures of obesity over a 19-month period and change in consumption of sugar-sweetened drinks. For each additional serving of sugar-sweetened drinks, both BMI (mean 0.24 mg/m^2) and frequency of obesity (odds ratio 1.6) increased after adjustment for anthropometric, demographic, dietary and lifestyle variables (14). If excessive sucrose does predispose to obesity it is clearly an indirect predisposing factor to Type 2 diabetes.

On the other hand, there is rather more support for the suggestion that foods rich in slowly digested or resistant starch or high in soluble dietary fibre might be protective. Countries with high intakes of these foods have low rates of diabetes and Trowell drew attention to the fact that the reduced mortality rates for diabetes during and after the Second World War paralleled the increased intake of dietary fibre during that period (15). These observations on their own provide no more evidence for a protective role for these foods than do comparable studies suggesting a causal role of sucrose. However there is some corroborative evidence for a protective role of dietary fibre (non-starch polysaccharide) and slowly absorbed or resistant starch and low glycaemic index foods which may be rich in these nutrients.

In a cross-sectional study of normoglycaemic men, intake of pectin (a soluble form of dietary fibre) was shown to be inversely associated with post-load blood glucose levels, independently of energy intake and body mass index, which could potentially have confounded the association (16). Although the study was a cross-sectional one, participants were unaware of their state of glucose tolerance so that dietary recall could not have been influenced thereby. In a prospective study involving over 65 000 US women aged 40–65 years, diets low in cereal fibre and with a high glycaemic load (i.e.

rich in high glycaemic index foods) were associated with an increased risk of Type 2 diabetes. Comparing the highest with the lowest quintile of intake of cereal fibre the relative risk of developing diabetes was 1.37 and for glycaemic load 1.47 (p for trend = 0.005 and 0.003), after adjusting for other important risk factors for diabetes (17). Experimental studies provide further confirmation. In controlled experiments, diets high in soluble fibre-rich foods (18) or foods with a low glycaemic index are associated with improved diurnal blood glucose profiles as well as long-term overall improvement in glycaemic control as evidenced by reduced levels of glycated haemoglobin (19).

Some other studies provide indirect support for this hypothesis. Diabetes risk appears to be lower in Seventh Day Adventists who are vegetarians than in those who are not strict vegetarians (20). The diet of vegetarians is characterized by a high intake of dietary fibre, but differs in other ways from that of non-vegetarians. In addition to not eating meat and animal products, vegetarians also have less saturated fat, more polyunsaturated fat and a diet which differs in micronutrient composition when compared with non-vegetarians.

DIETARY FATS

More than 60 years ago Hinsworth suggested that high intakes of fat increased the risk of diabetes in populations and individuals (21). West and Kalbfleisch confirmed these observations (22) but these studies are subject to similar biases to those already described for cross-sectional and case-control studies. Furthermore, diets which are high in carbohydrate are likely to be low in fat so that it may be impossible to disentangle the consequences of increased intakes of the former and low intakes of the latter. Nevertheless it is noteworthy that several prospective studies have found associations between intake of fat and subsequent risk of developing Type 2 diabetes. In the San Luis Valley Diabetes Study a high fat intake was associated with an increased risk of Type 2 diabetes and IGT (23) and in a follow-up 1–3 years later, fat consumption predicted progression to Type 2 diabetes in those with IGT (24). On the other hand, no association was found between fat intake and risk of Type 2 diabetes in a 12-year follow-up of women in Gothenburg, Sweden (25).

The type of dietary fat may also be relevant. Saturated fatty acids were positively related to fasting and postprandial glucose levels in normoglycaemic Dutch men, the effect being independent of energy intake and obesity (26). In a recent Italian study, intake of butter (rich in palmitic and myristic acids) was positively associated and use of olive oil (high in oleic acid), inversely associated with fasting glucose levels (27). In women in the United States the relative risk of developing diabetes was significantly reduced amongst those with the highest intake of vegetable fats (28). In a small group of Japanese Americans with IGT, intake of animal fat was related to progression of IGT to diabetes (29). A high intake of saturated fat is also associated with high fasting and postprandial insulin levels and high insulin levels during an oral glucose tolerance test (30,31). Polyunsaturated fatty acids are inversely associated with insulin levels (32).

The relationship between nature of dietary fat and Type 2 diabetes has also been studied using slightly more sophisticated laboratory measurements. Finnish subjects with IGT and undiagnosed Type 2 diabetes were reported to have higher proportions of saturated fatty acids in serum cholesterol esters compared to subjects with normal glucose tolerance and the ratio of polyunsaturated to saturated fatty acids in serum phospholipids has been shown to be inversely associated with insulin secretion and positively associated with insulin action (33). Experimental studies confirm the role of fatty acids as determinants of insulin function (34). Saturated fatty acids induce insulin resistance in isolated rat adipocytes (35).

A suggestion that n-3 polyunsaturated fatty acids may also have an important role in the development of diabetes first came from the study of populations consuming large amounts of fatty fish which are rich in these long-chain unsaturated fatty acids. Greenland and Alaskan Eskimos and Alaskan Indians have low rates of diabetes (36,37). In a recent prospective study of elderly men and women, habitual fish eaters were shown to have a 50% lower risk of developing glucose intolerance compared with those who are not regular fish eaters over a 4 year follow-up period (38). The n-3 polysaturated fatty acids have a wide range of metabolic effects and, of particular relevance, influence the production of eicosanoids

which in turn may have an appreciable effect on pancreatic β -cell function (39).

Dietary intervention studies provide further evidence for the role of different fatty acids. Replacement of linoleic acid by saturated fatty acids has been shown to result in an increase in blood glucose levels and insulin requirements (40). Replacement of complex carbohydrate by mono-unsaturated fatty acids produced lower blood glucose levels and reduced requirements for insulin in Type 2 diabetes patients treated with insulin (41). Addition of n-3 polyunsaturated fatty acids to the diet of healthy volunteers resulted in a significant increase in insulin sensitivity (42). Thus it appears that the effects of the various fatty acids on diabetes risk and measures of glycaemic control and insulin resistance are similar to their effects on lipoprotein-mediated risk of coronary heart disease. Saturated fatty acids are associated with a deleterious effect and monounsaturated fatty acids as well as n-3 and n-6 polyunsaturated fatty acids with potentially beneficial effects. Modifying intake of dietary fats may reduce the risk of developing Type 2 diabetes as well as reduce the risk of cardiovascular disease amongst those suffering from the condition.

PROTEIN

There are no firm epidemiological data concerning the role of protein intake in the aetiology of Type 2 diabetes, though the fact that meat-eating Seventh Day Adventists have higher rates than those who do not eat meat has been taken to suggest a possible deleterious effect of animal protein (43). The strong positive associations between animal protein and saturated fatty acids and vegetable protein and dietary fibre mean that it is almost impossible to disentangle separate effects in epidemiological studies. Some amino acids (e.g. arginine, leucine and phenylalanine) can influence β -cell function but the epidemiological approach clearly does not readily lend itself to examining further the role of individual amino acids. High intakes of proteins, especially animal protein, appear to be associated with an increased risk of nephropathy (44), and restriction of animal protein may help to delay progression of microalbuminuria to clinical nephropathy (45).

ALCOHOL

The relationship between alcohol and other dietary variables similarly complicates attempts to evaluate a potential aetiological role for alcohol. Furthermore, confounding by obesity, distribution of adipose tissue and smoking result in difficulties in interpreting the epidemiological data. In a French prospective study abnormal liver function tests used as an indicator of alcohol excess formed an independent predictor of 4-year diabetes risk in middle-aged men (46). In the Rancho Bernardo study increasing intakes of alcohol in obese men were associated with an increased risk of diabetes (47). However, a light to moderate intake of alcohol is associated with enhanced insulin sensitivity (48).

OTHER DIETARY FACTORS AND SMOKING

Several micronutrients, most notably chromium, zinc, magnesium and vitamin E, have been implicated in the pathogenesis of Type 2 diabetes and/or been shown to be associated with improved glycaemic control. However, no epidemiological studies have provided convincing support for the role of any of these nutrients in the aetiology of the disease. There is perhaps rather more support for the suggestion that vitamin D deficiency may be important. Vitamin D deficiency impairs insulin release followed, if prolonged, by impairment of insulin secretion and reduction of glucose tolerance which progresses to irreversible diabetes. Asians living in East London have a reduction in insulin secretion associated with vitamin D deficiency which is improved after treatment with vitamin D (49). There has been much recent interest in the observation that babies with a low birthweight and infants with a low weight at one year are at increased risk of developing IGT and Type 2 diabetes later in life. The precise role of maternal malnutrition in determining this phenomenon of 'programming' remains to be established (50). The role of smoking as a risk factor for Type 2 diabetes has received relatively little attention. Smoking induces insulin resistance (51) and cigarette smokers have been shown to be relatively glucose-intolerant and dyslipidaemic (52). Thus smokers might be expected to be at considerably increased risk of Type 2 diabetes.

PHYSICAL INACTIVITY

In 1972 Björntorp and colleagues suggested that physical training resulted in lower plasma insulin levels and improved insulin sensitivity (53). This has been convincingly confirmed in many subsequent experiments. In cross-sectional epidemiological studies Type 2 diabetes rates have been shown to be lower amongst physically active individuals than amongst those not having regular physical activity (54). The protective effect of physical activity against Type 2 diabetes has been confirmed in several prospective studies. For example, in the Nurses' Health Study women who engaged in vigorous exercise at least once a week had an age-adjusted relative risk of Type 2 diabetes of 0.67 compared with women who exercised less frequently than weekly (55). The relative risk was reduced after adjustments for BMI, but remained highly statistically significant. A similar graded reduction in risk of subsequently developing Type 2 diabetes associated with a graded increase in physical activity was observed amongst men participating in the Physicians' Health Study (56). This inverse association was particularly strong in men who were overweight and was not confounded by the presence of obesity. Furthermore, controlling for smoking, hypertension and other coronary risk factors did not materially alter the association.

POTENTIAL FOR INTERVENTION

The ultimate aim of identifying environmental risk factors for Type 2 diabetes lies in the hope of preventing the disease, or of stopping, or at very least delaying, the progression of IGT to Type 2 diabetes. Studies aimed at such primary or secondary prevention are important not only from the point of view of assessing the potential value of intervention programmes, but also because they can, at least in theory, provide definitive proof of causality of particular environmental factors in the aetiology of the disease. No controlled trials have examined the potential of modifying environmental factors in the primary prevention of Type 2 diabetes. Clearly this could only be undertaken in the context of national dietary intervention programmes. However, some studies have been undertaken to determine the role of lifestyle

modification programmes in reducing the risk of progression of IGT to Type 2 diabetes. The early and less definitive studies were reviewed in detail some time ago (57). Since then the results of two major controlled intervention trials have been published – the Da Qing study and the Finnish Intervention Trial (58, 59). In both studies, diet and exercise programmes were associated with an appreciable reduction in the risk of progression of IGT to Type 2 diabetes. The results of the large North American trial are awaited (60). Unfortunately, from the point of view of disentangling potential causal factors, a multifactorial approach involving all putative lifestyle factors (including recommendations to increase physical activity) has been adopted so that no conclusions can be drawn concerning individual components of the programmes. Furthermore, weight loss appears to be the major determinant of benefit, leading to the conclusion that any or all lifestyle factors which promote obesity may be involved in the aetiology of the disease.

CONCLUSIONS

Studies utilizing a variety of epidemiological approaches have implicated a range of lifestyle-related environmental factors in the aetiology of Type 2 diabetes. The limitations inherent in ecological studies, case-control and prospective studies; the difficulties of accurately assessing nutrient intake and the close associations between different dietary characteristics mean that it is almost impossible to disentangle separate effects in observational studies. The difficulties are compounded by the fact that many of the lifestyle-related factors are linked with the development of obesity, which in turn is a major determinant of the risk of developing Type 2 diabetes in individuals and populations. Intervention studies do, in theory, provide the means of studying individual putative factors, but there are unlikely ever to be any such studies because for obvious pragmatic reasons intervention studies focus on 'best bet' programmes which will include a range of lifestyle manipulations. For these reasons the best evidence concerning the aetiological role of individual factors is likely to come from relatively small carefully controlled studies using metabolic rather than clinical endpoints. In such studies it is possible to

control for potential confounding by alterations in energy intake and bodyweight. Studies of this kind which are presently available suggest that nature of dietary fat (saturated fatty acids being deleterious and certain polyunsaturated fatty acids being protective) and carbohydrate (soluble fibre-rich and low glycaemic index foods being beneficial) and physical inactivity may be directly related to the development of Type 2 diabetes as well as via their role in increasing the risk of obesity. It is difficult to envisage the epidemiological or indeed even the experimental study which will finally resolve this issue.

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Type 2 Diabetes: Genetic Factors

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TYPE 2 DIABETES MELLITUS: A MULTIFACTORIAL AND GENETICALLY HETEROGENEOUS SYNDROME

Type 2 diabetes mellitus is a heterogeneous syndrome resulting from defects of both insulin secretion and insulin action (1). The primary biochemical events leading to chronic hyperglycemia are still unknown in most cases (2). Type 2 diabetes seems to result from a complex interplay of genetic and environmental factors influencing a number of intermediate traits of relevance to the diabetic phenotype (β -cell mass, insulin secretion, insulin action, fat distribution, obesity). In fact, Type 2 diabetes appears to be composed of subtypes where genetic susceptibility is strongly associated with environmental factors at one end of the spectrum, and highly genetic forms at the other end. Although several monogenic forms of diabetes have been identified, such as maturity onset diabetes of the young (MODY) and maternally inherited diabetes and deafness (MIDD) (3,4), Type 2 diabetes seems to be a polygenic disorder in the majority of cases. Type 2 diabetes shows clear familial aggregation, but it does not segregate in classical Mendelian fashion. Type 2 diabetes seems to result from several combined gene defects, or from the simultaneous action of several susceptibility alleles, or else from combinations of frequent variants at several loci that may have deleterious effects when predisposing environmental factors are present. Type 2 diabetes is probably also multigenic, meaning that many different combinations of gene defects may exist among diabetic patients.

A variety of environmental factors can be implicated in the clinical expression of Type 2 diabetes, such as the degree and type of obesity, sedentarity, malnutrition in fetal and perinatal periods, lifestyle, and different kinds of drugs such

as steroids, diuretics, and antihypertensive agents. It is noteworthy that obesity, which is one of the so-called environmental determinants of Type 2 diabetes, is also clearly under genetic control (5). Both disorders are frequently associated and share many metabolic abnormalities, which suggests that they might also share susceptibility genes (6). Moreover, retrospective studies showed that low birthweight was associated with insulin resistance and Type 2 diabetes in adulthood (7,8). It has been proposed that this association results from a metabolic adaptation to poor fetal nutrition (9). However, the identification of gene variants that contribute both to variation in fetal growth and to the susceptibility to Type 2 diabetes suggest that this metabolic 'programming' could also be partly genetically determined (10).

These complex interactions between genes and environment complicate the task of identifying any single genetic susceptibility factor to Type 2 diabetes. Despite the evidences for a strong genetic background in Type 2 diabetes, very little about the genetic risk factors for Type 2 diabetes is known to date (11). Most of the available results were obtained by studying the highly familial and monogenic forms of diabetes with young age of onset (3).

MONOGENIC FORMS OF DIABETES

Maturity Onset Diabetes of the Young (MODY)

MODY is a familial form of non-insulin-dependent diabetes with autosomal dominant inheritance. Hyperglycemia in MODY subjects usually develops at childhood, adolescence or young adulthood, and is associated with primary insulin-secretion defects

(3, 12). The well-defined mode of inheritance with high penetrance and the early age of onset of diabetes allow the collection of multigenerational pedigrees, making MODY an attractive model for genetic studies. It is now recognized that MODY is not a single entity but presents genetic, as well as metabolic and clinical, heterogeneity. Mutations in six genes cause most of the MODY cases. These genes encode the enzyme glucokinase (MODY2/GCK) (13–15) and the transcription factors Hepatocyte Nuclear Factor 4 alpha (HNF-4 α /MODY1) (16, 17), Hepatocyte Nuclear Factor 1 alpha (HNF-1 α /MODY3) (18–20), Insulin Promoter Factor 1 (IPF-1/MODY4) (21, 22), Hepatocyte Nuclear Factor 1 beta (HNF-1 β /MODY5) (23), and NeuroD1/Beta2 (24). Moreover additional MODY genes probably exist, since there are families in which MODY does not co-segregate with markers tightly linked to the known MODY loci (25).

The prevalence of MODY is unknown, but it has been estimated that 2–5% of patients with Type 2 Diabetes may in fact have MODY (26). The relative prevalence of the different subtypes of MODY has been shown to vary greatly in studies of MODY families from different populations (25, 27–29). MODY2 represents 8–63% of cases (the most prevalent form in French families) and MODY3 21–64% of cases (the most prevalent form in British families). The other MODY subtypes are rare disorders in all these populations, having been described only in a few families, while additional unknown MODY locus or loci (MODY-X) represent 16–45% of the cases of MODY (the most prevalent form in German and Spanish families). These contrasting results may be due to differences in the genetic background of these populations, or else may reflect, at least partly, ascertainment bias in the recruitment of families.

Glucokinase Mutations and MODY2

Glucokinase phosphorylates glucose to glucose-6-phosphate in pancreatic beta-cells and hepatocytes, and plays a major role in the regulation and integration of glucose metabolism (30). More than 80 different GCK mutations associated with MODY have been observed to date (15, 31). Expression studies have shown that the enzymatic activity of the mutant proteins was impaired (32),

resulting in decreased glycolytic flux in pancreatic beta-cells (33). This defect translates *in vivo* as a glucose-sensing defect leading to an increase in the blood glucose threshold that triggers insulin secretion (34), and a right shift in the dose response curve of glucose-induced insulin secretion (35). Decreased net accumulation of hepatic glycogen and increased hepatic gluconeogenesis following meals were observed in glucokinase-deficient subjects and contribute to the post-prandial hyperglycemia of MODY2 (36). Despite these multiple defects in the pancreas and the liver, the hyperglycemia associated with GCK mutations is often mild, with fewer than 50% of subjects presenting overt diabetes (15). There is a lower prevalence of diabetes microvascular complications (retinopathy and proteinuria) in MODY2 than in other subtypes of MODY and late-onset Type 2 Diabetes (15, 37).

Mutations in Transcription Factor Genes and MODY

Positional cloning of MODY loci and studies in candidate genes have led to the identification of mutations in six transcription factors: HNF-1 α , HNF-1 β , HNF-4 α , IPF1 and NeuroD1/Beta2 (17, 19, 22–24). Gene targeting in animals has recently demonstrated that many of these islet-expressed genes have a key role in the fetal development, beta-cell differentiation, proliferation and neogenesis (38–40). Mutations in HNF-1 α account for most of the mutations associated with MODY identified in nuclear factors. More than 80 different mutations located in the coding regions or in the promoter were found in various populations (19, 20, 27, 41–45). An insulin secretory defect in the absence of insulin resistance was observed in diabetic and non-diabetic carriers of MODY3 mutations (46, 47), suggesting that HNF-1 α is indeed implicated in pancreatic beta-cell function. In contrast to the usually mild hyperglycemia due to glucokinase deficiency, MODY3 is a severe form of diabetes, often evolving to insulin-requirement. Microvascular complications of diabetes are observed as frequently in MODY3 as in late age of onset Type 2 diabetes subjects (37, 48). HNF-1 α is also expressed in the kidney, and a defect in the renal resorption of glucose is often associated to the pancreatic beta-cell

defect in MODY3 subjects (49, 50). Heterozygous knockout mice lacking one copy of HNF-1 α have a normal phenotype, while MODY3 subjects are all heterozygous for their mutations and fully express the diabetes phenotype (51, 52). This observation suggests that these mutations might have a dominant negative effect. However, experimental data show that only the mutations located in the transactivation domain of HNF-1 α have a dominant negative effect on HNF-1 α transactivation potential (53). Mutations located elsewhere in the protein do not interfere with the activity of the normal allele. The target genes associated with the beta-cell defect of MODY3 remain unknown, and contrasting results were observed in studies of knockout mice (52, 54–56), notably regarding the role of the insulin gene.

MODY1 is much less prevalent than MODY2 and MODY3, and only a few kindred other than the large American RW family were found to carry HNF-4 α mutations (17, 57–59). HNF-4 α is a member of the steroid/thyroid hormone receptor superfamily and upstream regulator of HNF-1 α expression. Interestingly, it was demonstrated that long-chain fatty acids directly modulate the transcriptional activity of HNF-4 α by binding as acyl-CoA thioesters to the ligand-binding domain of HNF-4 α (60). This binding results in the activation or the inhibition of HNF-4 α transcriptional activity as a function of chain length and the degree of saturation of the fatty acyl-CoA ligand (60). This observation contributes important data to the understanding of the role of dietary fats in the control of insulin secretion. Here again, the target genes of HNF-4 α associated with beta-cell defect are not clearly determined (61).

Mutations in HNF-1 β were recently described in a few families with familial diabetes with early onset consistent with MODY (23, 62). In these pedigrees HNF-1 β mutations were associated with diabetes and severe kidney disease which may appear before the impairment of glucose tolerance. Polykystic renal disease and/or particular histological abnormalities showing meganephrons were present in some subjects, suggesting that this gene could play a major role in kidney development and nephron differentiation. It is noteworthy that HNF-1 β and HNF-1 α can form heterodimers to bind to DNA (63).

All of these genetic defects in transcription factors lead to abnormalities of glucose home-

ostasis, and thereby promote the development of chronic hyperglycemia, through alterations in insulin secretion and, possibly, in the development of the pancreatic islets. In this regard, a deletion in the homeodomain transcription factor insulin promoter factor-1 (IPF-1 or IDX-1, STF-1, PDX-1), was found to co-segregate with MODY in a large kindred presenting a consanguineous link (22). This mutation results in a premature stop codon and a protein lacking a domain that is crucial for DNA-binding. The phenotype of the subjects who are heterozygous for the mutation ranges from normal to impaired glucose tolerance to overt non-insulin-dependent diabetes. One child who is homozygous for the mutation was born with pancreatic agenesis, and suffers from diabetes as well as exocrine insufficiency (21). IPF-1 is critically required for the embryonic development of the pancreatic islets as well as for transcriptional regulation of endocrine pancreatic tissue-specific genes in adults, such as the insulin, glucose transporter-2 (GLUT2) and glucokinase genes in beta-cells, and the somatostatin gene in d-cells. IPF-1 is normally expressed in all cells of the pancreatic bud, and its absence in mice arrests development at the bud stage leading to pancreatic agenesis (38).

The transcription factor NeuroD1 (also known as Beta 2) is involved in the regulation of endocrine pancreas development. In mice homozygous for a targeted disruption of NeuroD1, pancreatic islet morphogenesis is abnormal and hyperglycemia develops, due in part to inadequate expression of the insulin gene (39). Recently, mutations in NeuroD1 were shown to co-segregate in with Type 2 diabetes of early age of onset and autosomal dominant-like transmission in two Caucasian kindred (24). This observation suggests that NeuroD1 might also play an important role on endocrine pancreas development and/or insulin gene expression in humans.

Mitochondrial Diabetes and Wolfram Syndrome

Mitochondria contain their own genetic information in the form of a circular DNA molecule of 16 569 base pairs that encodes 13 subunits of the oxidative phosphorylation complex, 2 ribosomal RNAs and 22 transfer RNAs (tRNA) needed for mitochondrial

protein synthesis. Several mitochondrial cytopathies and syndromes caused by point mutations, deletions or duplications of mitochondrial DNA (mtDNA) and characterized by decreased oxidative phosphorylation are associated with diabetes (64, 65). Moreover, about 40 point mutations of mtDNA have been now identified in subjects and families having maternally inherited diabetes as the main phenotypic trait (66). Only one of these mutations, an A to G transition in the mitochondrial tRNA^{Leu(UUR)} gene at base-pair 3243, has been systematically tested and phenotypically characterized in several populations (4, 67–72). It co-segregates in families with diabetes and sensorineural deafness of maternal transmission, a syndrome known as maternally inherited diabetes and deafness (MIDD). In some populations, MIDD might represent 1–3% of all cases of Type 2 diabetes. The same mutation was also observed in patients with MELAS, a syndrome of mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes, which is often accompanied by diabetes and deafness (73). The mechanisms underlying the different phenotypic expression (MIDD or MELAS) are unknown, but might be related to the variable degree of heteroplasmy in different tissues.

Subjects with the 3243 mutation may present with variable clinical features, ranging from normal glucose tolerance to insulin-requiring diabetes. However, abnormalities in insulin secretion were found in all MIDD subjects that were tested, including those with normal glucose tolerance (74). The pathophysiological mechanisms leading to hyperglycemia and often to insulin-requiring diabetes in this syndrome are probably complex and multifactorial, and might include defects in insulin production, glucose toxicity, as well as insulin resistance. However, a defect of glucose-regulated insulin secretion is an early, possible primary abnormality in carriers of the mutation (74). This defect probably results from the progressive reduction of oxidative phosphorylation in beta-cells caused by the accumulation of mutant mitochondrial DNA in the cells (64, 68).

Wolfram syndrome or the acronym DIDMOAD describe patients with diabetes insipidus, diabetes mellitus, optical atrophy and deafness. Other endocrine and neurological abnormalities are often associated in this genetically and clinically heterogeneous syndrome. Wolfram syn-

drome is frequently transmitted as an autosomal recessive disorder by a locus mapped to the short arm chromosome 4. This gene, named WFS1, was recently identified (75, 76). It encodes wolframin, a protein showing no perceptible homology to known DNA or protein sequence (77). The physiological function of wolframin and its link to diabetes remain totally unclear. In contrast with this autosomal recessive transmission, a few cases of Wolfram syndrome were found to be associated with mitochondrial DNA mutations (78, 79).

POLYGENIC FORMS OF TYPE 2 DIABETES

Study of Candidate Genes

The majority of the genes found so far to play a role in the common forms of Type 2 diabetes have been identified by testing candidate genes, that is, genes selected as having a plausible role in the control of glucose homeostasis. This was the most used approach up to now to tackle the genetic determinants of Type 2 diabetes. Although this approach led to the identification of several susceptibility genes with small effects, no genes with moderate or major effect on the polygenic forms of diabetes have been identified. Possible explanations for this failure to identify genes with a major effect include the possibility that they do not exist. It is also possible that our ignorance of the pathophysiological mechanisms of Type 2 diabetes (and the genes that control them) has misled our choice of candidates. Reasons for candidacy are numerous: (1) known or presumed biological function in glucose homeostasis or energy balance in human; (2) gene implicated in subtypes of diabetes, like MODY; (3) gene associated with diabetes or associated traits in animal models; (4) gene responsible for an inherited disease which includes diabetes (mitochondrial cytopathies, Wolfram syndrome); (5) product differentially expressed in diabetic and normal tissues. The study of spontaneous (80), bred (81) or transgenic (38–40, 52, 82, 83) animal models of Type 2 diabetes has greatly improved our knowledge of candidate genes. The genes responsible for diabetes in these models may not necessarily be major players in typical Type 2 diabetes in humans, but such studies provide a

direct way to understand the molecular circuitry that maintains glucose homeostasis.

For obvious reasons, the insulin gene was among the first genes to be studied. Mutations in the coding regions of the insulin gene (chromosome 11p) have been reported in less than ten families, but are not consistently associated with Type 2 diabetes (84). However, mutations in the promoter region could affect the regulation of the insulin gene, leading to a decrease of transcription, and absolute or relative hypoinsulinemia. A variant allele of the promoter was observed in about 5% of African-Americans with Type 2 diabetes, and shown to be associated with decreased transcriptional activity (85). More recently, an association between Type 2 diabetes and paternally transmitted class III alleles of the variable region upstream of the insulin gene (INS-VNTR) was observed in British families (86). Interestingly, class III alleles were also found to be associated with increased length and weight at birth (87) and with a dominant protection against Type 1 diabetes (88) as compared with class I alleles.

The role of the MODY genes and of other transcription factors in the development of the more common forms of late-onset Type 2 diabetes is still under investigation. Regarding the MODY genes, most studies have excluded a major role in the genetic determinants of Type 2 diabetes. However, mutations in HNF-1 α were identified in African-Americans and Japanese subjects with atypical non-autoimmune diabetes with acute onset (89,90), and a common polymorphism in HNF-1 α was found to be associated with mild insulin secretion defects (91). Moreover, mutations in HNF-4 α (92) and IPF1 (93, 94) were recently identified in a few families with late-onset Type 2 diabetes. Several other transcription factors have been studied, and a mutation in Islet Brain 1 (IB1) was found to be associated with diabetes in one family (95). IB1 is a homologue of the c-jun amino-terminal kinase interacting protein 1 (JIP-1), which plays a role in the modulation of apoptosis. IB1 is also a transactivator of the islet glucose transporter GLUT2. The mutant IB1 was found to be unable to prevent apoptosis *in vitro*. It is thus possible that the abnormal function of this mutant IB1 may render beta-cells more susceptible to apoptotic stimuli, thus decreasing beta-cell mass. As glucotoxicity and lipotoxicity are known

to induce both apoptosis and transcription factor down regulation in pancreatic beta-cells, inherited or acquired limitations in IB1 activity could have deleterious effects in beta-cell function.

On the other hand, mutations in PPAR gamma that severely decrease the transactivation potential were found to be co-segregated with extreme insulin resistance, diabetes and hypertension in two families, with autosomal dominant inheritance (96). Interestingly, given the proposed role of PPAR gamma in adipogenesis, no affected family members had any evidence of lipoatrophy or abnormal fat distribution. All together, these data suggest that mutations in transcription factors may contribute to the genetic risk to Type 2 diabetes through various mechanisms: dysregulation of target genes involved in glucose or lipid metabolism (HNFs, PPAR gamma, IPF1, IB1), abnormal beta-cell development and differentiation (IPF1, NeuroD1/Beta2), dysregulation of beta-cell apoptosis (IB1). Deleterious mutations that significantly impair the transactivational activity of these transcription factors can be responsible in some families for monogenic-like forms of diabetes with late age of onset, which may represent an intermediary phenotype between MODY and the most common forms of Type 2 diabetes.

Other genes encoding key components of insulin secretion pathways were tested as potential candidates for a role in the genetic susceptibility of Type 2 diabetes. The pancreatic beta-cell ATP-sensitive potassium channel (IKATP) plays a central role in glucose-induced insulin secretion by linking signals derived from glucose metabolism to cell membrane depolarization and insulin exocytosis (97). IKATP is composed of two distinct subunits, an inwardly rectifying ion channel forming the pore (Kir6.2), and a regulatory subunit, a sulfonylurea receptor (SUR1) belonging to the ATP binding cassette (ABC) superfamily (98). The genes encoding these two subunits are located 4.5 kb apart on the human chromosome 11p. 15.1. Mutations in each of these genes may result in familial persistent hyperinsulinemic hypoglycemia of infancy, demonstrating their role in the regulation of insulin secretion (99). Studies in various populations with different ethnic background provided evidence for associations of single nucleotide polymorphisms (SNPs) in these genes with Type 2 diabetes (100–105). However, sib-pair

analyses in several populations indicated that SUR1/Kir6.2 region is not a major diabetogenic locus (101, 106, 107).

Key components of the insulin signalling pathways were also tested. They were at first thought to be important players in the context of the insulin resistance of Type 2 diabetes. Several of these genes are also expressed in pancreatic beta-cells, and recent results in knockout animals demonstrated that they also play an important role in the mechanisms of insulin secretion (82, 83). More than 50 different mutations have been found in the coding regions of the insulin receptor gene on chromosome 19p (108). However, patients with these mutations seldom present with the common form of Type 2 diabetes (109), but rather with syndromes of severe insulin resistance associated with leprechaunism, or with acanthosis nigricans, hirsutism, and major hyperinsulinemia (110). Missense variants in the coding regions of the gene encoding the first substrate for the insulin receptor kinase (IRS-1) on chromosome 2q have been detected in several populations (111–114). However, association of these variants with diabetes was not observed in all these studies. Similarly, an association between polymorphisms of the muscle glycogen synthase gene (GSY1) on chromosome 19q and Type 2 diabetes was observed in Finnish (115) and in Japanese (116) subjects but not in French subjects (117). Taken together, these results suggest that IRS-1 and GSY1 genes might act in some populations as minor susceptibility genes, which are neither necessary nor sufficient for disease expression, but may nevertheless modulate the phenotype of patients.

Other genes were shown to be implicated in the genetic susceptibility to insulin resistance. Although they do not seem to be directly linked or associated to Type 2 diabetes, they could also modulate the expression of diabetes. A common and widespread polymorphism at codon 905 of the gene encoding the glycogen-associated regulatory subunit of protein phosphatase-1 of the skeletal muscle was shown to be associated with insulin resistance and hypersecretion of insulin in Danish Type 2 diabetes subjects (118). A missense mutation in the intestinal Fatty Acid Binding Protein 2 (FABP2) gene on chromosome 4q was found to be associated with increased fatty acid binding, increased fat oxidation and insulin resistance in

the Pima Indians of Arizona (119), an ethnic group with the highest reported prevalence of Type 2 diabetes and insulin resistance in the world. A point mutation in the gene encoding the beta-3 adrenergic receptor was found to be associated with an increased capacity to gain weight in a population of morbidly obese subjects (120). The same mutation was also associated with reduced metabolic rate and early onset of diabetes (121), and with the development of upper body obesity and insulin resistance (122) in two Type 2 diabetic populations.

Positional Cloning of Type 2 Diabetes Genes

The candidate gene approach presents limitations as it is now clear that at least some Type 2 diabetes susceptibility genes are likely to code for proteins of unknown function or a function not obviously implicated in glucose metabolism. The genome-wide linkage approach attempts to locate these unknown genes by a systematic search throughout the genome. This consists of genotyping the entire genome of affected sib-pairs or families with panels of 250–300 anonymous polymorphic markers to identify regions showing excess of allele sharing with the disease. This strategy requires no presumptions as to the function of the susceptibility loci. This total genome approach has been successful in other multifactorial diseases such as Type 1 diabetes (123) and obesity (5). More than 20 genome-scans for Type 2 diabetes are currently underway, involving thousands of pedigrees from different populations and ethnic groups. One of the limitations of the genome-scan approach is the relatively low power of the method, unable to detect weak linkage signal, which is due to the low relative risk for diabetes in siblings (about 3–5-fold increase compared to the general population). Working on large family collections, in homogeneous ethnic groups, or in large pedigrees using quantitative traits instead of the dichotomous diabetes status could improve the efficiency of linkage detection. Moreover, because of the large number of markers that are tested, false positive results are likely to occur. Thus, stringent criteria for linkage ($p < 10^{-5}$) need to be used to minimize the bias due to multiple testing. Although a large number of regions of presumed

linkage have been mapped in various populations (124–127), identification of the susceptibility genes is proceeding at very slow pace.

Results of several genome-scans have already been published. A locus for Type 2 diabetes on chromosome 2q (NIDDM1) was localized in Mexican Americans (124), and it was shown that an interaction of this locus with a locus on chromosome 15 further increases the susceptibility to diabetes in this population (128). Linkage was found at a locus near *MODY3* on chromosome 12q in Finnish Type 2 diabetes families characterized by predominant insulin secretion defect (125). Evidence for an obesity–diabetes locus on chromosome 11q23–q25 (129) and linkage of several chromosomal regions with pre-diabetic traits (126) were observed in Pima Indians from Arizona, an ethnic group with a high prevalence of diabetes and obesity. A strong linkage between diabetes and chromosome 1q21–1q23 was reported in multi-generational families of Northern European ancestry from Utah (127). Linkages with diabetes and with the age at onset of diabetes were found in a region on chromosome 10q in Mexican American families from San Antonio (130). Evidence for the presence of one or more diabetes loci on chromosome 20 was found in different populations (131, 132). In these and other studies a large amount of loci showing only suggestive or weak indication of linkage with diabetes-related traits have also been reported, several of which fall in overlapping regions. Although many of these loci may represent false positive results, some may harbour true diabetes-susceptibility genes. Comparisons of linkage results in different populations or family collections and/or meta-analysis of the data may now help to guide positional cloning efforts. New statistical methods exploiting multiloci effects or analyzing quantitative traits should lead to more effective results from genome-scan data.

These genome scans have mapped loci within large chromosomal regions containing 10–20 million nucleotides. Now the challenge is to identify the diabetes-related genes within this interval. The classical approach, that consisted in building up a physical map of the region through contiguous artificial chromosomes spanning the entire region of linkage, followed by the cloning of the gene, is limited by the size of the regions of linkage. An integrated genomic approach might be needed. It would combine linkage disequilibrium

mapping, in order to define more precise gene locations, and techniques to pick out the genes of these smaller regions, such as micro-arrays for the identification of genes differentially expressed in diabetic and non-diabetic subjects. These investigations will benefit from recent technological developments in SNP identification and genotyping. Moreover, the results from the Human Genome project, which include genomic DNA sequences, expressed sequences and expression profile data-banks, will certainly make the identification of Type 2 diabetes susceptibility genes by positional cloning much easier. The recent identification by Graeme Bell and co-workers of NIDDM1 as the gene encoding calpain 10 (cAPN10), a non-lysosomal cysteine protease, demonstrates the feasibility of positional cloning of polygenic Type 2 diabetes genes. Currently, it is believed that less than 15% of the genetic determinants of Type 2 diabetes have been unveiled. However, it is likely that other genes contributing to the genetic risk of Type 2 diabetes will soon be discovered.

PERSPECTIVES

Taken together, all the genetic defects described so far account for not more than a few percent of all cases of Type 2 diabetes. The majority of the susceptibility genes to Type 2 diabetes still remains to be described. The fact that Type 2 diabetes is a genetically heterogeneous disorder implies that several primary defects contribute to the susceptibility to the disease. It seems reasonable to postulate that the combinations of deleterious genes are not the same in the obese or the lean forms of Type 2 diabetes, in the patients with an early or a late onset of the disease, in sporadic diabetic subjects or in patients having a strong family history of diabetes. The identification of Type 2 diabetes genes will improve our understanding of the molecular mechanisms that maintain glucose homeostasis and of the precise molecular defects leading to chronic hyperglycemia. A nosological classification of Type 2 diabetes based on primary pathophysiological mechanisms will then be possible. This could lead to the development of more specifically targeted anti-diabetic drugs or even gene-based therapies. Moreover, pharmacogenetic testing might then be

used to predict for each patient the therapeutic response to different classes of drugs. The identification of Type 2 diabetes genes will also provide the tools for the timely identification of high-risk individuals, who might benefit from early behavioural or medical intervention to prevent the development of diabetes. An important reduction in diabetes-related morbidity and mortality could be then expected, along with a reduction in the costs of the treatment of diabetes and its complications.

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Part III

Non-Caucasian Populations

Non-Caucasian North American Populations: African Americans

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SUMMARY

Present day African Americans originated in West Africa and came to the New World during the eighteenth-century slave trade. Their present heterogeneous West African, Native American and European genetic background may be the basis for their 1.5–2-fold greater prevalence of diabetes than whites. The majority of diabetes in adults is Type 2 diabetes. Some of the predisposing factors for diabetes in blacks are similar to whites (age, sex, family history), some are different (generalized obesity, impaired glucose tolerance) and for some there are no reliable data (regional obesity, diet, physical activity). The excess prevalence of diabetes in African Americans is unexplained by the known risk factors and may be related to their specific genetic and environmental interactions.

A unique pathophysiological aspect of Type 2 diabetes in African Americans is the presence of insulin-resistant and insulin sensitive variants. In contrast, insulin-resistance predominates in many other populations such as whites and Hispanics. The insulin-sensitive variant compared to the insulin-resistant variant has a lower cardiovascular disease risk. This may explain the paradox among blacks, who, despite a high prevalence of diabetes and hypertension have lower rates of coronary artery disease. The insulin-sensitive variant, characterized by insulin deficiency, may comprise up to 30% of diabetes in some African American groups. Insulin resistance appears to be more importantly linked with the amount of visceral adipose tissue in both African American men and women with diabetes and not with subcutaneous adipose tissue. Serum triglycerides levels are also

linked to visceral adipose tissue volume and liver fat content. Thus, the actual frequency of the insulin-sensitive and insulin-resistant subtypes may be related to the degree of visceral adiposity in the particular population which is likely to be both environmentally and genetically determined.

There are unusual clinical variants of Type 2 diabetes among African Americans: among those presenting with severe symptomatic hyperglycemia there is a component of pancreatic beta-cell recovery resulting in long-term remissions (>3 years) off anti-diabetic therapy without marked weight loss. In addition, adults not infrequently present with diabetic ketoacidosis yet have Type 2 diabetes: they are GAD and islet cell antibody negative, insulin-resistant, with relatively decreased insulin levels. They are obese, have family histories of diabetes and a clinical course typical of Type 2 diabetes, requiring diet, oral agents or insulin for control of hyperglycemia.

In contrast to adults, in whom Type 2 diabetes is more common than whites, among children Type 1 diabetes is much less frequent than in whites but more frequent than native Africans, in whom it is uncommon. This is thought to be due to a genetic admixture with European diabetes susceptibility genes. Among children and adolescents there is a distinct maturity-onset-diabetes of youth (MODY): acute hyperglycemic presentation, with and without diabetic ketoacidosis, variable obesity, positive family history of diabetes, absence of autoimmune markers and absence of an absolute requirement for insulin treatment.

The microvascular complications of diabetes, particularly retinopathy, nephropathy and amputations, affect African Americans disproportionately while the rates of macrovascular disease are lower.

PREVALENCE

Prevalence data for African Americans with Type 2 diabetes comes from the National Health Interview Survey (NHIS), an annual population-based interview of physician-diagnosed illnesses (1) and the Second National Health and Nutrition Examination Survey (NHANES II), 1976–80, which screened for diabetes mellitus using the 2-hour oral glucose tolerance test (2, 3). NHANES II data should be interpreted with some caution because of the small numbers of African Americans who completed the oral glucose tolerance test compared to whites ($n = 351$ vs 3348). These epidemiologic data did not distinguish African Americans by their complex genetic background including European, West African and Native American Indian (4, 5).

The age-adjusted prevalence of physician-diagnosed diabetes is comparable in African Americans and whites below the age of 45 years, 2-fold greater over age 45 years, and 16% in African Americans over age 75 years (Figure 9A.1). These

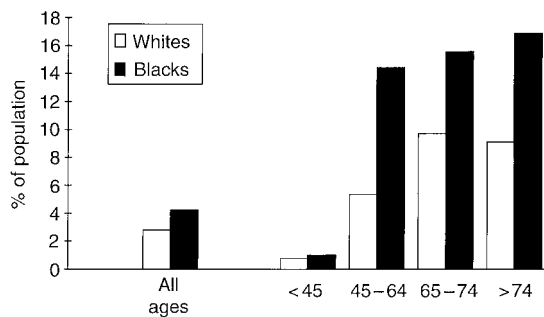


Figure 9A.1 Percentage of diagnosed diabetes among US blacks and whites, 1994, NHIS

Source: National Center for Health Statistics (1)

represent large numbers of subjects with diagnosed diabetes (Table 9A.1). The prevalence of diabetes in adults has increased ~4 fold from 1963 to 1990 (Figure 9A.2) with African American women having the highest rates and largest increases (6).

NHANES II, using oral glucose tolerance testing, found nearly half of both African American (and white) individuals with diabetes in the United States are undiagnosed, suggesting a large burden of potential diabetic complications (2, 7). Figure 9A.3 shows total rates of diabetes (diagnosed and undiagnosed) by race, sex and age (7). African American women have higher rates at all ages except in the oldest age group of 65–74 years. Figure 9A.4 shows the separate rates of previously and newly diagnosed diabetes and impaired glucose tolerance by age in African Americans and whites (2). The overall age standardized prevalence of diagnosed and undiagnosed diabetes in African Americans is 1.5 times whites.

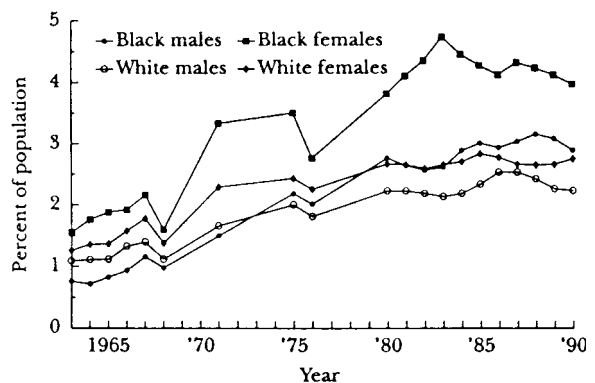


Figure 9A.2 Time trends in the percentage of black and white men and women with diagnosed diabetes, US, 1963–90 (NHIS)

Source: National Center for Health Statistics (182)

Table 9A.1 Number of persons (in 1000s) with diagnosed diabetes, US 1992–94 (NHIS)

Age (years)	1992		1993		1994		1992–1994 Average	
	Black	White	Black	White	Black	White	Black	White
<45	216	1033	304	1151	260	1086	260	1090
45–64	408	2238	578	2413	740	2314	575	2322
65–74	367	1710	292	1576	242	1572	300	1619
≥75	155	1106	141	1161	164	1053	153	1107
Total	1146	6087	1315	6331	1406	6025	1288	6138

Sources: National Center for Health Statistics (1, 183, 184)

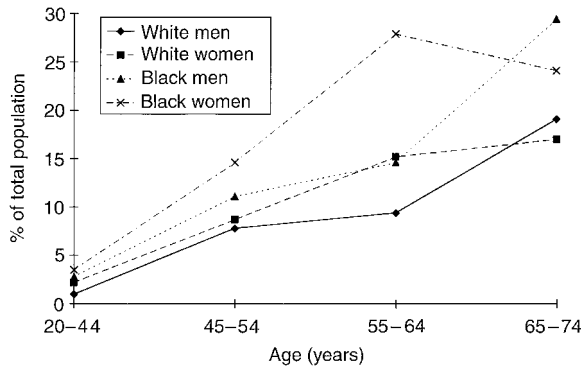


Figure 9A.3 Percentage of the population with diagnosed and undiagnosed diabetes (WHO criteria), by age, sex and race, 1976–80 (NHANES II)

Source: Reproduced from (7) by permission

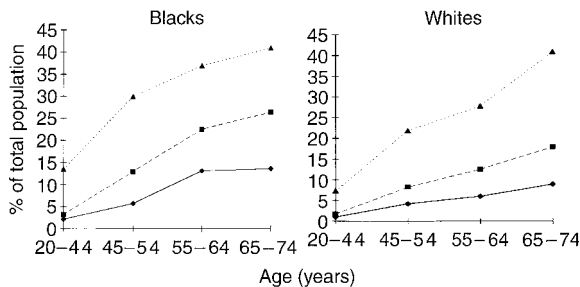


Figure 9A.4 Percentage of the population with glucose intolerance—WHO criteria (diagnosed diabetes [solid line], undiagnosed diabetes [dashed line] impaired glucose tolerance [dotted line]) by race and age

Source: Reproduced from (2) by permission

INCIDENCE

The incidence of diabetes in African Americans has been estimated from NHANES I (1971–75) follow-up data until 1987 (8). Among 11 097 participants (9532 white and 1566 black) who were between the ages of 20 to 70 years at baseline, 880 incident cases developed. Since blood glucose was not originally measured, it is possible that some of the cases which developed represent previously undiagnosed diabetes. The age-adjusted incidence of diabetes over the duration of the study was 15.0% in African American women and 10.9% in men (comparable data in whites was 7% for both sexes).

RISK FACTORS FOR TYPE 2 DIABETES

Information on risk factors is derived from cross-sectional studies since there are no good longitudinal data.

Age, Sex and Family History of Diabetes

Both age and sex are risk factors for diabetes, with African American women having a greater risk than men and both sexes having a greater risk with increasing age, Figure 9A.3 (1–3,6–8).

Family history of diabetes was determined in NHANES II: among previously and newly diagnosed African American diabetic subjects, age 20–54 years, ~25% had a parent and ~50% had a sibling with diabetes. In contrast, in individuals without diabetes, 19% had a parent with diabetes and 8% had a sibling with diabetes. The age-standardized prevalence of diabetes increased with numbers of diabetic first-degree relatives (Table 9A.2). African American individuals with 0, 1 and >2 relatives with diabetes had prevalence rates of diabetes of 7.8%, 11.8 and 23.3% respectively; corresponding rates for whites were 4.6, 8.4 and 16.3% (9). This supports a possible dose effect for inherited diabetes risk factors (10).

Candidate Genes, Diet and Physical Activity

There are few data on African Americans on the relationship of these factors to diabetes. While

Table 9A.2 Family history of diabetes as a risk factor for diabetes

	Relative rates of diabetes* by number of family members with diabetes	
	1 vs 0	≥2 vs 0
Black	1.5	3.0
White	1.8	3.6

*Ratios of age standardized rates of diagnosed and undiagnosed diabetes, age 20–74.

Source: Reproduced by permission from Harris MI. Epidemiological correlates of Type 2 diabetes in Hispanics, whites and blacks in the US population. *Diabetes Care* (1991); **14** (suppl 3): 639–648.

candidate genes do not explain the common forms of diabetes (11–14), the Z+4 allele of the glucokinase gene was found to have an age-, sex- and BMI-adjusted odds ratio of 2.9 with onset of diabetes ~10 years earlier in subjects of African ancestry (15,16). NHANES II dietary data showed similar nutrient distributions among African American and white diabetics (7). Although higher levels of habitual physical activity are associated with lower prevalence of diabetes in various population studies (17–25), cross-sectional data showed increased work activity and decreased diabetes (previously and newly diagnosed) in Mexican Americans but not in African Americans or whites (10).

Socio-economic Status

In NHANES II, the rate of diabetes in African Americans declined with increasing income from poverty to middle-income without a further decline in the upper income level (7, 10, 26). Less than elementary school education was associated with a higher rate of diabetes compared to education beyond this. After adjusting for obesity and age however, income and education were not strong risks for diabetes in African Americans.

Impaired Glucose Tolerance (IGT)

Often considered a pre-diabetic state (27), IGT constitutes nearly two-thirds of the total glucose intolerance in the US population (IGT, diagnosed and undiagnosed diabetes) (28). In contrast to diabetes, age-specific prevalence rates are similar in African Americans and whites. In whites and African American males, IGT increases with age, but in African American females, IGT declines after age 55 years. Among African American women age 65–74, the lower rate of IGT is not due to greater conversion to diabetes since the total glucose intolerance is lower (2) and may reflect increased mortality in this group.

Obesity

Table 9A.3 shows diabetic subjects are more obese than non-diabetic subjects; African American

Table 9A.3 Mean body mass index (BMI) in persons age 20–74 years, NHANES II, (1976–80), based on diabetes status

	Black		White	
	Men	Women	Men	Women
Previously DX diabetes	29.4	31.0	26.9	28.2
Newly Dx diabetes	*	31.4	26.7	31.3
Impaired glucose tolerance	27.5	29.7	27.4	27.4
Non-diabetic	25.3	26.0	25.2	24.2

Source: Cowie CC, Harris M et al. *Diabetes in America*, 2nd edn. National Institute of Health, 1995: appendix 7.9, p. 141, reproduced by permission.

women are more obese than white women regardless of glucose tolerance status (26). The percentage of African American (58.8%) and white (45.2%) women with Type 2 diabetes who are obese (BMI > 30 kg/m²) is greater than African American or white men (24.4 and 20.5% respectively) and highest among African American women (27).

The increased prevalence of Type 2 diabetes among African Americans is unlikely to be due simply to increased obesity. After adjusting for covariates, obesity was associated with a higher risk of diabetes among African Americans relative to whites (26): at ideal bodyweight, the risk of diabetes was similar in African Americans and whites, but rose to 1.7 times at 150% of ideal bodyweight. This may be because BMI is not the ideal measure for metabolically important risk factor(s) for diabetes; measures of central or visceral adipose tissue may be better markers of increased risk. In other groups, longitudinal studies show the progression of normal to impaired glucose tolerance is associated with an increase in insulin but without an increase in bodyweight in 30% of cases; these cases had an increase in central obesity (29,30).

Regional Obesity

Although central obesity is associated with numerous adverse health outcomes (31–33), its role in African Americans is uncertain due to inadequate longitudinal studies. Whether the adverse effects of central obesity are mediated through insulin resistance or whether it is simply a marker for other defects is unknown. Beginning in

childhood, non diabetic African Americans have greater central obesity than whites (34–36). Among whites, diabetes is more frequent with increased central obesity (32,33). Longitudinal NHANES I follow-up data suggest that higher central obesity predicts diabetes in both African Americans and whites (7). However, cross-sectional NHANES II data show the frequency of diabetes is independent of central obesity (subscapular:triceps skinfold thickness) in blacks but not whites (27). Similarly, glucose intolerant and normoglycemic Afro-Caribbean men had similar measures of central obesity (WHR, WTR, sagittal abdominal diameter) while glucose-intolerant European men had greater central obesity than their normoglycemic counterparts (37); Afro-Caribbean men had lower while Afro-Caribbean women had higher waist girths than their respective European counterparts (37,38,39). These inconsistencies suggest that central obesity, as measured anthropometrically, may not be an optimum interracial yardstick for metabolically important fat depots: Conway (40) and others (41,42) report the WHR (anthropometry) measures 23% less visceral adipose tissue determined by magnetic resonance imaging in African American compared to white women. Thus, the diabetes risk of regional obesity must be assessed with direct techniques.

A unifying hypothesis may be that among African Americans, insulin deficiency is as important a risk factor for diabetes as central obesity with its attendant insulin resistance (40–42). Longitudinal studies are needed to delineate the relative roles of insulin deficiency as well as general vs regional obesity as risk factors for diabetes.

Insulin Resistance

Using cross-sectional data, an increase in underlying insulin resistance in African Americans has been proposed to explain their increased prevalence of diabetes (43,44). Insulin resistance is typically inferred from elevated fasting plasma insulin levels or from insulin responses to oral or intravenous glucose. The frequently sampled intravenous glucose tolerance test (FSIVGTT) (45,46) and the euglycemic insulin clamp ('gold standard') are used less often to determine insulin resistance (47).

The case for increased insulin resistance among African Americans compared to whites is difficult to make with certainty from the cross-sectional data available. Variable fasting *plasma insulin* levels have been reported in African Americans compared to whites (higher in six studies [48–52] including children (53), the same in eight studies [54–61] and lower in one study of newly diagnosed diabetics [62]). There is no consistent relationship between the fasting plasma insulin and the insulin responses to oral or intravenous glucose. All five studies which measured insulin responses showed higher insulin responses in African Americans than in whites but only one reported higher fasting plasma insulin, the rest were similar to whites. Additionally, higher insulin responses to stimuli may represent decreased hepatic extraction (55, 59) or differences in proinsulin–insulin ratios (63); also fasting plasma insulin is not a good measure of insulin resistance (64). Thus, based on plasma insulin as surrogate for insulin-resistance, it is not clear whether African Americans are more insulin-resistant than whites.

Using the *FSIVGTT-SI*, Osei reported that non-diabetic African Americans without significant differences in BMI were more insulin-resistant than whites (59,43). Similarly, the IRAS epidemiology study (52) found that non-diabetic African Americans compared to whites were more insulin-resistant after multivariate adjustment for the increased obesity, smoking and sedentary behavior in African Americans. Osei (43) reports among African Americans, non-diabetic first-degree relatives of Type 2 diabetic subjects were as insulin-resistant as non-diabetic controls and had similar insulin and glucose responses to oral glucose despite a greater BMI (28 vs 24). In contrast, among whites, the first-degree relatives had a greater BMI and were more insulin-resistant than controls. Comparing the African American and white relatives, despite a 52% greater insulin resistance in blacks, their insulin levels in response to oral glucose were paradoxically similar. Osei's data suggest: (1) relative to their insulin resistance, African Americans are relatively insulin-deficient; (2) in the range of 24–28 kg/m², the BMI may not equally measure physiologically equivalent obesity in whites as in African Americans.

In contrast, two studies in non-diabetic African Americans subjects used the *euglycemic insulin clamp* and reported no differences in insulin action

compared to whites: one studied overweight African American and white men with similar body mass indices (30.8 vs 32.9 kg/m²) and percent body fat levels (25 vs 30%) (61) and the other (65) studied lean young non-hypertensive African American men (BMI 23.8) in whom insulin action was similar to published data in control subjects (66,67).

Thus, whether underlying insulin resistance, independent of obesity, is a risk factor for the excess prevalence of diabetes in African Americans is complex and unknown at the present.

IS THERE A METABOLIC INSULIN RESISTANCE SYNDROME IN AFRICAN AMERICANS?

Insulin resistance, glucose intolerance, hyperinsulinemia, central obesity, dyslipidemia, hypertension and macrovascular disease are components of the metabolic insulin resistance syndrome (68). If the syndrome exists in a population and the components are causally related, then targeting the primary defect might eliminate the cascade of abnormalities. Selective reporting of the components makes assessment difficult in African Americans; the association of hyperinsulinemia and hypertension is weakest (Table 9A.4).

Hyperinsulinemia

Increased plasma insulin levels were associated with higher triglyceride, glucose and LDL-cholesterol levels in both African American and white non-diabetic subjects; this association was strongest for lean and less so for obese subjects (51,76). Among young African American subjects, after adjusting for percent body fat, WHR was associated with various cardiovascular risk factors [triglyceride, HDL-cholesterol, LDL cholesterol (women only), apo-lipoprotein A-1 and B, uric acid, systolic BP]; fasting plasma insulin only partly explained these associations (40,57), suggesting that hyperinsulinemia may be a marker and not the basis for the metabolic syndrome. Reports show African Americans have more favorable lipid profiles than whites including lower triglycerides and higher HDL-cholesterol levels despite similar or higher fasting plasma insulin

levels, central obesity and glucose intolerance (48,49,56,69,70). However, within the African American population, plasma insulin is related to central obesity, glucose and plasma triglycerides (48,49,56), Table 9A.4. For the association of hyperinsulinemia and hypertension, some show a relationship (65,56,48), the majority do not (51,55,61,71,73–75).

Insulin Resistance

Several reports show an inverse relationship between clamp-derived insulin resistance and triglycerides in African American diabetic subjects (71,72). Chaiken (71) found *no* relationship with insulin resistance and hypertension in diabetic African American subjects; Saad (61) found similar results in non-diabetic African American but not white men. Karter reported an association of insulin resistance (SI derived from FSIVGTT) and waist circumference among African Americans which was weaker than in Hispanics and whites (60).

PATHOGENESIS OF TYPE 2 DIABETES IN AFRICAN AMERICANS

Insulin-sensitive and -resistant Variants in Type 2 Diabetes in African Americans

Type 2 diabetes in African Americans is a heterogeneous disorder with insulin-sensitive and insulin-resistant variants identified using the euglycemic insulin clamp method (77). In contrast, most studies (66,78,79) with few exceptions (80,81,82) report Type 2 diabetes to be a disorder of insulin resistance. The two variants are notably different in terms of cardiovascular risk factors and body composition (72,83,84). The insulin-sensitive variant has low lipid levels while the insulin-resistant variant has higher lipid levels.

The relationship of insulin action to obesity was studied: most obese African American Type 2 diabetes subjects (BMI > 30 kg/m²) were insulin-resistant, but below this level, they were equally likely to be insulin-resistant as insulin-sensitive (85). Further body composition studies using 23 scan computed tomographic techniques showed among modestly obese to lean diabetics (BMI 26.3 men

Table 9A.4 Association of plasma insulin or insulin resistance to the components of the metabolic syndrome X in black subjects

	Plasma insulin	Insulin resistance	Blood pressure	Glucose intolerance	Trig	HDL- chol	Central obesity SSST/waist/WHR	Comments
Fontbonne Telecom (48)	X		Yes	Yes	Yes		Yes	Associations found in groups based on high and low plasma insulin level Children and adolescents—selected by extremes of plasma VLDL and LDL cholesterol levels Ref (54): X-sectional data, association with central fat not seen in thin or sexually immature children; Ref (73): 6-year longitudinal data
Freedman (54)	X		No		Yes		Yes	
Jiang Bogalusa (73)	X							
McKeigue (56)	X		Yes	Yes	Yes		Yes	Association reported for mean only
Nabulsi (51)	X		No	Yes	Yes		Yes	Associations stronger for lean versus obese subjects
Folsom	X						Yes	
ARIC (76)								
Folsom (50)	X				Yes	Yes	Yes	Association of % body fat and CV risk factors not explained entirely by plasma insulin levels
Manolio								
CARDIA (57)	X						Yes	
Karter	X	X						
IRAS (60)								
Chaturvedi (49)	X				Yes			
Cruikshank (55)	X		No	Yes				
Falkner (65)	X	X	Yes					
Saad (61)	X	X	No					Young lean hypertensive and normotensive men Young modestly obese US men Association found in whites but not blacks
Osei (74)	X				No	No	Yes	1st-degree non-diabetic relatives of Type 2 diabetic subjects
Gaillard (75)	X		No	Yes	Yes*	No		1st-degree relatives of Type 2 diabetes US blacks $n = 200$ *association only in highest insulin quintile
Chaiken (71)		X	No		Yes	Yes*		Diabetic subjects *men only
Banerji (84, 86)		X			Yes		Yes	Diabetic subjects Central obesity = total visceral fat measured by computed tomography

Trig = serum triglyceride levels HDL-chol = serum HDL-cholesterol levels SSST = subscapular or skinfold thickness
 WHR = waist to hip ratio

and 27.7 women), insulin-sensitive subjects had significantly lower visceral or intraabdominal adipose tissue volume compared with the insulin-resistant variants (84). In contrast, there were no differences in subcutaneous adipose tissue volume. Comparing men and women with Type 2 diabetes, total visceral adipose tissue volume was not different while total or subcutaneous adipose tissue was 2-fold greater in women (84). Insulin-mediated glucose disposal, derived using euglycemic clamp studies, was inversely related to visceral adipose tissue in both men and women while there was no such relationship with subcutaneous adipose tissue, Figure 9A.5. Increased visceral adipose tissue was related to increased liver fat (measured by CT density) (86). Liver fat content may alter the dynamics of hepatic insulin clearance (87) and thus, insulin resistance and hyperinsulinemia may both be the result of increased visceral adipose tissue and hepatic fat. Whether insulin sensitivity or visceral adipose tissue is genetically or environmentally determined is not known; however, differences in HLA-DQ subtyping in the resistant and sensitive variants (88) suggest a genetic component.

Insulin-sensitive subjects have low plasma LDL-cholesterol and triglyceride levels compared to insulin-resistant subjects, suggesting markedly

different cardiovascular disease outcomes (72,83). Serum triglyceride is inversely related to insulin mediated glucose disposal levels, visceral fat and liver fat (86). The presence of insulin-resistant and insulin-sensitive diabetic subtypes with differing cardiovascular risk factors is consistent with the lower serum triglyceride levels and higher HDL-cholesterol levels found among African Americans and Afro Caribbeans compared to whites (48,51,56,69) and their lower rates of cardiovascular disease (6,55).

Several studies estimate the frequency of insulin-sensitive compared to insulin-resistant subtypes. Chaiken reports that 30% or 27 of 90 unselected African American clinic-based Type 2 diabetes subjects with a BMI ≤ 30 kg/m², were insulin-sensitive (euglycemic insulin clamp technique) (71). Ginsberg showed that following treatment of hyperglycemia, some African Americans Type 2 diabetes subjects were normally insulin-sensitive (89). In contrast, a small subset of the IRAS population-based study showed that only 11% of African American Type 2 diabetes subjects with a BMI < 30 kg/m² ($n = 60$) were insulin-sensitive, using the FSIVGTT-S1 (44).

Whether differences in frequency of insulin sensitivity among studies of African Americans

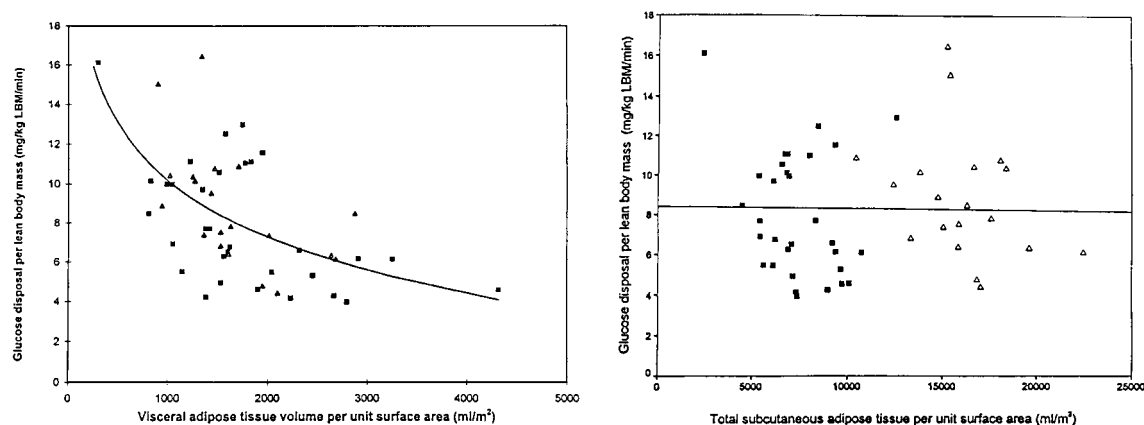


Figure 9A.5 Relationship of insulin-mediated glucose disposal ($\text{mg} \cdot \text{kg} \text{ lean body mass (LBM)}^{-1} \cdot \text{min}^{-1}$) during a $1 \text{ mU} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ euglycemic insulin clamp with adipose tissue distribution in black men (filled squares) and women (open triangles) with Type 2 diabetes

Panel A: Glucose disposal and total visceral adipose tissue volume (ml/m^2 body surface area, BSA); equation for line shown is $y = -4.15 \ln(x) + 38.86$. Correlation coefficient = -0.58 , $p = 0.0001$

Panel B: Glucose disposal and total subcutaneous adipose tissue volume (ml/m^2 body surface area, BSA), correlation coefficient = -0.27 , $p = \text{not significant}$

Source: Reproduced from (84) by permission.

with Type 2 diabetes are due to differences in amounts of visceral adipose tissue, inherent population differences or technique is not known. Insulin action measured by the FSIVGTT-S1 may not be equivalent to euglycemic insulin clamp technique in diabetic subjects (45). Therefore, based on the evidence, one can conclude that above a BMI of 30, African Americans with diabetes are likely to be insulin-resistant and below this, up to 30% are likely to be insulin-sensitive.

Pancreatic Beta-cell Failure

Since diabetes in African Americans is metabolically heterogeneous (6, 62, 67, 69, 70, 77, 82), it suggests that a larger proportion of diabetes may be accounted for by poorer beta-cell reserve occurring in the absence of marked insulin resistance. This concept is supported by: (1) UKPDS data showing Afro-Caribbean blacks had lower insulin secretion and were more insulin-sensitive than European, based on the HOMA method (62); (2) physiological data showing markedly insulin-deficient (insulin-sensitive) versus relatively insulin-deficient (insulin-resistant) subtypes in African Americans (77) as well as South African black data showing marked insulin deficiency with Type 2 diabetes (90); and (3) epidemiological data showing more African American adults with diabetes use insulin than whites (91). Although insulin deficiency as a primary etiology for diabetes has also been reported in non-African American populations (lean white US male veterans, Swedish and Japanese subjects [80–82]), it is not considered very common.

CLINICAL VARIANTS OF DIABETES IN AFRICAN AMERICANS

Remission in Diabetes

African American subjects with Type 2 diabetes who present with severe hyperglycemia may develop long-lasting remissions (92, 93). At the time of presentation, these individuals require hospitalization for severe symptomatic hyperglycemia (mean glucose 600 mg/dl, 33.3 mM) and following a period of treatment, with anti-diabetic pharmacologic agents they are able to discontinue

these agents and remain in near normoglycemic remission with *normal* HbA1C levels. They are able to maintain this for years on their own version of a 'diet' including occasional icecream, cake and barbecue (92, 94–99).

The development of remission is *not* associated with: (1) marked weight loss; (2) reversal of stressful illness; or (3) a 'transient honeymoon', or variant of immunologically mediated Type 1 diabetes as evidenced by absent islet cell and glutamic acid decarboxylase antibodies (92).

The *clinical characteristics* of 72 individuals who developed remission were: mean age 48 years, BMI 27.6 kg/m² (range 21–35); two-thirds were men. All had newly diagnosed Type 2 diabetes and remission developed within 12 months. Most patients participated in intensive glycemic monitoring and regulation. Although the hemoglobin A1C was within normal range and mean fasting plasma glucoses were 110 mg/dl (6.1 mmol/l), oral glucose tolerance testing showed that 36/72 (50%) had a diabetic glucose tolerance test (2 hour plasma glucose 239 mg/dl or 13.3 mmol/l), 24/72 (33%) had impaired glucose tolerance and 12/72 (25%) had normal glucose tolerance. Nearly all the individuals with normal glucose tolerance were insulin-sensitive, whereas only half of those with diabetic or impaired glucose tolerance were insulin-sensitive, using the euglycemic insulin clamp technique.

Long-term follow-up of 8 years showed that remission was maintained for a median of 40 months or 3.3 years (Figure 9A.6) (93). A small separate subset have been in remission for 10–15 years. Additionally, once in remission, the usual medical or surgical 'stresses' did not perturb glucose homeostasis and precipitate a relapse to hyperglycemia.

To determine whether *remission could be prolonged* with low doses of pharmacologic agents, a small double-blind placebo-controlled study was performed: treatment with glipizide (1.25–2.5 mg/day) for 3.5 years significantly prolonged the duration of remission compared to placebo (100).

To determine the *frequency of remission*, all newly diagnosed Type 2 diabetes subjects hospitalized with symptomatic hyperglycemia over 300 mg/dl (16.7 mmol/l), were treated intensively after discharge with multiple doses of insulin, diet and diabetes education. The hypothesis was that intensive glycemic regulation would reverse any element of glucose toxicity and potentially allow

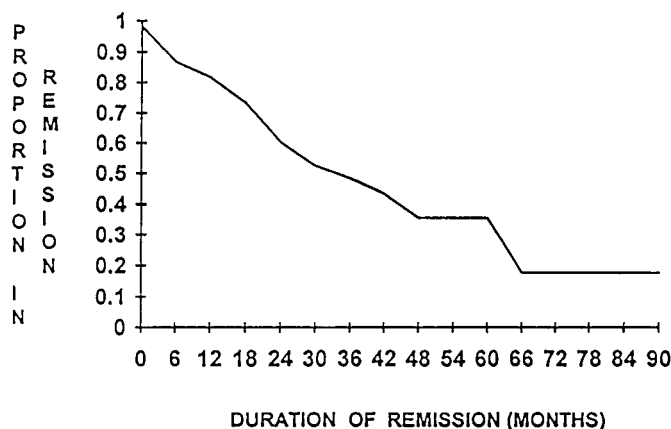


Figure 9A.6 Proportion of black individuals remaining in remission over time: survival curve

Source: Reproduced from (93), Figure 1, by permission

for the recovery of pancreatic beta-cell secretory capacity essential for the remission. Of the first 26 patients followed for 120 days, 40% developed a remission (101). This series has been extended to over 100 patients with similar results. Comparing those who did and did not develop a remission, presenting plasma glucoses, BMI, change in weight with treatment and HbA1C levels achieved with treatment were similar. The *mechanism for remission* must in some way be based on the recovery of insulin secretory capacity since those who developed a remission had a greater recovery of insulin secretion. On the basis of a previous series, individuals who are in remission are as likely to be insulin-resistant as insulin-sensitive and therefore this would not distinguish remitters from non remitters.

Umpierrez (102) reports that initial insulin treatment of African American subjects presenting with severe hyperglycemia results in a partial recovery of insulin secretory capacity with good glycemic control being maintained with low doses of sulfonylureas.

Morrison (103) has reported 'phasic diabetes' in Jamaican blacks: patients who present with severe symptomatic hyperglycemia and then do not return for treatment for prolonged periods and are relatively asymptomatic despite hyperglycemia.

Thus, near normoglycemic remissions, with normal HbA1C levels, occur in a predictable percentage of newly diagnosed African American Type 2 diabetes subjects who are intensively treated at the outset; this phenomenon is unasso-

ciated with weight loss, reversal of medical illness or 'stress', islet cell antibodies and does not appear to occur in longstanding diabetes. The duration of remission is significant and can be prolonged with low doses of sulfonylureas. The mechanism is related to the recovery of pancreatic insulin secretion. This phenomenon has not yet been exploited as a widespread approach to the treatment of diabetes in blacks.

Diabetic Ketoacidosis (DKA) in African American Adults with Type 2 Diabetes

Adult African Americans may present with DKA as their initial manifestation of diabetes, often without any precipitating events. A series of 21 cases (80% were newly diagnosed) showed that following treatment these individuals had a clinical course of Type 2 diabetes (104). Their mean presenting plasma glucose was 693 mg/dl (38.5 mM), pH 7.18, age 45 years and BMI 28.7 kg/m². Metabolic studies performed several months after the episode found all were insulin-resistant with significant residual C-peptide levels (but less than normal controls) in response to oral glucose stimulation. Because of the clinical course, metabolic studies and the uniform absence of glutamic acid decarboxylase antibodies these subjects are considered to be Type 2 diabetes. Interestingly, these subjects had an increase in either HLA DR 3 or DR4. Morrison (103) has reported similar cases in Jamaican blacks, who

present with DKA or severe hyperglycemia who are ultimately not insulin-dependent.

Umpierrez (105) also reported African Americans presenting with DKA, all of whom were eventually considered to be Type 2 diabetes: none had islet cell antibodies and 25/35 obese patients with DKA and 16/22 hyperglycemic patients without DKA were able to discontinue insulin treatment during follow-up. Initially, insulin response to carbohydrate stimulus was minimal, however after 3 months, there was significant improvement albeit not to normal. Among 56 consecutive admissions of African American patients who presented to hospital with DKA, 25% were newly presenting and 75% were previously diagnosed. Among the latter, 67% had stopped their insulin, 14% had an infection, 5% had other illnesses and 14% had no identifiable cause (106).

Atypical Diabetes of Childhood

Not all diabetes in childhood represents autoimmune Type 1 diabetes and a distinct minority has an atypical version. Winter (107) described African American youths who presented with severe hyperglycemia, varying degrees of obesity, with and without ketoacidosis, who subsequently did not have an obligate requirement for insulin. There was no evidence of autoimmune markers nor an increase in frequency of HLA DR3 and HLA DR4. They represented ~9% of their clinic population. In a community incidence study, Lipton found that 7 of African American boys and 16% of African American girls were obese and many had positive family histories of diabetes suggesting atypical diabetes (108). Another clinic-based study notes that 50% of African American children and adolescents with Type 2 diabetes had presented with diabetic ketoacidosis and were obese. Type 2 diabetes was diagnosed by virtue of the lack of insulin dependence for short-term survival and lack of autoimmune markers. They did not identify an autosomal dominant mode of inheritance (109).

Insulin-dependent Diabetes Mellitus in African American Children

Among African American children, Type 1 diabetes is much less common than among whites (91).

The incidence of Type 1 diabetes among African American children <15 years of age varies geographically from 12.0 to 3.3 per 100 000 per year (110–112). In contrast, among whites, the incidence ranges from 13.8 to 16.9 per 100 000 per year. As with other groups, diabetes is diagnosed less often in the summer. There may be a higher prevalence among girls than boys (108, 111–115). The frequency of childhood diabetes in African Americans, whose slave ancestors originated in Western Africa, is intermediate between Western African children (in whom it is rare) and American whites (116, 117). It has therefore been hypothesized that Type 1 diabetes occurs in African Americans primarily as a result of an influx of Caucasian-derived diabetes susceptibility genes (118–120). The regional differences in frequency of Type 1 diabetes in US blacks may reflect differences in genetic admixture with Caucasians or different genetic-environmental interactions.

Type 1 diabetes is an autoimmune disorder. Polymorphism among certain class II immunoregulatory amino acid residues is strongly associated with Type 1 diabetes. In humans, the class II genes are found in the major histocompatibility complex in the HLA-D region of the short arm of chromosome 6. Specific alterations in amino acid sequences affect peptide-binding and antigen-presenting capacities of the major histocompatibility complex (121). There is an increased frequency of HLA DR3 and HLA DR4 in Type 1 diabetes populations, the highest frequency being associated with heterozygous HLA DR3/HLA DR4 genotypes (122). While the frequency of HLA DR3 and HLA DR4 is lower in the African American population (123) compared to whites, their frequencies are increased in both African American, Afro-Caribbean (black) and white Type 1 diabetes populations (124–126). HLA DR7 and HLA DR9 are also positively associated with Type 1 diabetes in blacks but not in whites (127). Among blacks, the HLA DR and HLA DQ relationships are different from whites: the HLA DQA1 allele, DQA1*0301 and the HLA DQB1 alleles, DQB1*0201 and DQB1*0302 are positively associated with Type 1 diabetes (128).

The presence of aspartic acid at the 57th position of the HLA DQ beta chain confers resistance to Type 1 diabetes while a non-aspartic acid residue is strongly associated with susceptibility in many populations, including African

Americans (120, 129, 130). Interestingly, among African Americans and whites with Type 1 diabetes there was no difference in the frequency of this marker.

COMPLICATIONS OF DIABETES

Retinopathy

African Americans with diabetes have more retinopathy than whites (131): up to 40% more severe retinopathy (self-reported, NHIS, 1977) (7) and 30–300% more blindness in diabetic African American men and women respectively compared to their white counterparts (132–134). This may be related to a greater frequency or to risk factors and to inadequate health care delivery: a report of 51 adult African American diabetic subjects who received an initial ophthalmologic examination showed the median time to be 11.5 years after diagnosis and 37.5% had severe retinopathy (135).

Although African Americans do have more retinopathy than whites, the data do not suggest that they are inherently more susceptible to retinopathy than whites. NHANES III data, using fundal photography in diagnosed diabetics, showed that while any retinopathy was 46% higher in African Americans than whites (prevalence 18.2% vs 26.5%, $p = 0.07$), there was no difference after adjusting for risk factors for retinopathy, including blood pressure and severity of diabetes (duration of diabetes, hemoglobin A1C level, treatment with insulin and oral agents) (133). The prevalence of proliferative retinopathy was similar in the two groups (0.9% and 1.8% for AA and whites respectively). Similarly, there was no difference in non proliferative retinopathy (direct ophthalmoscopy) in Afro-Caribbean Jamaicans compared to whites with Type 2 diabetes after correcting for glycemia and other risk factors (134).

Among 70 consecutive newly diagnosed Type 2 diabetic African American subjects who presented with symptoms of hyperglycemia, 15% had background retinopathy when examined within 0–9 months of diagnosis (7 field fundal photographs) (136) which is similar to that in another study of urban blacks (137). These data are comparable to other populations (138).

Nephropathy

End-stage Renal Disease (ESRD)

Prevalence and incidence. Among both African Americans and whites with ESRD, diabetes accounts for 30% of ESRD (139, 140). Data from the Michigan Kidney Registry, from 1974 to 1983 (470 African American and 861 white diabetics with ESRD) shows an annual age-adjusted rate of 127.8/100 000 African American diabetics and 50.2/100 000 white diabetics, with an African American:white incidence ratio of 2.55 (141). Figure 9A.7 shows that the incidence in African Americans is bimodal with peaks at age 20 and 60 years (2) while whites have a single peak at age 30 years. Thus, the excess incidence of diabetic ESRD is attributable to Type 2 diabetes and not to Type 1 diabetes (African American:white incidence ratio 4.31 [95% CI 3.6–5.52], and 1.03 [95% CI 0.73–1.36], respectively). Stephens reported similar data (142). Most African Americans with diabetic ESRD had Type 2 diabetes (776) while most whites had Type 1 diabetes (58%) (141). Pugh confirms these data in African Americans with ESRD (84% Type 2 diabetes, 13% Type 1 diabetes) but differs in whites (59% Type 2 diabetes, 39% Type 1 diabetes) (143).

The *risk of diabetic ESRD* depends on type of diabetes and race (141). The estimated 10-year risk of diabetic ESRD, for African Americans and whites combined, is 5.2% for Type 1 diabetes and 0.50% for Type 2 diabetes (African Americans have an 8-fold higher and whites have a 20-fold higher risk). The 10-year risk of diabetic ESRD is four times greater in African Americans than whites with Type 2 diabetes (1.06% vs 0.27%) and 1.62 times greater with Type 1 diabetes (8.7% vs 5.38%).

Overall, the 5-year *survival with diabetes and ESRD* is 24–30% compared to 48% with non-diabetic ESRD (139). Paradoxically, despite a higher prevalence of hypertension and incidence of diabetic ESRD, African Americans have better survival on *dialysis* treatment than whites (144–146). Data from the Michigan kidney registry in patients with age of onset of ESRD ≤ 65 years during the years 1974–1983 and followed through 1988 (284 African American and 311 white patients), showed the median survival time was 27 months for Africans with Type 2 diabetes and 16 months for whites (45% longer in African

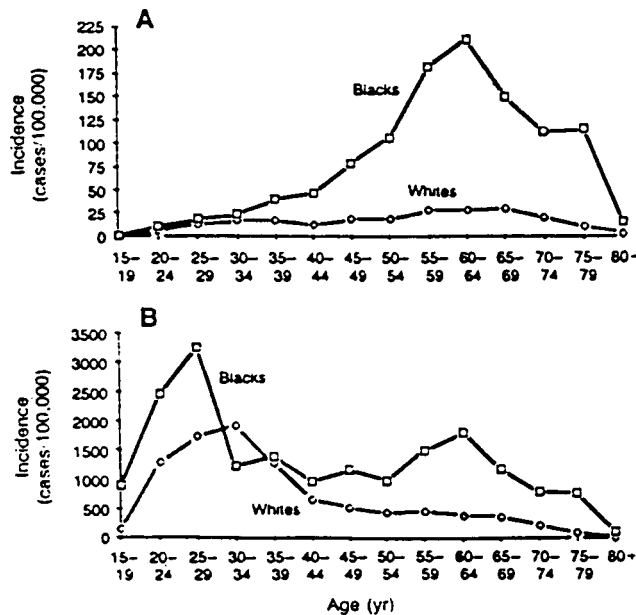


Figure 9A.7 Age-specific rates of the incidence of diabetic end-stage renal disease among blacks and whites in Michigan, 1974–1983

Panel A shows the incidence per 100 000 general population and panel B the incidence per 100 000 diabetic patients

Source: Reproduced from (141), Figure 1, page 1076, by permission

Americans than whites). In contrast, *transplantation* was associated with equal and lower death rate than dialysis for both races without significant differences by type of diabetes (147). This advantage in survival persists after adjusting for various co-morbidities known to affect survival, including type of diabetes. Data from this study showed that at the time of ESRD African Americans had a significantly higher prevalence of LVH and higher blood pressure but interestingly, lower frequency of CHF (58.5 vs 71.5 $p < 0.05$), lower frequency of MI (23.5% vs 33.1%, $p \leq 0.10$) and a longer duration between first MI and ESRD (56.3 vs 34.9 months, $p \leq 0.10$).

The reason for the higher rates of ESRD in African Americans is not known. Variations in blood pressure, glycemic control, socio-economic status and access to health care are reported not to account for the observed 4-fold increase in African Americans versus whites with Type 2 diabetes (148). For example, after controlling for the increased prevalence of Type 2 diabetes, glucose, BP, male sex and CHF, the likelihood of a serum creatinine > 2 mg/dl was 91% higher in African Americans than whites (149).

Inherited or genetic factors may account for the higher rates of ESRD. Freedman reports a familial predisposition for ESRD among African Americans with Type 2 diabetes (150) with an 8-fold greater increase in ESRD in individuals with a close relative with ESRD independent of glycemic control (after adjusting for smoking, hypertension and cholesterol levels). The susceptibility to ESRD is independent of the presence of Type 2 diabetes in African Americans and is similar to data from the Pima Indians and whites with Type 1 diabetes (151, 152). HLA associations may mark African American Type 2 diabetes patients with hypertension at risk for nephropathy compared to those without hypertension (153).

Early diabetic nephropathy. Since ESRD takes years to develop and itself causes hypertension, it is difficult to determine the relative roles of antecedent vs subsequently developing hypertension, glycemic control, duration of diabetes, microalbuminuria and hyperfiltration in the pathogenesis of diabetic nephropathy (154–156). In cross-sectional and longitudinal studies Chaiken reports the natural history of early nephropathy in

terms of duration of diagnosed diabetes and hypertension in 194 African American Type 2 diabetes subjects (155). *Overt nephropathy* (albumin excretion rates or AER > 300 mg/24 h) was correlated with: (1) duration of diabetes; (2) decrease in glomerular filtration rates (GFR, measured with ^{125}I -iothalamate infusion) and increase in serum creatinine, and all these patients were hypertensive. *Incipient nephropathy* (AER 30–300 mg/24 h) was correlated with duration of diabetes and 80% of this group were hypertensive. Analysis in terms of the duration of diabetes and the presence or absence of hypertension showed that subjects who remained *normotensive* had normal renal function regardless of duration of diabetes (normal GFR and serum creatinine). In *hypertensive subjects with Type 2 diabetes*, Chaiken found: (1) a decrease in GFR with duration of diabetes of greater than 1 year; and (2) with Type 2 diabetes > 10 years, 36% had impaired renal function (GFR < 80 ml/m² and/or serum creatinine > 1.4 mg/dl; 75% of these subjects have microalbuminuria or proteinuria. Within the group with longstanding diabetes, subjects who developed their hypertension after the diagnosis of diabetes were more likely to have nephropathy compared to those who developed hypertension prior to or at the time of diagnosis of diabetes (17/20 [85%] vs 7/13 [54%] respectively, $p < 0.05$), suggesting that nephropathy resulted in hypertension.

Within the first year of diagnosis of Type 2 diabetes in African Americans, Chaiken (157) showed an absence of microalbuminuria in subjects (mean age 47 years) with or without hypertension. In contrast, Goldschmid (154) reported 30% to have microalbuminuria (mean age 52 years). The reason for this difference is unknown but may be due to the older age, or delay in presentation of diabetes in Goldschmid's patients. Similarly to Chaiken, he found the risk factors for nephropathy were duration of diabetes and hypertension; multivariate analysis showed HbA1C did not predict nephropathy. Dasmahaptra (156) reported 50 t of 116 African American clinic-based patients had increased AER, but did not report data for new-onset patients. AER correlated with age of onset, hypertension and BMI but not with duration of diabetes, age, HbA1C or lipids.

Thus, early diabetic nephropathy, characterized by microalbuminuria, is associated with duration

of diabetes and hypertension. The role of glycemia is not clear. It is not known whether urinary microalbumin excretion rates are associated with cardiovascular risk as in some groups (158, 159).

Early glomerular hyperfiltration has been variably associated with subsequent nephropathy in Type 1 (160–163) but not Type 2 diabetes (164–167). Chaiken reports hyperfiltration in 36% (15/42) of newly diagnosed (<1 years) African American Type 2 diabetic subjects in good glycemic control (GFRs ≥ 140 ml/min/m² measured using a constant infusion of ^{125}I -iothalamate) (168–170). Hyperfiltration occurred mostly in younger patients and up to age 62 years and persisted up to 10 years after the diagnosis of diabetes in 14–20% of subjects. It did not predict deterioration of renal function (170).

Amputations and Peripheral Vascular Disease

Based on hospital discharge records, amputations are higher for African Americans with diabetes than whites (171). Statewide data from California (1991) estimated age adjusted amputation rates were 95.3 versus 55.0 per 100 000 for African American and white diabetics respectively (172). A major problem with such statistics is lack of long-term data integrating glycemic control, co-morbid conditions and socio-economic factors including access to health care and delay in diagnosis.

Based on such data, it is likely that neuropathy is greater in African Americans with diabetes but few data are available.

Cardiovascular Disease

Diabetic African Americans have more macrovascular disease than non-diabetics (173, 174). However, among diabetic subjects, African Americans have *less* atherosclerotic cardiovascular disease than whites. The frequency of angina and myocardial infarction was 2.3 and 3.0 times greater in newly diagnosed and 50–20% higher in previously diagnosed whites compared to African American diabetic subjects in NHANES II (7). This is of interest because newly diagnosed African Americans smoked more than whites (42% vs 28.7%) and smoking is a major C-V risk factor (7). Similarly, Afro-Caribbean blacks in

England had half the hospitalizations for heart attacks (6% vs 13%) compared to whites despite the greater rate (31% vs 14%) of diabetes (7, 8).

The lower rate of myocardial infarction and angina in African Americans compared to whites with Type 2 diabetes is consistent with their lower serum triglycerides and higher HDL cholesterol levels (adjusted for BMI) (9). African American men and women with diabetes versus those without had significantly *lower* total LDL-cholesterol and triglycerides and higher HDL-cholesterol (NHANES II) (69) (Figure 9A.8). In contrast, LDL-cholesterol was slightly *higher* in white diabetics versus non-diabetics (68). These epidemiologic data showing lower rates of macrovascular disease and favorable lipids are consistent with the

heterogenous pathophysiology of Type 2 diabetes in African Americans: up to 30% of African American diabetics are insulin-sensitive with lower triglyceride and LDL-cholesterol levels (67, 72). Also, non-diabetic African Americans compared to whites have higher HDL cholesterol levels and lower triglyceride levels (175–178).

Hypertension is a major risk factor for both macrovascular and microvascular disease and African Americans with and without diabetes have higher blood pressure than whites (7). The frequency of hypertension in the general population increases with age; however, among African Americans and whites with diabetes, the frequency of hypertension decreases after the age of 55 years. This may be related to increased mortality of

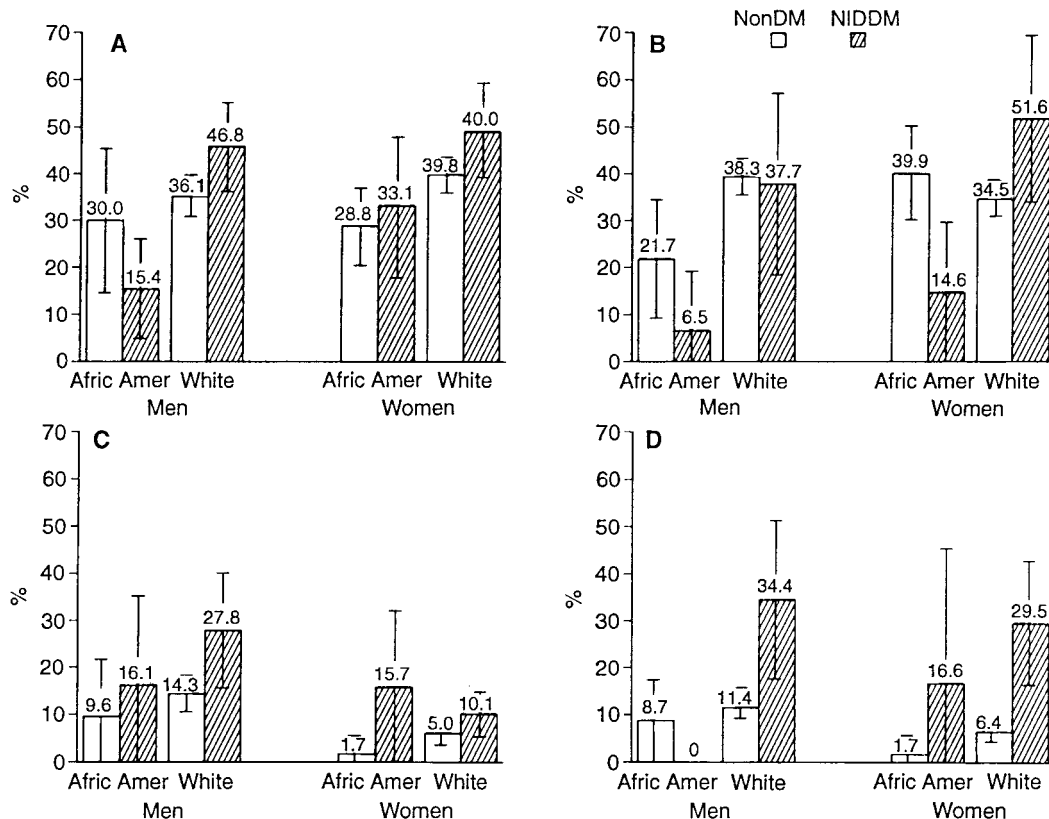


Figure 9A.8 Frequency of dyslipidemia in black and white adults, age 40–69 years with and without Type 2 diabetes, US 1976–80, NHANES II

Panel A: total cholesterol >240 mg/dl, (B) LDL-cholesterol >160 mg/dl, (C) HDL-cholesterol <35 mg/dl, (D) fasting triglyceride >250 mg/dl

Source: Reproduced from (69) by permission

diabetic subjects with hypertension. The majority of non diabetic African Americans and whites *do not* have hypertension (60% and 70% respectively). The majority of diabetics *do* have hypertension: 63%–80% among African Americans and 40–60% among whites.

Mortality of Diabetes

22-year mortality data from the NHANES I study showed the age-adjusted mortality rate for non-Hispanic blacks with Type 2 diabetes was 23% higher than for non-Hispanic whites (179). The mortality for African American women and men with diabetes was significantly higher than for those without diabetes (40% and 50% respectively) (179, 180). Diabetes was listed as an underlying cause of death in only 7.7% of diabetic men and 13.4% of diabetic women. This confirms that mortality data among African Americans (and others) with diabetes suffers from severe under-reporting: the data are derived from hospital death certificates which list proximal cause but not underlying illness (1). Mortality rates for African American and whites are similar at age < 15 years for Type 1 diabetes (0.1 per 100 000 population) (181–184).

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Non-Caucasian North American Populations: Native Americans

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NATIVE AMERICANS

Indigenous peoples lived in every region of North America for thousands of years before Europeans arrived. In this chapter, the term Native American will be used to refer to the descendents of these indigenous peoples. Native Americans probably originated from three distinct waves of migration from East Asia across the Bering land bridge (1, 2). The oldest of these migrations, that of the Paleo-Indians, is thought to have occurred 16 000 to 40 000 years ago (3, 4). The Paleo-Indians were followed by the Na-Dene about 12 000 to 14 000 years ago (4), and by the Eskimos and Aleuts starting about 9 000 years ago (3, 4).

The US government recognizes 325 Native American tribes and 226 Alaskan Native villages while approximately 2.33 million people in the US identify themselves as Native Americans (5). Likewise, Canada recognizes three distinct Aboriginal groups: Indian, Inuit and Metis, and according to the 1991 census just over 1 million Canadians claim 'some Aboriginal origin'. In general, Native Americans face widespread economic and educational problems (6).

DIABETES IN NATIVE AMERICANS

Diabetes was apparently rare among Native Americans until the middle part of the twentieth century (7, 8, 9). However, since World War II diabetes has become one of the most common serious diseases in many Native American tribes

(10), and in 1987, there were at least 72 000 Native Americans in the US with diagnosed diabetes (11). Diabetes occurring in Native Americans is almost exclusively Type 2 diabetes (10). The Pima Indians of Arizona have participated in a longitudinal study of diabetes, obesity, and diabetes complications since 1965 (12). Data from this study reveal that the Pimas have the highest recorded prevalence and incidence of Type 2 diabetes in the world (13, 14), and that insulin resistance is the major early abnormality in the pathogenesis of Type 2 diabetes (15, 16). High rates of diabetes have also been observed in other Native American tribes (10, 17, 18), and in diverse societies worldwide that have recently adapted to Western culture (19–21). People of Pima heritage living in Mexico may have a lower prevalence of obesity and Type 2 diabetes than their counterparts in Arizona, US, possibly due to lifestyle factors (22).

MAGNITUDE OF THE PROBLEM OF TYPE 2 DIABETES IN NATIVE AMERICANS

Prevalence

Estimates of prevalence are influenced by the method of ascertainment and by the definition of diabetes. A large number of studies have reported the prevalence of clinically diagnosed diabetes among Native Americans in the US (23–26). The prevalence of diagnosed diabetes varies across tribes and is, generally, higher than in the US population (23–26). The age-adjusted rate of

clinically diagnosed diabetes among all Indian Health Service (IHS) patients was 6.9%, which was nearly three times the US all-races rate, and of the 11 IHS areas examined in this study, only the Alaska area had a lower prevalence than the all-races US rate (26). However, there are indications that the rates of diagnosed diabetes among Alaska Natives may also be increasing (27). In Canada, one study reported the age-standardized prevalence of diagnosed diabetes among Aboriginal people ranging from 0.18% among Chukchi and Eskimo of Chukota, 0.79% among Eskimo/Inuit of Alaska, 1.86% among Athapaskan Indians in Alaska, to 2.27% among Aleuts in Alaska (28). Another study among aboriginal Canadians reported age-sex-adjusted rates varying from 0.8% in the Northwest Territories to 8.7% in the Atlantic region (29). In the Canadian Aboriginal Peoples Survey of 1991, the overall prevalence of self-reported diabetes in Aboriginal people was 6.0, and varied from 1.9% in Inuit (Eskimo), 5.5% in Metis, to 6.4% in Indians (30).

Studies based on clinically diagnosed cases rather than systematic testing may underestimate the prevalence of diabetes because a large proportion of Type 2 diabetes may remain undiagnosed (31). Prevalence studies of diabetes in Native Americans based on systematic testing in the community are available for only a few tribes (32–35), and are summarized in Table 9B.1. Among the studies reported in Table 9B.1, only Lee et al. (32) estimated the prevalence based on

systematic glucose tolerance testing and classification by WHO (36). The other three studies (33–35) used a variety of ascertainment methods, and did glucose tolerance testing only on subjects meeting certain criteria on other tests. In a population-based study among Algonquin communities in Quebec, the age–sex standardized prevalence of Type 2 diabetes among people ≥ 15 years old was 19.1% in Lac Simon and 9% in River Desert (37). In the same two communities, the prevalence among 30–64 year olds was 48.6% in women and 23.9% in men (38). Mexican Americans in the US also have high rates of diabetes, and their prevalence ranges from 3.8% among 20–44 year olds to 23.9% among 45–74 year olds (39).

Overall, the prevalence of diabetes in Native Americans is higher than the rate of 6.6% in the US general population (31). An epidemiological study that compared the Pima Indians with a predominantly white population of Rochester, Minnesota, gives further evidence that Native Americans have a higher prevalence of diabetes (13). Age-sex standardized diabetes prevalence for Pimas was 12.7 times that of Caucasians, and by contrast, diabetes prevalence in Rochester was higher in men than in women. The prevalence of diabetes in the Pima Indians, has increased during three successive decades (Figure 9B.1) (40). Overall, the prevalence of diabetes increased by 29% in men between 1965–74 and 1985–94, and by 35% in women during the same period.

Table 9B.1. Age-adjusted prevalence of diabetes in Native Americans from population-based studies

Author	Study population	Prevalence*		
		M (%)	F (%)	T (%)
Lee (32)	Men and women aged 45–74 yrs:			
	Pima/Maricopa/Papago, Arizona	65	72	70
	Apache, Caddo, Comanche, Delaware, Fort Sill	38	42	40
	Apache, Kiowa, Wichita, Oklahoma			
	Oglala, Sioux, Cheyenne River Sioux, Devils Lake	33	46	40
	Sioux, North and South Dakota			
Rith-Najarian (33)*	Men and women of all ages, Red Lake Chippewa Indians	13	16	15
Sugarman (34)*	Men and women aged 20–74, Navajo Indians, Shiprock	14	18	17
Hall (35)**	Men and women aged ≥ 20 years, Navajo Indians, Many Farms-Rough Rock	11	14	12

* Prevalence rates are standardized to US general population for the relevant ages.

** These studies used a variety of ascertainment methods, and did glucose-tolerance testing only on subjects meeting certain criteria on other tests.

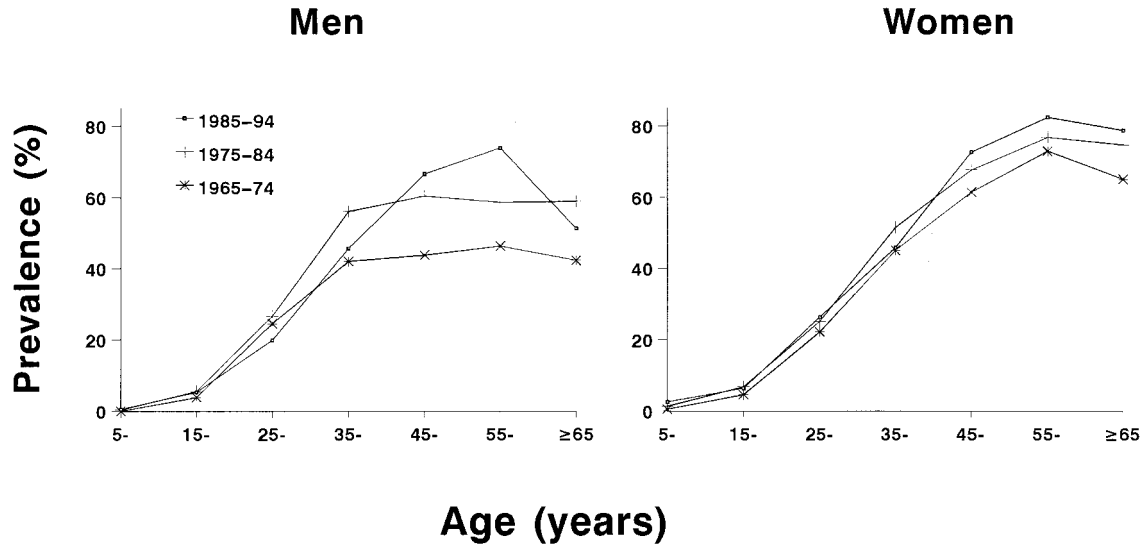


Figure 9B.1 Age-sex-specific prevalence of diabetes in Pima Indians in three time periods. Prevalence rates were estimated from data from all subjects examined in each of the 10-year periods 1965-74, 1975-84, and 1985-94

Source: Updated from data in reference (40)

Why is the prevalence of diabetes increasing? Prevalence can increase for two reasons: improvement in survival and/or increase in the rate of development of new cases. The length of survival following the onset of diabetes may have increased

over time, due to better treatment or due to a change in the natural history of the disease. However, diabetes has contributed little to mortality rates in Pimas under the age of 55 years (41), and therefore, an improvement in survival is

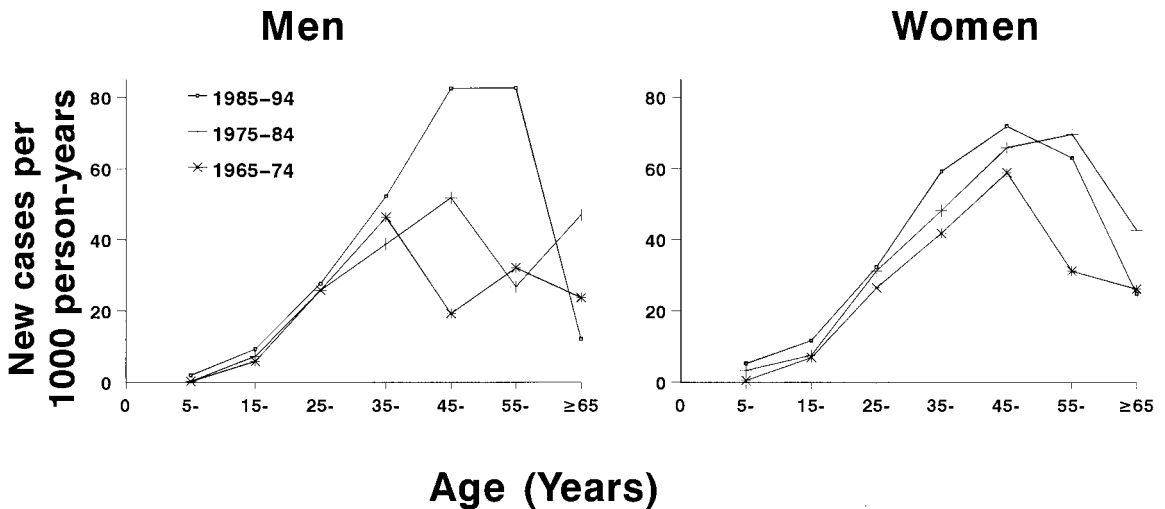


Figure 9B.2 Age-sex-specific incidence rates of diabetes in Pima Indians during three decades. Incidence rates are expressed as new cases of diabetes per 1000 person-years of observation of non-diabetic subjects. Cases and person-years are divided into three time periods: 1965-74, 1975-84, and 1985-94

Source: Updated from data in reference (40)

an unlikely explanation for the increase in prevalence among younger Native Americans. This suggests that at least part of the increase in prevalence is due to an increase in the incidence of the disease.

Incidence

The Pimas have the highest reported incidence of diabetes in the world—19 times the rate of diagnosed diabetes in the predominantly white population of Rochester, Minnesota (13)—and high incidence of diabetes has also been reported in other Native American tribes in the US (33), and Canada (42). Figure 9B.2 shows the age-sex-specific incidence of diabetes in Pima Indians during three successive decades. The incidence rates vary by age, peaking between 35 and 44 years in men in 1965–74, and 45 and 54 years in men in more recent years. Among women, the incidence rates peaked between 45 and 54 years in 1965–74 and in 1985–94, and 55 and 64 years in 1975–84. The incidence of diabetes has also increased over three successive decades at most ages and in both men and women. Overall, the age-adjusted incidence increased by 102% in men and by 87% in women between 1965–74 and 1985–94.

Why is the incidence of diabetes increasing? The dramatic increase in incidence of diabetes over a relatively short period of time emphasizes the overriding importance of environmental determinants among persons with an underlying genetic susceptibility.

DETERMINANTS OF TYPE 2 DIABETES

Genetic Factors

Genetic factors may be important determinants of Type 2 diabetes in Native Americans. The prevalence of Type 2 diabetes is higher in individuals of full Native American heritage than in those with genetic admixture (32, 43–45), possibly because full heritage Native Americans have a greater dose of diabetes susceptibility genes than admixed individuals. Familial aggregation of diabetes occurs in several Native American populations (32, 46, 47). For example, among Pimas, a parent who developed diabetes at a younger age is

more likely to transmit diabetes to an offspring than is a parent with an older age of onset (Figure 9B.3) (40). Thus, individuals who develop diabetes at younger ages may have a greater ‘load’ of diabetes susceptibility genes than those who develop the disease later in life. Similarly, the prevalence of Type 2 diabetes is higher in relatives of leaner diabetic Pimas than in relatives of heavier individuals with the disease (48), suggesting that the genetic factors which result in Type 2 diabetes are at least partially separate from those that cause obesity.

While familial aggregation of a disease suggests the potential importance of genetic factors, segregation analysis can determine whether this aggregation is consistent with a particular mode of inheritance. Among Seminoles, analyses of 1 h post-load glucose concentrations were consistent with the hypothesis that a single genetic locus has a major effect on these levels, but the degree of dominance at this putative locus could not be determined (49). Among Pimas, segregation analyses were consistent with a major effect of a single locus influencing age of onset of disease (50). On the basis of these analyses, it is tempting to speculate that familial aggregation of Type 2 diabetes among Native Americans may be explained in large part by the action of a single genetic locus.

More precise knowledge of the genetics of Type 2 diabetes would be obtained if a particular genetic

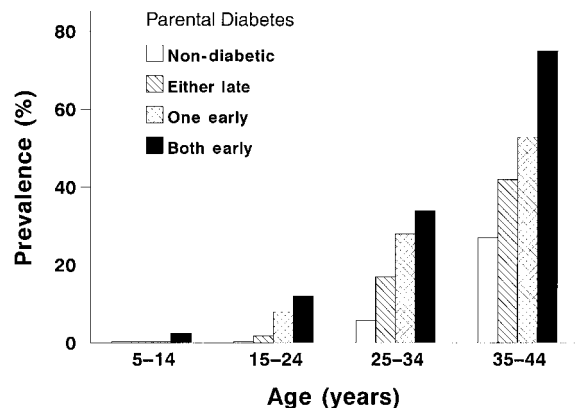


Figure 9B.3 Prevalence of diabetes by presence and age of onset of diabetes in parents. Diabetes was defined as of the last examination in the parents. Parents whose onset of diabetes was before age 45 were classified as ‘early’

Source: Updated from data in reference (40)

marker was strongly associated with or linked to the disease. Among Pimas, there is a modest association of Type 2 diabetes with HLA-A2 phenotype (51) and also with alleles at the glycogen synthase locus (52). Tentative evidence of linkage to Type 2 diabetes has also been observed with markers on chromosomes 1y, 7y and diabetes and obesity was linked to 11y (53). Tentative evidence of linkage of the intestinal fatty acid binding protein with insulin resistance, an important physiologic abnormality underlying Type 2 diabetes, has also been observed in Pimas (54); this locus may also be linked to 2 h post-load insulin levels in Mexican Americans (55). At present, the significance of these findings with respect to the etiology of Type 2 diabetes in Native Americans remains unclear. Further research into the genetics of Type 2 diabetes will, hopefully, lead to a better understanding of the pathogenesis of the disease.

Perinatal Factors

Among the Pimas, perinatal factors have an influence that modifies their genetic predisposition. Rates of diabetes are higher among subjects who were of very low or very high birthweight, whose mothers had diabetes during the pregnancy, or who were not breastfed.

As mentioned above, diabetes is a familial disease, occurring more frequently in those with a diabetic parent, whether that parent be the father or the mother. However, the diabetic intrauterine environment presents a risk for the early development of diabetes in Pima Indians which is in addition to the genetic predisposition (56). Before the age of 10 years, Type 2 diabetes is virtually limited to those children whose mothers had diabetes during the pregnancy, and half of the offspring of diabetic pregnancies have already developed diabetes by the time they reach child-bearing age. This results in a vicious cycle of diabetes begetting diabetes (57).

Higher rates of diabetes are found among adults who were at the extremes of birthweight (58). Rates of diabetes among those with birthweights below 2.5 kilograms or over 4.5 kilograms are nearly twice as high as among those with intermediate weights. This very likely represents selective survival of those low-birthweight infants with a predisposition to Type 2 diabetes.

Breastfeeding for a period of at least 2 months is associated with a 50% reduction in rates of diabetes (59). The reasons for this have not been fully explored, but may relate to a nutritional intake more suited to an infant's growing needs, either because of the differences in breast- and bottlefeeding *per se* or because mothers who choose to breastfeed continue to feed their children differently than those who do not.

Environmental Factors

A number of factors, which are potentially modifiable, including obesity, dietary composition, and physical inactivity are thought to contribute to the progression from genetic susceptibility to Type 2 diabetes (60–62).

Obesity

Obesity is a powerful and well-established risk factor for the development of Type 2 diabetes (46). As shown in Figure 9B.4 the age–sex-adjusted incidence of diabetes in Pima Indians increases with body mass index (BMI), a measure of obesity. Furthermore, the incidence of diabetes increases with the duration of obesity ($\text{BMI} \geq 30 \text{ kg/m}^2$), and

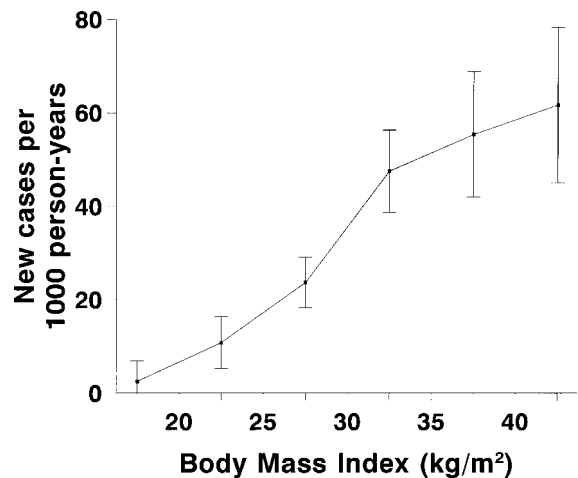


Figure 9B.4 Age–sex-adjusted incidence of diabetes in Pima Indians by body mass index (BMI), with 95% confidence intervals

Source: Updated from data in reference (40)

compared with Pima Indians with less than 5 years of obesity, those with 5–10 years of obesity have 1.4 times the incidence of Type 2 diabetes, and those with at least 10 years of obesity have 2.4 times the incidence (63). The distribution of body fat may also be important, and central obesity is related to the risk of diabetes (64–66). Those who gain weight most rapidly are most likely to develop diabetes, whereas those who lose weight are at the lowest risk (67).

As seen in Figure 9B.5, the prevalence of obesity among Native Americans is higher than in the US general population in both males and females and at all ages (68). The overall prevalence of obesity (BMI ≥ 31.1 kg/m² for men, ≥ 32.3 kg/m² for women) among Native Americans was 13.7% for men and 16.5% for women, higher than the US rates of 9.1% and 8.2% respectively (68). Data from the Pimas are consistent with this finding. Furthermore, the mean BMI in Pima adults has increased over time (Figure 9B.6), and a secular increase in the prevalence of overweight has also been reported in the Navajo Indians (35). Pima children have also, on average, become heavier during this century, and continue to do so (64).

Diet

Diet has been linked to the development of diabetes for over 2500 years (69), but the precise

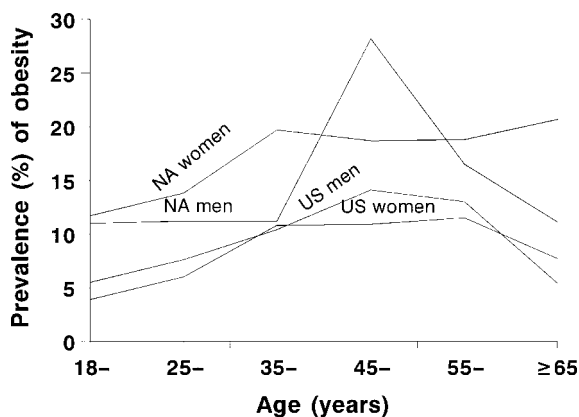


Figure 9B.5 Age-sex-specific prevalence of obesity (BMI ≥ 31.1 kg/m² for men, ≥ 32.3 kg/m² for women) in Native Americans and US all races, 1987

Source: Adapted from data in reference (68). Data source: National Medical Expenditure Survey (NMES)

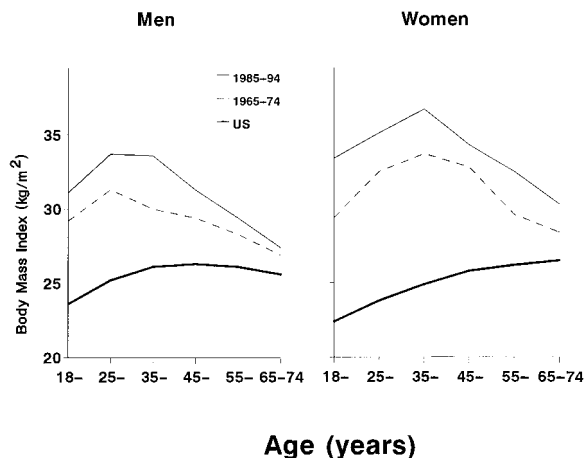


Figure 9B.6 Mean BMI in Pimas for two periods and in the US, white population. The Pima data from each period were used for all subjects examined in each of the 8-year periods 1965–72 and 1981–88

Source: Updated from data in reference (64). The US data are from NHANES II (1976–1980)

role of dietary factors, which has been reviewed elsewhere (70), remains ambiguous. Few data are available in Native Americans linking dietary factors with the development of Type 2 diabetes, except for one study in the Pima Indians which found that a high calorie diet may be associated with diabetes (71). The traditional Pima diet, derived from local agricultural produce, is believed to have been high in fiber, and low in fat (40), but the Pima diet changed during this century and is now nutritionally similar to the diet in the rest of the US (72). Similar secular changes in the diet of other Native American populations have also occurred, and in particular, the fat content of Native American diets appears to have increased dramatically—from 17% of total calories in the pre-European contact diet to 38% in the current diet (73).

Physical Activity

Increased physical activity may have a protective effect on the development of Type 2 diabetes (61). In Pima Indians the age-adjusted prevalence of Type 2 diabetes in 15–36-year-old subjects was lower in those with higher amounts of leisure physical activity in the preceding year (Figure 9B.7).

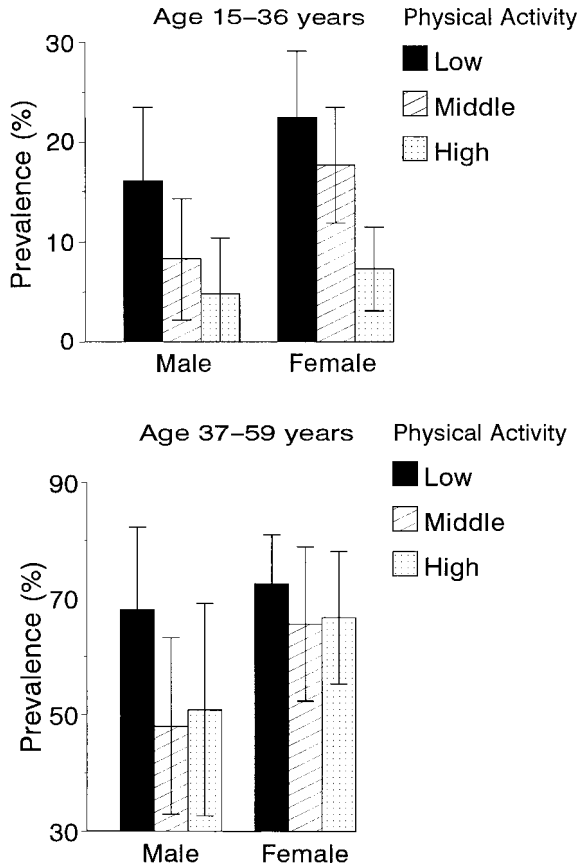


Figure 9B.7 Age-adjusted prevalence of Type 2 diabetes and 95% confidence interval by tertile groups of past year leisure physical activity in Pimas aged 15–36 (upper panel) and 37–59 years (lower panel)

Source: From data in reference (74)

Among 37–57-year-old subjects, those with the lowest levels of physical activity also had the highest prevalence of diabetes (74). Similarly, Zuni Indians with diabetes were less likely to have exercised frequently than were those without (75).

COMPLICATIONS OF TYPE 2 DIABETES

The frequency of several important vascular and non-vascular complications of Type 2 diabetes in Native Americans is examined, with particular emphasis on those that exert a significant influence on mortality.

Vascular Complications

Nearly all of the excess mortality associated with either type of diabetes is found in persons with proteinuria (76–78). Figure 9B.8 shows the age–sex-adjusted death rate among Pima Indians according to the presence or absence of diabetes and proteinuria. The death rate in diabetic subjects without proteinuria was no greater than in non-diabetic subjects, but the rate in those with clinical proteinuria was nearly 4-fold higher. The excess deaths in diabetic subjects with proteinuria are due principally to cardiovascular or renal disease (77–79), leading to the inference that proteinuria reflects widespread vascular damage in both small and large vessels (80). The frequency with which proteinuria leads to life-threatening cardiovascular disease or to renal failure in persons with diabetes depends on the frequency of other risk factors for these diseases. For example, persons in whom Type 2 diabetes develops later in life may have a higher risk of death from cardiovascular disease than persons in whom diabetes develops at a younger age, because of greater exposure to risk factors for cardiovascular disease that precede the onset of diabetes (81). Conversely, persons who develop Type 2 diabetes at a younger age may be more prone to develop end-stage renal disease, particularly if their risk of cardiovascular disease is low (82).

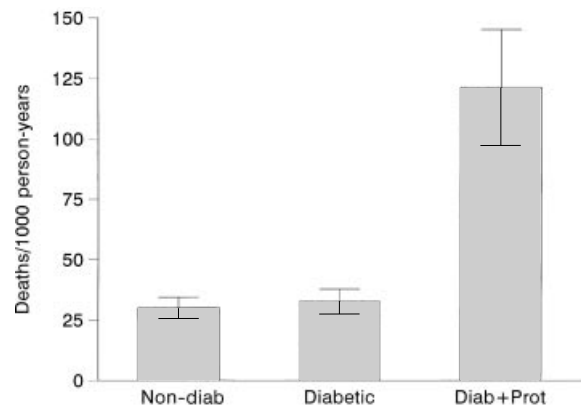


Figure 9B.8 Age–sex-adjusted death rates and 95% confidence intervals in 1426 Pima Indians ≥ 45 years of age. Rates are shown for non-diabetic subjects without proteinuria (Non-diab), diabetic subjects without proteinuria (Diabetic), and diabetic subjects with proteinuria (Diab+Prot). Proteinuria was defined by a protein-to-creatinine ratio ≥ 1.0 g/g

Source: From data in reference (78)

Although a rise in albumin excretion characteristically occurs after the onset of Type 2 diabetes, it may also precede Type 2 diabetes. The prevalence of elevated urinary albumin excretion (albumin-to-creatinine ratio ≥ 30 mg/g) is twice as high in Pima Indians with impaired glucose tolerance as in those with normal glucose tolerance (Figure 9B.9) (83). This suggests that even small elevations of the plasma glucose concentration may have an impact on vascular function.

With the onset of Type 2 diabetes, the prevalence of elevated urinary albumin excretion is even higher, and both the magnitude and frequency of the elevation are related to the duration of diabetes. Among Pima Indians with diabetes of up to 5 years duration, the prevalence is 29%, and in those with diabetes ≥ 20 years it is 86% (Figure 9B.9). Microalbuminuria (albumin-to-creatinine ratio = 30–299 mg/g) accounts for 82% of the prevalent cases among Pima Indians with <5 years of diabetes, but for only 22% in those with diabetes ≥ 20 years. Hence, the majority of Pima Indians with diabetes of long duration are at increased risk of premature death from vascular disease. A high prevalence of elevated urinary albumin excretion has also been reported in persons with diabetes from other Native American tribes (84).

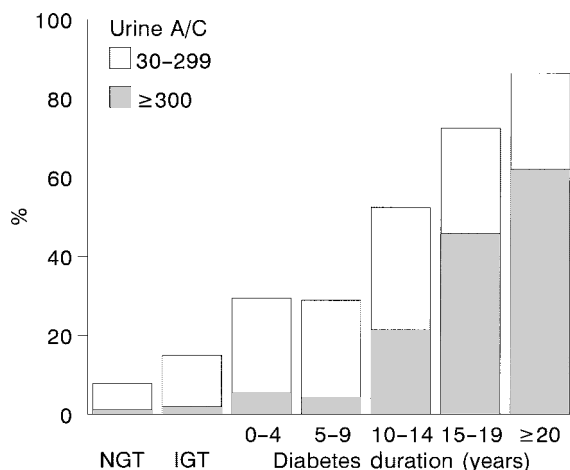


Figure 9B.9 Prevalence of elevated urinary albumin-to-creatinine ratios in 2728 Pima Indians ≥ 15 years of age with normal glucose tolerance (NGT), impaired glucose tolerance (IGT), and in diabetic subjects by duration of Type 2 diabetes

Source: Adapted from data in reference (83)

Cardiovascular Disease

The Strong Heart Study (85) used identical survey methods to examine the prevalence of myocardial infarction and coronary heart disease in 4549 subjects from 13 Native American tribes in Arizona, Oklahoma, and North and South Dakota. The prevalence of coronary heart disease in these subjects is shown in Figure 9B.10 according to sex, diabetes, and center (86). Diabetes was associated with a significantly higher prevalence of heart disease in each of the centers (86), but Indians in Arizona had lower prevalence rates than those from the other centers. The lower prevalence of coronary heart disease among Indians in Arizona may be related, in part, to their low cigarette consumption and to their low concentrations of total and low-density lipoprotein cholesterol in comparison to the other tribal groups (86).

Cardiovascular disease is the leading underlying cause of death in diabetic adults in the United States (87), and is also the leading cause in Native Americans (88,89), although the mortality rate due to cardiovascular diseases in Native Americans is lower than in the US general population

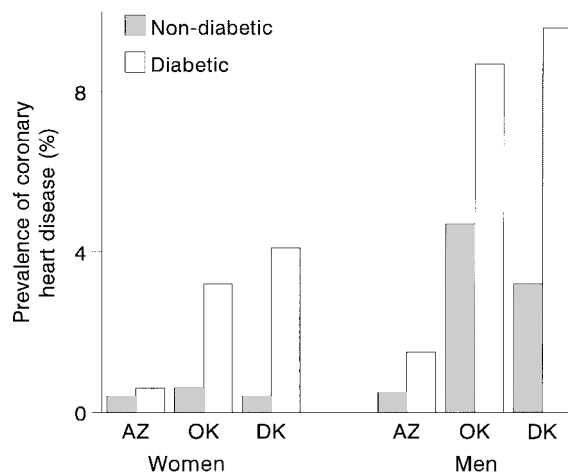


Figure 9B.10 Prevalence of coronary heart disease by sex, study center, and presence of diabetes in the Strong Heart Study, 1989–1992 (86). Criteria for coronary heart disease included definite myocardial infarction, evidence in the medical record of coronary angioplasty or bypass surgery, thrombolytic therapy, a positive angiogram, or angina pectoris by Rose questionnaire when accompanied by Minnesota Code 4.1 or 5.1 or a verified history of myocardial infarction

(90). Tribal variations in cardiovascular mortality, however, are striking, just as they are for the prevalence of cardiovascular disease. Southwestern tribes, such as the Navajo and Pima Indians, have low mortality rates from cardiovascular disease, nearly all of which is found in those with diabetes (82,90), whereas the Northern Plains Indians have rates as high as or higher than the general population of the United States, and a much greater proportion of cardiovascular deaths are found in those without diabetes, particularly among men (90). Death rates from cardiovascular disease in southwestern Native Americans however, are rising (91,92).

Renal Disease

Among the Pima Indians, half of those with Type 2 diabetes develop nephropathy within 20 years of the diagnosis of diabetes (93), and the presence of proteinuria is usually associated with an irreversible deterioration of renal function that often leads to end-stage renal disease. The cumulative incidence of end-stage renal disease in diabetic Pimas is 40% after 10 years and 61% after 15 years of proteinuria (94). The proportion of renal failure attributable to diabetes, however, varies widely by tribe (Table 9B.2) (95–99). Nevertheless, in 1988–91, the age–sex-adjusted incidence of end-stage renal disease in Native Americans was over three times that in whites and 64% of the renal failure was attributed to diabetes (99). In Pima Indians, renal failure was the leading cause of death in those with diabetes, accounting for 23% of the deaths from natural causes during the years from 1975 to 1984 (87). Recently, however, cardiovascular disease has replaced renal disease as the

leading cause of death among diabetic Pimas (91). In recent years, Pimas have survived longer after the onset of ESRD, giving them a greater opportunity for developing fatal cardiovascular disease (100).

Stroke

There are few data on the frequency of strokes in Native Americans. The prevalence of strokes among diabetic Alaska Natives is similar to that reported in diabetic whites (27). In Pima Indians, the presence of diabetes does not substantially influence the death rate from strokes, and the duration of diabetes does not influence the rate of stroke deaths (Figure 9.B11) (101).

Retinopathy

Retinopathy is a frequent complication of diabetes in all populations, and Native Americans are no exception (102). The frequency of vision-threatening proliferative diabetic retinopathy, however, is much higher in Native Americans than in whites with Type 2 diabetes (103–105). In Pima Indians, the cumulative incidence of proliferative retinopathy was 14% after 20 years of diabetes (103), and in Oklahoma Indians the cumulative incidence was 18.6% after 13 years of follow-up (105).

Lower-extremity Amputations

More than 50 000 amputations each year are performed on diabetic patients in the United

Table 9B.2 Incidence of end-stage renal disease (ESRD) in several Native American tribes, compared with the United States

Tribe	Incidence rate ratio (tribe/US)	Prevalence of diabetes in subjects with ESRD (%)
Navajo (92)	4	50
Zuni (93)	14	36
Tohono O'odham (95)	9	72
Ute (95)	22	78
Pima (94)	23	93
All US Native Americans (96)	2.4	64

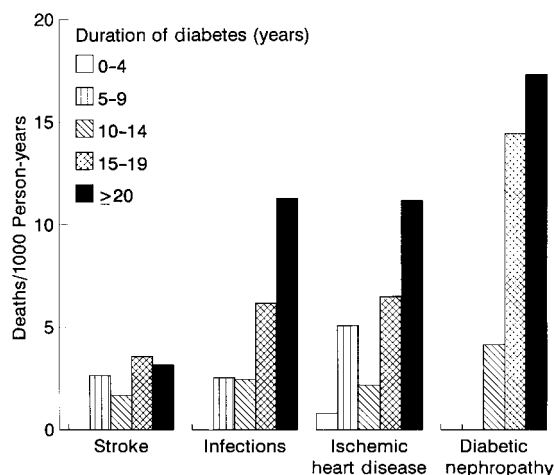


Figure 9B.11 Age-sex-adjusted cause-specific death rates in diabetic Pima Indians aged ≥ 35 years for stroke ($n = 18$), infections ($n = 28$), ischemic heart disease ($n = 35$), and diabetic nephropathy ($n = 46$) in relation to the duration of diabetes

Source: Reprinted from data in reference (101)

States (106), and the rate of amputation among diabetic patients is about 15 times that in non-diabetic patients (107). Longitudinal studies of amputation rates in Pima Indians and in Indians from Oklahoma indicate substantially higher incidence rates of lower extremity amputations in these Native American populations than in the general US population (108, 109).

Non-vascular Complications

Diabetic persons are generally considered to be more susceptible to bacterial and fungal infections than are non-diabetic persons (110). In accordance with this observation, diabetic Sioux Indians were four times as likely to have tuberculosis as those without diabetes (111), and southwestern Indians with diabetes were more likely to have disseminated coccidioidomycosis than those without (112). In Pima Indians, infection is the only major cause of death other than ischemic heart disease and diabetic nephropathy that is related to the duration of diabetes (Figure 9B.11) (101). Nevertheless, the death rate from infections in diabetic Pima Indians was not significantly greater than in those without diabetes in 1975–84 (101).

Periodontal Disease

Periodontal disease, a chronic inflammatory disease of the periodontal tissues, is a complication of diabetes that is frequently overlooked. It is exceedingly common even in persons without diabetes, but prospective studies in Pima Indians indicate the age-sex-adjusted incidence is nearly three times as high in subjects with diabetes as in those without (113), and after 20 years of diabetes 75% of diabetic Pima Indians are edentulous. Although the rates of periodontal disease in other Native American populations are not known, they are likely to be high given the high rates of Type 2 diabetes. The inflammatory nature of periodontal disease may hinder metabolic control (114), and may inhibit proper dietary intake (115, 116).

CONCLUSION

In summary, principal contributors to mortality in Type 2 diabetes are renal and cardiovascular disease. The frequency with which each of these complications occurs may depend on factors such as age, duration of diabetes, and underlying genetic susceptibility. Proteinuria is a marker for both diseases, and nearly all of the burden of excess mortality in diabetes befalls those with gross proteinuria. Native Americans, who have higher rates of Type 2 diabetes than many other populations and who often develop diabetes at a young age, and consequently have higher frequencies of these life-threatening complications. Moreover, they also have higher frequencies of other complications that may not lead to premature death, but which substantially reduce their quality of life.

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Mexico

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INTRODUCTION

Although diabetes mellitus has been recognized clinically for thousands of years, it is only within the past several decades that intensive scientific study of the epidemiology of the disease has been conducted. The prevalence has increased dramatically over time, and it is now one of the main causes of morbidity and mortality in the world, with significant differences among racial/ethnic groups. Mexico has a population currently estimated at 100 million. The country has undergone dramatic and very rapid socio-economic changes during the last decades, which have induced profound demographic and epidemiological changes. Internal migration has been massive, the proportion of the population living in urban areas increased from 42.6% in 1950 to 71.4% in 1990 (Figure 10.1). Infant mortality dropped 14.4% from 1970 to 1990 and life expectancy rose from 63.5 to 73.9 years during the same period (1). Around 50% of the Mexican population is still young, but in the 65 years and older age group, the growth rate of the population is 4%, that is, more than twice the actual growth rate of the total population. Current estimates suggest that by the year 2030 there will be 14 million Mexicans in this age group (1).

Changes in health and disease are related to the demographic, economic, social and cultural transformations of society. The epidemiological transition is a multifactorial phenomenon characterized by a decline of the death rate due to infectious and parasitic diseases and by an increment in the death rate related to chronic-degenerative diseases, acci-

dents and violence. Every country experiences this phenomenon in different ways. In Mexico, there have been significant changes in the main causes of death during the last 40 years. Currently in first place are cardiovascular problems, followed by neoplastic diseases, accidents and violence and in fourth place is diabetes (2).

This doesn't mean that diseases that characterize the transition period have diminished in importance; infectious and parasitic diseases are still the main cause of morbidity, linked to the fact that a very large group of Mexicans, around 40 million, live in poverty.

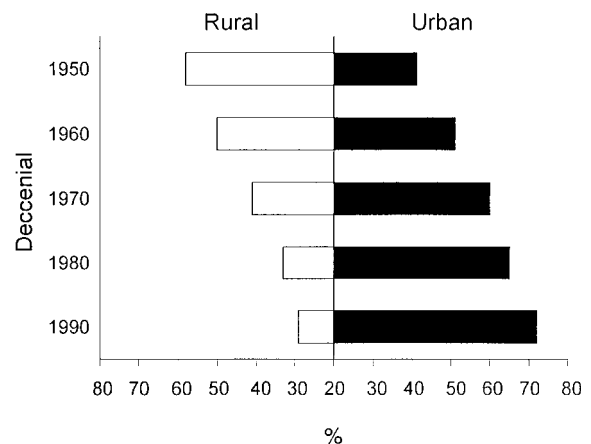


Figure 10.1 Rural-urban transformation of the Mexican population in the last 40 years (1)

Source: Mexican Census

PREVALENCE OF DIABETES

The prevalence of Type 2 or non-insulin-dependent diabetes varies widely. Populations of developing countries, minority groups and disadvantaged communities in industrialized countries now face the greatest risk (3). Projections made from current epidemiological data in Mexican American populations suggest that the incidence of Type 2 diabetes will continue to escalate in this ethnic group, closely related to the increased rates of obesity, the genetic background, and the trend for diminished physical activity (4–6). Diabetes-related complications will also occur more frequently because of the early appearance of the disease, its underdiagnosis and undertreatment, and the high prevalence of hypertension, dyslipidemias and smoking (7–12).

Mexico is probably on the rising scale of the diabetes epidemic. In the early 1960s, several reports on non-representative groups of Mexican individuals disclosed prevalences of diabetes in ranges of 2–3% (13, 14). Over the past 30 years, diabetes has become a public health problem with considerable medical, social and economic consequences.

An increasing frequency of diabetes mellitus has been documented in Mexico, among other countries. There are three lines of evidence. First, the mortality rate due to diabetes, which had increased gradually since the 1940's, recently increased sharply. The Health Department's statistical profiles (15) show an increase from 4.8 deaths per 100 000 in 1950 to 30.8 per 100 000 deaths in 1990 (Figure 10.2). Diabetes ranks among the leading five causes of death in

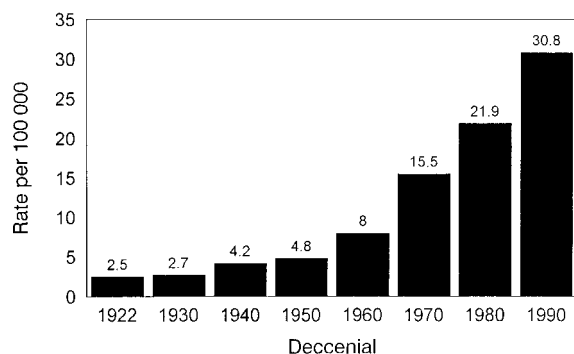


Figure 10.2 Decennial mortality rates due to diabetes in Mexico

Source: Data obtained from death certificates (15)

Mexico even though there is a lack of uniformity in the certification of cause of death. Frequently deaths among diabetic subjects are due to cardiovascular complications with no mention of diabetes in the death certificate (16). Figure 10.3, shows the mortality rates due to diabetes in the different states of Mexico. It is important to note, as clearly seen in the figure, that the northern states and Mexico City have the highest mortality and likely prevalence of the disease. The southern states, those with lower income per capita, have the lowest death rates related to diabetes. Similar trends are observed related to the prevalence of obesity, hypertension, hypercholesterolemia and cardiovascular disease (17).

Second, the Social Security Organization (Instituto Mexicano del Seguro Social), with a coverage of almost half of the Mexican population, has an information system that offers the following data: the diabetes mortality rate of hospitalized patients increased from 2000 to 6000 deaths per 100 000 hospitalized patients between 1977 and 1984 and, in 1980, there were 433 148 consultations for diabetes at the primary-care level; this number has increased progressively in subsequent years reaching 1 529 307 in 1985. Diabetes is one of the main reasons for consultation, surpassed only by acute respiratory and intestinal infections and arterial hypertension, and it is the main cause of death in patients admitted to the hospitals of the Instituto Mexicano del Seguro Social (18).

Third, epidemiological surveys of diabetes prevalence (Table 10.1), have revealed a stepwise increase from 2 to 3% of the adult population since 1963, when the first available data were obtained in Mexico, to around 8% in the most recent surveys (19–23).

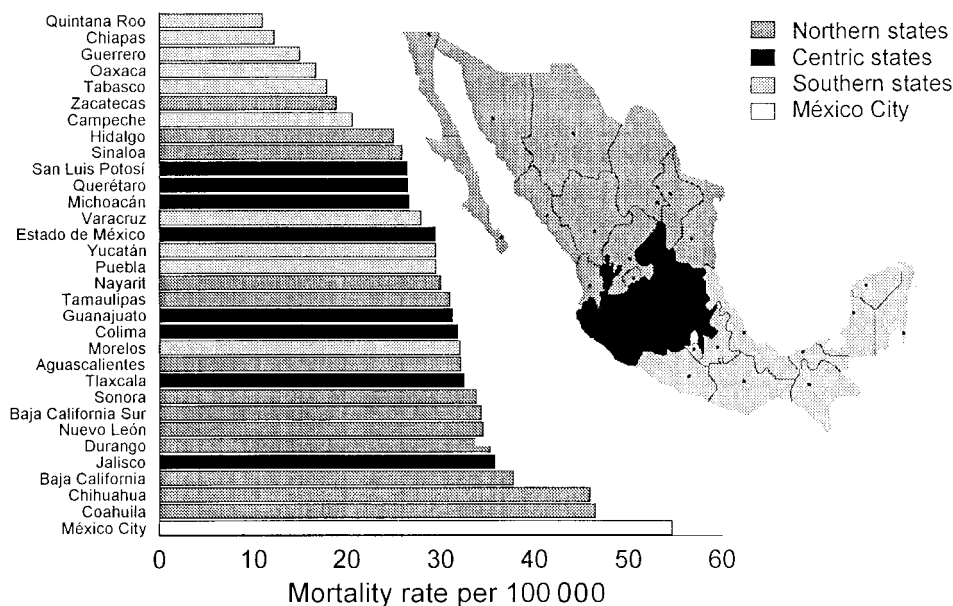
The rise in diabetes-associated mortality in the 1960s prompted the early surveys. In the 1970s, the prevalence was from 1.2 to 4.6% with an estimated mean of 3%. Studies conducted in the 1980s show almost a 2-fold increased prevalence of the disease, although most studies were done in urban settings with older participants, so discrepancies between studies could be explained by differences in the population sampled, by diagnostic criteria and in the detection methods. In the 1990s absolute figures are similar to those reported in the 80s, the prevalences ranging from 8.1 to 12.9%.

The Encuesta Nacional de Enfermedades Crónicas (ENEC or Chronic Diseases National

Table 10.1 Prevalence of diabetes mellitus in Mexico. Results of different surveys in the last three decades

Year	Author	Place	R/U	Age (years)	<i>n</i>	Prevalence (%)
1963	Chávez	Yucatán	R	10–80	776	1.3
1963	Leal	San Luis Potosí	R	10–70	3356	3.2
1964	Zubirán	México City	U	10–70	6056	2.3
1974	Fernández	México State	R	10–70	129	4.6
1974	Rivera	Durango	R	10–70	349	2.9
1985	Santos	Monterrey	U	17–80	500	10
1987	Ovalle	Monterrey	U	15–75	763	7.5
1989	Vargas	Yucatán	U	20–70	3487	12.6
1989	Quibrera	San Luis Potosí	U	15–75	1024	11.0
1991	González	México City	U	36–64	649	12.9
1992	Posadas	México City	U	20–69	812	8.1
1993	NSCD	National	U	20–69	19 000	8.2

R/U = Rural or Urban

**Figure 10.3** Mortality rates from diabetes in the different states of Mexico

Source: Subsecretaría de Coordinación y Desarrollo. Dirección General de Estadística, Informática y evaluación. Mortalidad en 1990. 1992: pp. 55–86

Survey), was performed by the Dirección General de Epidemiología de la Secretaría de Salud (Department of Health) and the Instituto Nacional de la Nutrición Salvador Zubirán in 1993 (22, 23). This probabilistic study covered the entire country, sampling residents aged 20–69 from towns of more than 2500 inhabitants. Four regions were differentiated: North, Center, South and the metropolitan area of Mexico City. The survey included a selected sample of 19 000 individuals.

The crude prevalence of diabetes was 6.7% for fasting and random plasma venous samples and 8.2% when the results of the glucose tolerance testing were included. Use of the glucose tolerance test showed an 18.3% underestimation of diabetes and a prevalence of 10% of individuals with glucose intolerance. The distribution of diabetes increased in the states with the largest urban concentrations and was associated with advanced age, increased body mass index, and most affected

were the lowest income groups with the lowest levels of education. Almost 25% of people aged 65–69 were diabetics, however, 57.5% of the individuals with diabetes belonged to the working population, aged 20–59. The survey reveals almost one newly discovered case for each previously diagnosed. In these newly diagnosed cases, almost one-fourth were discovered by glucose tolerance testing.

Another survey done in Mexico City (21) included a sample of 805 adults. The participants, 20–90 years of age and living in the city, were selected by the method of multistage cluster sampling with proportional allocation. The crude rate prevalence of Type 2 diabetes was 8.7%, with an age-adjusted rate of 10.6% for females and 6.0% for males. Age strongly influenced diabetes prevalence with a chi square risk tendency of 39.1 ($p < 0.00005$). A significant proportion (5.9%) of younger individuals (35–44 years of age), were affected by the disease. Diabetes was associated with advanced age, had a greater impact in the low-income group and showed increased odds ratios for hypertension, dyslipidemias and myocardial infarction in men and women, and for obesity only in women.

When exploring the impact of the new ADA diagnostic criteria for diabetes in the Mexico City survey (24) the following data were observed: the prevalence of newly diagnosed diabetes using the old and the new criteria was 23.1% vs. 32.3% in males ($p = 0.31$) and 27.5% vs. 36.3% in females ($p = 0.32$) respectively. The crude prevalence rate of diabetes increased from 8.7 to 9.3% ($p = 0.427$), the age-adjusted rate increased from 10.6 to 11.2% for women ($p = 0.643$) and from 6.1 to 6.5% for men ($p = 0.493$). The prevalence of impaired fasting glucose was 4.8%. Those individuals with impaired fasting glucose or newly diagnosed diabetes with FPG between 126 and 140 mg/dl had a more atherogenic risk profile than individuals with a normal carbohydrate metabolism.

Recently another survey in a low-income neighborhood in Mexico City (19), disclosed a prevalence of Type 2 diabetes two to three times higher than in non-Hispanic whites in the US, but still significantly lower than in Mexican Americans (25). Another study, in San Luis Potosí, compared urban and rural populations (20); the prevalence of Type 2 diabetes was 11% in the urban population and 0.9% for individuals in the rural area.

In the urban population, the highest prevalence of diabetes was observed in the very low income group.

Finally, a recent study was done with the aim of determining the prevalence of diabetes and examining its association to food intake, anthropometric and metabolic variables and other coronary risk factors in both the urban and rural elderly Mexican population (26). Diabetes prevalence was higher in males than females for all the age groups; 16.7% vs. 9.5% in adults and 30.8% vs. 22.8% in the elderly. Using a multivariate stepwise logistic regression, elderly individuals had the following variables independently associated to diabetes: gender (male sex), diminished carbohydrate intake in the diet, central distribution of adiposity and functional disability. Diabetes in the elderly was significantly associated with hypertriglyceridemia, impaired functional status and an increased prevalence of ischemic heart disease. Individuals living in rural areas had a significantly lower prevalence of diabetes and other coronary risk factors.

DIABETES IN EARLY ADULthood

Diabetes, as previously mentioned, also strikes a significant group of younger individuals. In the survey done in Mexico City (21), 5.9% of individuals in the 35–44 years age group were affected by the disease. In the National Survey of Chronic Diseases (22,23), in the country as a whole, diabetes was diagnosed in 0.5% of the population in the 20–30 age group and in 3.0% of the 30–40 age group. Because our current population pyramid has a large base of younger individuals, these data can be extrapolated and include a number of approximately 300 000 diabetics in the 20–40 age group that represents a tremendous impact on our public health facilities in the years to come.

Contrary to what has occurred with Type 2 diabetes, insulin-dependent diabetes is uncommon in Mexico, with a calculated incidence of approximately 2/100 000 individuals (27). Secondary causes of diabetes such as pancreatitis, neoplasias or undernutrition are probably even more rare. With these data in mind, it is reasonable to conclude that probably 6 or 7 of every 10 cases of diabetes in the 20–40 years age group are

Type 2 diabetes expressed at an earlier age and probably related to a high genetic susceptibility and/or to such adverse environmental or metabolic factors as obesity, hyperandrogenism and diminished physical activity.

Neufeld et al. (28) showed that Type 2 diabetes accounted for 31% of the new cases of diabetes in Mexican American youths. Treviño et al. (29) observed that low-income Mexican American children ate higher than recommended amounts of fat and had a higher percentage of energy from fat and saturated fats. On the other hand, their reported daily fruit and vegetable intake was half that recommended by national dietary guidelines. A large percentage of these children were at unacceptable physical fitness levels. Finally 60% of them had a first-or second-degree relative with diabetes.

DIABETES AND PREGNANCY

The prevalence of gestational diabetes in Mexico is around 7.5%. Several studies done in the cities of Puebla, Monterrey and Cd Juárez with samples ranging from 118 to 1221 individuals disclose prevalences from 2.3 to 11.0% (23).

Gestational diabetes is a serious problem in Mexico, with a great impact on perinatal mortality. In our country some women with an early diagnosis or several risk factors for gestational diabetes have the good fortune to be referred in their 25th week of pregnancy to tertiary care centers. Perinatal mortality rates in those women with gestational diabetes is <6 per 1000 live births. Unfortunately, in most cases diagnosis is delayed or is made retrospectively after delivery. In these cases the mortality rates rise several-fold with perinatal mortality of 30–42% in different surveys done in the country. When tested in the postpartum period, women with gestational diabetes are subsequently found to have impaired glucose tolerance in 15–20% or Type 2 diabetes in 11–21%, of the cases, based in different surveys done in Mexico City, San Luis Potosí and Monterrey (18).

NATURAL HISTORY OF GLUCOSE INTOLERANCE IN MEXICO

The prevalence of glucose intolerance in different surveys done in different states of Mexico goes

from 4.6 to 20.3% with a mean of 10% (23). One study done at the Instituto Nacional de la Nutrición Salvador Zubirán (30) included 111 persons with a mean age of 48 years with diagnosis of glucose intolerance. Their follow-up demonstrated a 5-year conversion to diabetes in 23.4% and after 10 years in 46%. The high progression rate resembles that of other populations with a large genetic pool of diabetes and is even higher than that observed in Mexican American populations.

INSULIN-DEPENDENT DIABETES MELLITUS

Type 1 diabetes is uncommon in Mexico with a calculated incidence of approximately 2/100 000 individuals (27), one of the lowest incidences when compared with different surveys in the world. Serologic findings of HLA antigens in Mexican insulin-dependent diabetic patients showed a significant association of DR3, DR4, DQ2, DQ8 and a protective effect of DR11, DR15, DQ5, DQ6 and DQ7. Positions 57 and 74 of the DRBI locus apparently contributed greatly to the expression of IDDM in Mexican Mestizos (31). In different clinical studies with Type 1 diabetic patients in various tertiary care centers throughout the country, that have been carried out during recent years, the mean glycosylated hemoglobin levels reported were in the poor control ranges, offering a poor perspective for diabetes-related late complications in this population. Recently, intensive treatment programs have been introduced to improve this scenario but only a minority of the patients have access to them.

DIABETES-RELATED COMPLICATIONS

Several epidemiological and clinical studies have shown an association between increased insulin concentrations and higher prevalence of obesity, hypertension, glucose intolerance, Type 2 diabetes, hypertriglyceridemia and hypoalphalipoproteinemia (32,33). The clustering of these metabolic abnormalities leads to an increased risk for atherosclerotic heart disease, the main cause of death in the adult population of most developed countries as well as in several states of Mexico. The prevalence of insulin-resistant-related metabolic disorders was

high in a random sample of the Mexico City population (34), and associated to the highest quartiles of fasting insulin levels (Table 10.2). Results of the National Survey of Chronic Diseases (22,23), show arterial hypertension to be twice as common in persons with diabetes, myocardial infarction and stroke were three to four times more frequent than in non-diabetic individuals.

There are marked differences between populations in the occurrence of atherosclerotic vascular disease, and these differences are mainly explained by the prevalence of lifestyle-related coronary risk factors, mainly the type of diet and associated hypercholesterolemia. In addition to the results of cross-cultural epidemiologic studies, changes in mortality and morbidity from CHD related to changes in lifestyles and coronary risk factors give strong support to the concept of powerful environmental or lifestyle determinants of the frequency of CHD in populations (11, 12, 34–36).

Although cardiovascular diseases, particularly coronary artery disease and myocardial infarction, are apparently less frequent in Mexican diabetics than in diabetics from developed countries, this is often the result of a subjective appreciation or generalization of some results. Cardiovascular diseases are the leading cause of death in Mexico and several studies have found a substantial prevalence of cardiovascular problems, including myocardial infarction, among Mexican diabetics.

Some conditions, such as peripheral vascular disease, are more prevalent in Mexican than in non-Hispanic whites (7). In another study, Haffner et al. (37), compared the prevalence of hypertension in 1500 Mexican Americans who participated in the San Antonio Heart Study and 2280 low-income Mexicans who participated in the Mexico City Diabetes Study. The crude prevalence of mild hypertension was 17.1 and 17.4% in Mexican men and women, compared to 24.4 and 22.0% in Mexican American men and women with $p < 0.001$ and $p < 0.005$ respectively. These differences could be related to greater physical activity, lower body mass index, and the consumption of a high-carbohydrate, low fat-diet in the Mexican population.

In some reports, Mexican genetic ancestry and/or difficult access to optimal care has been related to a higher prevalence of diabetic nephropathy and retinopathy than that observed in other ethnic groups. A high prevalence of microvascular complications was reported in a large sample of Mexican Type 2 diabetics, treated at the Instituto Nacional de la Nutrición Salvador Zubirán (38), of whom 15.9% had nephropathy and 52.7% had retinopathy (44.6% background and 8.1% proliferative). In the National Medical Center of the Mexican Institute of Social Security, a tertiary referral center, diabetes nephropathy was the first cause of renal failure, accounting for 43% of 300

Table 10.2. General data and anthropometric and metabolic variables according to quartile of insulin concentrations in males

Insulin (μ U/ml)	Quartile 1 <5.665	Quartile 2 5.666–8.520	Quartile 3 8.521–12.70	Quartile 4 >12.701	p^*
<i>n</i>	99	99	101	97	
Age (yrs)	40.7 $\pm$ 13.6	37.0 $\pm$ 12.9	39.0 $\pm$ 11.9	41.4 $\pm$ 12.9	ns
BMI (kg/m^2)	24.3 $\pm$ 2.6	25.1 $\pm$ 2.5	26.6 $\pm$ 3.0	28.7 $\pm$ 4.2	<0.001
WHR	0.942 $\pm$ 0.07	0.946 $\pm$ 0.05	0.956 $\pm$ 0.06	0.982 $\pm$ 0.08	<0.001
SBP (mmHg)	118.0 $\pm$ 17.5	119.0 $\pm$ 13.3	122.0 $\pm$ 16.7	125.0 $\pm$ 17.7	<0.05
DBP (mmHg)	75.1 $\pm$ 10.5	75.1 $\pm$ 10.4	77.2 $\pm$ 11.7	80.1 $\pm$ 10.7	<0.005
TC (mg/dl)	206.7 $\pm$ 44.4	204.9 $\pm$ 51.0	205.7 $\pm$ 38.6	212.2 $\pm$ 36.5	ns
TG (mg/dl)	141.2 $\pm$ 75.4	154.3 $\pm$ 97.7	172.7 $\pm$ 91.3	206.0 $\pm$ 107.2	<0.001
LDL-C (mg/dl)	140.7 $\pm$ 38.9	139.6 $\pm$ 45.4	140.3 $\pm$ 33.1	141.4 $\pm$ 33.9	ns
HDL-C (mg/dl)	43.4 $\pm$ 10.9	40.6 $\pm$ 10.5	37.7 $\pm$ 9.3	37.9 $\pm$ 9.6	<0.001
LDL-C/HDL-C	3.34 $\pm$ 1.00	3.83 $\pm$ 2.66	3.94 $\pm$ 1.42	3.93 $\pm$ 1.21	<0.001
Lp(a) (mg/dl)	19.6 $\pm$ 28.3	16.0 $\pm$ 21.3	19.1 $\pm$ 28.5	13.6 $\pm$ 29.7	<0.05
Glucose (mg/dl)	89.0 $\pm$ 10.0	97.1 $\pm$ 24.2	101.6 $\pm$ 33.9	99.0 $\pm$ 22.0	<0.001

BMI = Body mass index; WHR = Waist to hip ratio; SBP = systolic blood pressure; DBP = diastolic blood pressure; TC = total cholesterol; TG = triglycerides; LDL-C = low density lipoprotein cholesterol; HDL-C = high density lipoprotein cholesterol; Lp(a) lipoprotein(a).

The values are expressed as mean $\pm$ standard deviation.

* ANOVA

consecutive cases (39). Diabetes is the main cause for non-traumatic amputations and Eye Institutes report diabetes as one of their main causes for consultation. Diabetic retinopathy is very common in Mexican diabetic individuals; in a population-based study designed to estimate the prevalence of diabetic retinopathy in low-income areas of Mexico City (40,41), 214 Type 2 diabetic patients had a complete ophthalmologic examination. It was found that 29.4% of men and 23.3% of women had preproliferative retinopathy, 5.9% of men and 5.4% of women had proliferative retinopathy, and macular edema was diagnosed in 8.2% of the men and 4.7% of the women. Diabetic retinopathy was associated with a longer duration of diabetes, chronic poor control and microalbuminuria.

Finally, as a result of a population-based survey (42) in a low-income area of Mexico City, 12.5% of diabetic individuals compared to 6.4% of subjects with normal glucose tolerance were hospitalized during a 3-year period. At least 30% of this excess demand was potentially preventable, since hospitalization was related to lack of attention to diabetic control and foot problems.

DISCUSSION

Age-standardized global estimates of diabetes prevalence in the 20–74 years range have been published recently (3). The data from Mexican Americans in San Antonio, Texas (25), Mexicans

from a low-income neighborhood in Mexico City (19) and the results of a survey in a representative sample of Mexico City (21) are presented in Table 10.3. The prevalence of diabetes found in Mexico City is comparatively lower than that observed in Mexican Americans but very similar to that observed in the country as a whole (22).

The population diagram distribution of under-developed countries is characteristically pyramidal in shape, with a very wide base, represented by large numbers of young people, particularly in the first two decades of life, and a quick narrowing due to a rapidly decreasing number of older adults.

Over the past 50 years, the proportion of elderly people in the population has increased and the population distribution in the urban and rural areas has reversed. Age distribution is still pyramidal, with the majority of individuals aged less than 20 years, but the absolute number of adults aged over 50 and 60 years is increasing and chronic degenerative diseases begin to appear as a more frequent cause of death.

Rural–urban differences in lifestyle are more pertinent to the impact of diabetes in a developing country, because urbanization of large segments of a rural population is a typical socio-economic phenomenon in such countries. Urban life means a Westernization of lifestyle characterized, among other things, by more calories, especially from refined carbohydrates and fats, and less physical work. An additional negative factor may be the stress of living in large cities. These diabetogenic

Table 10.3 Age-specific prevalence of diabetes mellitus

Prevalence (%)						
Ethnic group	Sex	Age specific (Yr)			Crude rate n/N (%)	Age-adjusted rate (%)
		35–44 n/N (%)	45–54 n/N (%)	55–64 n/N (%)		
Mexican American (San Antonio, TX)*	M	9/119 (7.6)	24/121 (19.8)	43/150 (28.7)	76/390 (19.5)	17.8
	F	29/222 (13.1)	56/235 (23.8)	85/239 (35.6)	170/696 (24.4)	23.0
Low-income barrio (Mexico City)*	M	8/134 (6.0)	11/92 (12.0)	10/48 (20.8)	29/274 (10.6)	12.3
	F	10/185 (5.4)	20/116 (17.2)	24/64 (37.5)	54/365 (14.8)	18.5
Mexican (Mexico City)**	M	5/98 (5.1)	6/74 (8.1)	10/33 (30.3)	21/205 (10.2)	11.0
	F	9/140 (6.4)	9/53 (17.0)	12/35 (34.3)	30/228 (13.2)	15.7

M = Males, F = Females, n = Diabetics subjects, N = Total subjects

*From Haffner et al. (37).

**From Posadas et al.(21).

influences tend to be more marked in recent migrants (36), in whom changes in lifestyle are more dramatic and the genetic susceptibility pool less diluted or deselected.

A cause of great concern is seeing how changes in the physical environment and lifestyle, such as have occurred in Mexican Americans, can result in major causes of morbidity and mortality (25) and even override genetic susceptibility in the expression of Type 2 diabetes and other traits. Unfortunately, as is demonstrated by the recent surveys, the conditions that predispose to an increased prevalence of diabetes and related complications are already present in Mexico (21,23,38,41,43). Gradual genetic dilution and progressive socio-economic improvement will eventually lessen the predisposition to diabetes of the Mexican people, but not before the disease and its complications have taken their toll among many of them. In Mexico, the rural population has a greater Indian American ancestry than among urban dwellers. The newly arrived migrants of the large cities rapidly adapt to the urban milieu, losing their rural nutritional and activity habits and becoming increasingly stressed. In addition, it is well known that the Mexicans, particularly those of Indian or mixed origin, share with other Indian American groups a high genetic susceptibility to Type 2 diabetes (25). Considering diabetes prevalence rates separately, one sees almost a 5-fold difference between the rural and the urban statement. Probably the increased physical activity of rural dwellers does have a protective role against the development of diabetes (36). Further support of this assumption is provided by the fact that age-adjusted prevalence of diabetes is higher in sedentary workers compared with those engaged in heavy physical activity.

The thrifty genotype hypothesis invokes the proposal that in traditional populations subject to periods of 'feast and famine', a survival advantage was conferred on those whose metabolism stored energy with maximum efficiency (44). With modernization and the accompanying assured supply of highly refined calories, coupled with a sedentary lifestyle, the thrifty genotype became disadvantageous, leading to obesity, hyperinsulinemia and insulin resistance and eventually to pancreatic beta-cell decompensation and diabetes (36), as seems to happen in the Mexican population, where the genotype probably has a high prevalence and penetration.

It is now known that adverse environmental conditions, perhaps related to less than optimal nutrition in fetal and early life, are associated with an enhanced risk of both diabetes and cardiovascular disease many decades later. These same conditions are also associated with the development in adult life of abdominal obesity and the insulin-resistance syndrome.

In the United Kingdom, Barker et al. (45) noted that those geographic regions that had suffered from high rates of infant mortality 50 or more years before, tended to exhibit high rates of a number of chronic diseases, among them diabetes and cardiovascular disease, many decades later. These findings suggested that among those who survived the adverse conditions of their early life, whatever adverse conditions had been responsible for the high infant mortality rate produced long-lasting consequences that contributed to chronic diseases in adult life. Later, it was shown that low birth-weight and low rates of weight gain in the first year of life were risk factors for hypertension, diabetes and cardiovascular disease in adult life. It is hypothesized that an impaired development of the endocrine pancreas in early life may predispose the individual to eventual beta-cell failure and Type 2 diabetes. Early nutritional deficiencies could limit the development of adipocytes, so that when challenged with excess calories in later years, individuals with limited numbers of adipocytes, and possibly with impaired ability to differentiate new adipocytes, would tend to experience hypertrophy of their available adipocytes, leading to adverse metabolic consequences. Another unifying hypothesis points out that insulin resistance is an underlying genetically transmitted defect that predisposes to glucose intolerance and diabetes, central obesity, hypertension and dyslipidemias which, taken together, lead to premature cardiovascular disease. Whatever the reason—the genetic trait, detrimental environmental factors, undernutrition *in utero* or the thrifty genotype—the clustering of these metabolic problems has reached epidemic proportions in our country.

CONCLUSIONS

A conservative estimated general prevalence of diabetes for Mexico could be 8% of the adult population (almost 98% Type 2 diabetes), 10%

for impaired glucose tolerance and 7.5% for gestational diabetes. As observed in many countries, the surveys reveal one newly discovered case of diabetes mellitus for each previously diagnosed.

In this setting of epidemiological transition, the prevalence of diabetes is rapidly and continuously increasing and the incidence of diabetic complications is already a heavy burden on the Mexican medical system, particularly in those states that harbor the largest urban concentrations.

There is a critical need for resources to be allocated to programs for primary and secondary prevention, which must be well structured and organized so that proper standards of care are followed to prevent progression of the disease and its complications.

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Latin America

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INTRODUCTION

Diabetes mellitus is a universally distributed syndrome which is recognized in countries and populations independently of their development status. As far as Type 1 diabetes is concerned, great variability in its incidence is observed worldwide (1), and a role for both genetic and environmental factors has been shown. On the other hand, considering the frequency of the diabetic syndrome in populations, Type 2 diabetes is beyond doubt the most frequent type, characterized by a marked heterogeneity of clinical features.

The population of Latin America is a heterogeneous group, made up of the descendants of Hispanics, Portuguese and other European Caucasians, Africans, American Indians and Japanese. This admixture is quite common in many countries and such populations reflect not only great racial and genetic heterogeneity but also socio-economic and cultural diversity.

Diabetes in Latin America is an issue of great interest. Type 1 diabetes and Type 2 diabetes patterns in such heterogeneous populations are difficult to predict and the incidence rates of Type 1 diabetes vary dramatically among them. Population-based studies on Type 2 diabetes prevalence show that some populations exhibit rates comparable to those found in developed countries.

since standardized epidemiological data are now being collected from several countries around Latin America, allowing international comparisons. DIAMOND participating centers are required to register all new cases diagnosed under 15 years of age. However, accurate population-based registries are still limited and little information has been published from Latin American countries. Most of the available data on Type 1 diabetes incidence come from regional surveys and may not represent the whole country. Others have not yet validated their completeness and should be interpreted with caution. In the international context, studies on Type 1 diabetes epidemiology among children of Spanish and Portuguese heritage are much needed as an attempt to identify determinants of Type 1 diabetes throughout the world. As far as Iberian heritage populations are concerned, great variability in incidence is detected among ethnic groups. It has been demonstrated that much of the incidence variation is positively related to the percentage of Caucasians in the population (2). Racial admixture and local environmental factors might provide important data about the genetic–environment interaction. Table 11.1 summarizes the available data on Type 1 diabetes incidence in Latin American countries.

Argentina

EPIDEMIOLOGY OF TYPE 1 DIABETES IN LATIN AMERICA

The lack of standardized data has made it difficult to determine the true magnitude of Type 1 diabetes in Latin America. The WHO Multinational Project for Childhood Diabetes (DIAMOND Project) started in 1990 has lessened the problem,

As Argentina is located in the southern part of South America, seasons are usually well defined. The population is 95% Caucasian. Avellaneda, a DIAMOND participating center, is a suburb of Buenos Aires located by the La Plata River at latitude 34.5° south. The primary source of ascertainment was composed of kindergarden and elementary schools while hospitals, private

Table 11.1 Annual incidence rates (per 100 000) of Type 1 diabetes in some Latin American countries

Country and area	Study period	Age group (yr)	Estimate of ascertainment (%)	Incidence			M/F ratio
				M	F	T	
Argentina							
Avellaneda (3)	1985–90	<15	NA	–	–	6.7	NA
Brazil							
São Paulo (9)	1987–91	<15	> 90	5.6	9.5	7.6	0.61
Chile							
Santiago (11)	1990–91	<15	100	–	–	2.5	NA
Santiago (10)	1992	<15	NA	–	–	3.0	NA
Colombia							
Bogota (2)	1990s	NA	NA	–	–	3.7	NA
Cuba (11)	1978–80	<15	NA	2.5	2.8	–	0.89
Mexico							
Mexico City (11)	1984–86	<15	NA	0.4	0.7	–	0.57
Paraguay (2)	1990s	<15	NA	–	–	1.8	NA
Peru							
Lima, Cuzoo, San Martin (12)	1980–88	<15	90	–	–	0.6	NA
Lima (13)	1985–91	<15	85	–	–	0.4	NA
Puerto Rico (15)	1985–89	<15	NA	–	–	10.0	NA

NA, not available; M, male; F, female

References in parenthesis.

clinics, diabetologists and pediatricians represented the secondary sources. The degree of ascertainment permitted validation of the study. The annual Type 1 diabetes incidence rates reported for the period 1985–90 varied between 5.3/100 000 (1988) and 7.6/100 000 (1990) inhabitants under 15 years of age in Avellaneda (3). No sex preponderance or age peak was found nor was any seasonal trend detected either. Such data probably represent one of the highest rates observed in Latin America, which are in agreement with the association between Type 1 diabetes incidence and Caucasian ethnicity. In the international context, Avellaneda showed an Type 1 diabetes risk situated between that of Japan and Northern European countries and near the average figures of Southern Europe (except for Sardinia) (4–6).

Brazil

This tropical country has an area of 8.5 million km² which represents almost half of South America. Population-based reports on Type 1 diabetes started in a defined population from the state of São Paulo in January 1987. This state is

considered a developed area, located in the southern part of Brazil, crossed by the Tropic of Capricorn. Migration from Europe, Africa, and Asia has made the Brazilian population ethnically heterogeneous. The majority of the population is white (54%), followed by mulatto (39%), and black (6%); less than 1% is of Asian origin and only 0.1% is Amerindian, according to the 1991 national census. Particularly in the state of São Paulo, where data on Type 1 diabetes incidence are available, the population is 75% white, mainly of Portuguese and Italian origin, 5% black, 18% mulatto, and 0.9% Asian (7). Three cities from this state have participated in a prospective population-based study. Data of newly diagnosed Type 1 diabetes patients under 15 years of age have been collected according to the methods recommended by the Diabetes Epidemiology Research International group (8). Reports from physicians have been considered the primary source of case identification and school surveys as the main secondary source. Until December 1991, the average annual incidence of childhood Type 1 diabetes was 7.6/100 000 inhabitants (95% confidence interval, 5.6–9.7) (9). Such a rate has been interpreted as an intermediate Type 1 diabetes risk, which is similar to that found in Argentina (3). A

tendency to female excess was noticed (male-to-female ratio of 0.61). The highest rates were found in the 5–9-year-old age group for girls and 10–14-year-old age group for boys. Validation procedures showed satisfactory completeness of each source and the degree of ascertainment for the combined registry was >90%. Since the incidence rate in the state of São Paulo might not necessarily be representative of the Brazilian population, the study was extended in 1991 to other centers with different climatic and ethnic characteristics. Unpublished information concerning the period 1991–94 pointed to lower overall incidence rates than those previously reported, being similar between genders. Despite north–south contrasts, significant within-country variation in Type 1 diabetes incidence has not been shown in Brazil.

Chile

Climatic conditions in Chile differ from other countries in Latin America because winter temperatures are markedly low several months a year. The population is 25% Caucasian and the majority is Mestizo (Indian-European admixture). During 1986–89, a retrospective study pointed to a low incidence rate (1.9/100 000 inhabitants) in the capital, Santiago (10). Since 1990, data on incidence has been collected prospectively according to DIAMOND recommendations. During a 2-year period (1990–91) the overall incidence rate was 2.5/100 000 inhabitants per year, and no difference was detected between sexes (11). The highest rate was found in the 10–14-year-old age group. Case ascertainment was estimated at 100%. More recent data presented at the 15th IDF Congress showed that low rates are still observed in rural and urban populations from Santiago. In 1992, the Type 1 diabetes incidence was 3.0/100 000 inhabitants under 15 years old (10).

Colombia

Colombia is located in the northwest corner of South America. Its population has experienced much genetic admixture, which started with the Spaniards mingled with the native Indians (Mestizos) and later continued with the influx of black slaves from Africa. Data on Type 1 diabetes incidence in this

country are very limited. A published report from the population living in the capital, Bogotá, at the beginning of the 1990s pointed to an annual incidence rate of 3.7/100 000 inhabitants under 15 years of age (2).

Cuba

The population living in this tropical island located in the Caribbean has predominantly Black and Hispanic ancestry and the percentage of Caucasians is around 37% (2). Data on prevalence of Type 1 diabetes, which referred to the 0–14-year-old age group and to the period 1979–1980 showed a rate of 0.15/1000 (12). Concerning incidence data, the reported rates for 1978–80 were 2.5/100 000 (95% confidence interval 2.1–3.0) and 2.8 (95% confidence interval, 2.4–3.3) per year for boys and girls under 15 years of age, respectively (12). No estimate of ascertainment is provided for either study.

Mexico

Mexico City is one of the largest and most crowded cities in the world. Its population has a genetic admixture mainly from the native Indians mixing with the Spaniards (Mestizos). The apparent low incidence of Type 1 diabetes in this country is based on data collected in Mexico City during the period 1984–86 (12). An estimate of ascertainment was not provided. The incidence rates were 0.4/100 000 (95% confidence interval, 0.3–0.5) and 0.7 (95% confidence interval, 0.5–0.9) per year for boys and girls under 15 years of age, respectively.

Paraguay

Unpublished information pointed to low incidence rates in Paraguay, being around 1.8/100 000 inhabitants under 15 years old in the early 1990s (2).

Peru

Epidemiological data on the incidence of Type 1 diabetes in children under 15 years old come from

the provinces of Lima (coast), Cuzco (highlands) and San Martin (jungle), representing 28% of the total Peruvian population in this age group (13). The great majority of this population is made up of Mestizos and only 15% are Caucasians. The Peruvian registry was based on the diagnosis of Type 1 diabetes according to WHO criteria, before 15 years of age at the time of the diagnosis. Primary source data were obtained from 25 hospitals and the secondary source was the Peruvian Diabetes Association with 90% validation. The annual incidence observed for the period 1980–88 was 0.6/100 000 inhabitants (13). The Type 1 diabetes incidence survey in the capital, Lima, has been conducted according to the DIAMOND project. The Population under 15 years old in the early 1990s was around 2 122 900 inhabitants. From 1985 to 1987 the degree of ascertainment dropped below 90%, which improved in 1988 and 1990, when incidence rates were 0.72 and 0.47/100 000, respectively (14). Considering the period 1985–91, the mean case ascertainment was 85% and the annual incidence rate was 0.41/100 000 inhabitants. Such a rate represents one of the lowest incidence rates observed worldwide (15), suggesting that this Mestizo population may be genetically protected from Type 1 diabetes. A role for environmental factors needs to be investigated.

Puerto Rico

Like Cuba, Puerto Rico is a tropical island with a population of Hispanic descent and a similar genetic admixture is observed. However, the life-style and economic resources are more like those of the USA. Using hospital records as the primary source and the government diabetic registry as the secondary source for the years 1985–89, the Type 1 diabetes incidence rate showed to be 10.0/100 000 inhabitants under 15 years with a slight preponderance in girls (15, 16). The highest rate was found in the 11–14-year age group. Based on the rates observed in the Hispanic population from Colorado and Cuba (9.7 and 2.5/100 000 per year, respectively), it was suggested that the pattern of Type 1 diabetes in Puerto Rico may be the result of a genetic–environmental interaction that is more similar to that from Hispanic Americans than to that from the Cuban popula-

tion. These data showed that, besides genetic factors and latitude, a number of other factors must be involved in Type 1 diabetes occurrence.

Venezuela

Although data on incidence of Type 1 diabetes in Venezuela are not available in the international literature, regional epidemiological reports have been made (17). A review of 91 cases of Type 1 diabetes, registered in a hospital in the capital, Caracas, during the period 1986–91, showed that 56 subjects were born in this country and had at least one parent also born in Venezuela. The analysis of this group of subjects revealed that 37.5% were boys and the mean age of onset was 7.0 ± 4.3 years old; for girls the mean age was 7.4 ± 4.2 years (range: 0.9–16.2 years). The distribution by age frequency followed a bimodal pattern and the peaks corresponded to the phases when children are more exposed to environmental factors such as virus infections.

EPIDEMIOLOGY OF TYPE 2 DIABETES IN LATIN AMERICA

Since Type 2 diabetes has been recognized as a major public health problem in Latin America, attempts have been made to assess its prevalence. However, the majority of the studies available nowadays are not based on standardized methods and criteria for diagnosis (WHO, 1985) (18) which limit international comparisons. Also, it is well known that for diseases such as diabetes frequency is strongly age-related, and age differences between populations can confound direct comparisons of crude rates. We will summarize some population-based studies conducted in Latin America. Few studies included standardized age groups and age-adjusted rates. As far as incidence of Type 2 diabetes is concerned, this rate could only be calculated by monitoring the population continuously, or by repeated cross-sectional surveys. The resources required for such studies are often considerable. Furthermore, it is well known that a substantial proportion of subjects with Type 2 diabetes remain undetected in the community, and incidence estimates based upon routine data sources are much less reliable than they are for

Type 1 diabetes. For these reasons, this type of study is even more rare in Latin America and no data have been published. Table 11.2 summarizes the available data on Type 2 diabetes prevalence in Latin American countries.

Argentina

A study on prevalence of diabetes in the cities of Rosario and Santa Fe, Argentina, was carried out in 1967 (19). The diagnosis was based on 2 h blood

Table 11.2 Prevalence of Type 2 diabetes in some Latin American countries

Country and area	Study period	Age group (yr)	Diagnostic criteria	Glycemia cut-off value (mmol/l)	Prevalence (%)		
					M	F	T
Argentina							
Rosario, Santa Fe (19)	1967	NA	2 h glycemia after mixed meal	>8.3	—	—	6.1, 4.3
Avellaneda (20)	1976	20–69	2 h capillary glycemia after 75 g oral glucose	≥8.3	—	—	8.0
Humboldt (20)	1976	20–69	2 h capillary glycemia after 75 g oral glucose	≥8.3	—	—	5.8
La Plata (21)	1987	20–74	2 h capillary glycemia after 50 g oral glucose	>8.3	—	—	2.7
Resistencia (22)	1990s	>15	self-reported	—	—	—	3.8
Brazil							
Nine cities, general population (23)	1986–88	30–69	2 h capillary glycemia after 75 g oral glucose	≥11.1	—	—	7.4
Xingu, indigenous community (27)	1979	>15	1 h venous glycemia after 100 g oral glucose	>10.8	—	—	0.0
Bauru, Japanese-Brazilians (30)	1993	40–79	2 h venous glycemia after 75 g oral glucose	≥11.1	12.4 21.7	11.6 11.4	(Issei) (Nisei)
Chile							
Santiago, general population (33)	1979	>20	2 h venous glycemia after 50 g oral glucose	≥8.3	—	—	6.5
Mapuche, indigenous community (35)	1985	NA	NA	NA	—	—	1.0
Colombia							
Bogotá (36)	1988–89	≥30	2 h venous glycemia after 75 g oral glucose	≥11.1	7.3	8.7	NA
Cuba							
Havana, Artemisa (37)	1970	NA	2 h venous glycemia after 100 g oral glucose	≥7.8	—	—	3.8
Jamaica							
General population (41)	1970s	≥15	2 h capillary glycemia after non-standardized meal	>9.4	—	—	6.1
Mexico							
Mexico City (49)	1992	35–64	2 h venous glycemia after 75 g oral glucose	≥11.1	6.0	10.6	8.1
Paraguay							
Asunción (51)	1991	20–74	2 h venous glycemia after 75 g oral glucose	≥11.1	—	—	8.9
Peru							
Lima (52)	1990s	NA	2 h venous glycemia after 75 g oral glucose	≥11.1	—	—	4.4
Trinidad							
General population (53)	1961–62	All	2 h venous glycemia after 100 g oral glucose	≥9.4	—	—	1.9

NA, not available; CHO, carbohydrate
References in parenthesis

glucose levels after receiving a mixed meal containing at least 50 g of carbohydrate. Glycemia >8.3 mmol/l was considered positive for diabetes. About 5% of the population aged 20–70 years (22 351 inhabitants for Rosario and 10 148 inhabitants for Santa Fe) was included. Rates of 6.1 and 4.3% were found, respectively, and at least half of the cases of diabetes were undiagnosed. Another survey was conducted in 1976 among 596 subjects aged 20–69 years, living in an urban area of the province of Buenos Aires (Avellaneda district), now using 75 g oral glucose load. A 2 h capillary glycemia ≥ 8.3 mmol/l was indicative of diabetes (20). A prevalence rate of 8.0% was found. Using the same age group and diagnostic criteria, a lower rate (5.8%) was observed in the rural area of Humboldt (province of Santa Fe) (20). When adjusting these results to the WHO criteria (18), the diabetes prevalence rates in the province of Buenos Aires (urban area) and Santa Fe (rural area) markedly dropped from 8.0 and 5.8% to 4.0 and 1.8%, respectively. In 1987, a prevalence of 5% has been reported from La Plata City (21). This rate may have been an underestimate, since the survey was based upon a 50 g oral glucose challenge. More recently, a study was conducted in a selected urban population living in Resistencia City (22). The diagnosis of Type 2 diabetes was self-reported and 2797 individuals were questioned. An overall prevalence rate of 3.8% was found and the male-to-female ratio was 0.67. Such study design underestimates the true prevalence rate and the population sample studied may not be representative of the whole population.

Brazil

Little information was available concerning diabetes among the Brazilian population until 1986. A cross-sectional home survey was conducted from 1986 to 1988 in a random sample of 21 847 individuals aged 30–69 year in nine Brazilian cities (23). The 1980 Brazilian census (24) provided the basic demographic data to characterize the population and to assess representativeness of the eligible samples. Besides a questionnaire, fasting capillary glycemia was determined in the screening phase. Subjects with previously diagnosed diabetes, or with a fasting capillary glycemia ≥ 11.1 mmol/l at screening, were considered to

have diabetes. All persons with fasting capillary glycemia ≥ 5.6 mmol/l and every sixth consecutive negative screenee (<5.6 mmol/l) were scheduled for an oral GTT. Results from the sixth negatives were extrapolated to all negative screenees. Using WHO criteria for diagnosis (18), the overall age-adjusted rates for diabetes and impaired glucose tolerance (IGT) were 7.4 and 7.7%, respectively. Both conditions showed to be more prevalent in the south and southeast regions, also the most industrialized areas. The highest rate of diabetes was found in São Paulo city (9.7%), located in the most economically developed region of Brazil. Age strongly influenced diabetes prevalence, with the rate in the 60–69-year-old group (17.4%) being 6.4 times higher than that seen among people aged 30–39 (2.7%, $p < 0.01$). For age adjusted rates, no difference was found in diabetes prevalence between men (7.4%) and women (7.4%); however, women had a higher rate of IGT than men (8.4 vs. 6.7%, $p < 0.01$). Rates of diabetes and IGT were similar in whites and non-whites. Almost half of the diabetic subjects in the studied age group were undiagnosed. Data obtained in this study indicated that the occurrence rates of diabetes and IGT in Brazil are similar to those found in countries such as the USA, Italy, Israel, Argentina and others (25, 26).

Another survey based on oral GTT was carried out in a Brazilian indigenous population, living in the 'Parque Nacional do Xingu' along the Xingu River, located in the State of Mato Grosso, Central Brazil (27). Their diet included mainly manioc and fish, and Upper Xingu Indians are well nourished. In 1979, 106 of them received a 100 g glucose load and a venous blood sample was taken 1 h later. Considering 10.83 mmol/l as the cut off value for diagnosis, diabetes was not found among the Upper Xingu Indians. In spite of intermittent contact with civilized society, diabetes does not represent a cause of morbidity and mortality among these Brazilian Indians, contrasting to the North-American Indians (28).

Also of great interest in Brazil was the study of diabetes in migrant populations. Brazil has the largest population of Japanese origin located outside Japan, the majority living in the State of São Paulo. This community differs from other migrant populations in Brazil concerning its genetic and cultural homogeneity. During 1987–90, data regarding the prevalence of diabetes were

restricted to self-reported surveys (18). Recently, a population-based survey, using 75 g oral GTT and WHO diagnostic criteria (18), was conducted in the Japanese Brazilian community aged 40–79 years, living in the city of Bauru, São Paulo State (30). These data showed high prevalence of Type 2 diabetes and IGT, even higher than in the general Brazilian population (23), specially among men. Age-adjusted rates for Issei (first-generation) men and women were 12.4 and 11.6%, respectively; for Nisei (second-generation) men the prevalence of diabetes was significantly higher than the women's rate (21.7% vs. 11.4%). These findings were in accordance with those from Fujimoto et al. (31), obtained in the Japanese American community in Seattle, USA.

Chile

Initial prevalence rates of Type 2 diabetes in Chile were based upon post-prandial glycosuria and certainly the rate of 1.2% did not reflect the true magnitude of the disease in this country (32). In 1979, a prevalence survey was conducted in the population >20 years of age from Santiago, according to the recommendations of the 'Plan Latino-Americano de Diabetes' (33), covering 1100 people. A 50 g oral glucose load was used, with 2 h whole venous blood for glucose determinations. A 2 h glycemia ≥ 8.3 mmol/l was indicative of diabetes. Such procedures resulted in a prevalence rate of 6.5%, which is within the range of rates found in many Western countries. Similar rates were found in both sexes and in the different socio-economic levels. In 44% of the cases identified by the survey, the diabetic condition was undiagnosed. An estimate of the prevalence using the National Diabetes Data Group criteria (34), whose cut-off point for the 2 h whole blood glycemia is 10.0 mmol/l, resulted in a prevalence of 5.3% for the same population. Contrasting rates were observed when indigenous populations were studied. Among the Mapuche community, a prevalence rate of Type 2 diabetes of 1% was reported (35), in contrast to the situation encountered in several American Indian populations in the USA (28). The magnitude of diabetes in the whole country is still unknown and studies using WHO criteria (18) have not yet been published.

Colombia

Almost 6 million Colombians live in the capital city, Santafè de Bogotá, which is located on a plateau at the altitude of 2600 m. Considering the high rate of drift in Colombia, a relatively stable, urban community of medium-low socio-economic status (named San Isidro, in Santafè de Bogotá) was chosen for the diabetes survey, which was carried out in 1988–89 (36). The study sample was representative of 70–80% of the urban population of this country with regard to Hispanic ethnicity and socio-economic status. The age range studied was 30–80 and more years and WHO diagnostic criteria were adopted, using 2 h blood glucose values after a 75 g oral glucose challenge. Age-adjusted prevalence rates of diabetes were 7.3% (95% confidence interval, 3.7–10.9) and 8.7% (95% confidence interval, 5.2–12.3) for men and women, respectively. Less than 40% of the diabetics were aware of such diagnosis. For IGT, age-adjusted prevalence was 3.1% for men and 7.2% for women. Thus, abnormal glucose tolerance (diabetes and IGT combined) was found in 10.4% and 15.9% of the Colombian men and women, respectively. These rate levels have been considered moderate prevalences. Rates of abnormal glucose tolerance prevalence in urban Colombians and Brazilians are comparable to rates seen in whites in similar settings in Europe and North America (26).

Cuba

In 1970, 8186 subjects from one urban (Havana) and one semi-urban area (Artemisa) in Cuba were screened for diabetes, using a two-step procedure (37). Only those presenting glycosuria, positive family history of diabetes, abnormal obstetric history and obesity were asked to have a 100 g load of glucose. Diagnosis of diabetes was set when blood glucose 2 h post-load was ≥ 7.78 mmol/l. About 3.8% showed to be diabetic and the prevalence was higher in the urban than in the rural population. A proportion of 2.3% had 2 h blood glucose between 6.6 and 7.7 mmol/l. A total of 44 807 diabetic subjects were registered in the whole country, and 1% of them were ≤ 15 years old. An alarmingly high prevalence rate of abnormal glucose tolerance is verified when analyzing the

Hispanic HANES data obtained in the population aged 20–74 years (38). Cubans living in the US showed age-adjusted prevalence rates of 11.8% (95% confidence interval, 9.0–14.5) and 4.5% (95% confidence interval, 2.5–6.4) for men and women, respectively. A similar situation is described for Puerto Ricans living in New York City (26).

Jamaica

Initial studies on prevalence of diabetes in Jamaica started in 1958, and the diagnosis was solely based on the presence of glucose in urine tests (39). A low rate of 0.7% was detected but the degree of underestimation was not known. In a subsequent survey, a population sample aged 25 to 64 years underwent a 1 h 100 g oral glucose tolerance test (40). The prevalence increased from 1.8% in men and 0% in women aged 25–34 years to a maximum of 14.5% in men aged 45–54 years and to 17.0% in women aged 55–64 years. A further study included about 0.3% of the total Jamaican population aged 15 years or more (41). Using a cut-off value of 9.4 mm/l for 2 h post-non-standardized meal capillary glucose, the prevalence of diabetes was 6.1%. Apart from the inappropriate methodology and diagnostic criteria, prevalence rates of Type 2 diabetes appear to be as high as in many developed countries (25, 26).

Mexico

A number of prevalence studies, restricted to relatively small populations, have yielded estimates in the range of 1.3–6.0% (42). Given the differences in diagnostic criteria, time interval among the surveys (they span nearly 30 years) and age structure of the populations studied (with the proportion of those aged over 30 years ranging from 25 to 65%), it is difficult to draw any confident conclusion about the national level or pattern of diabetes from these data. The National Health Survey (NHS) conducted in Mexico in 1988 was self-reported and 1.2% referred to had diabetes (43). This crude rate for the total population is somewhat lower than the one recorded for the USA by the National Health and Nutrition Examination Survey (NHANES) of self-reported diabetes (1976–80) (38), but this is largely attributed to the fact that

Mexico's age structure is heavily weighted to the young, whose risk is lower. Analysis of age-specific rates reveals that this country has very similar prevalence rates to the USA, and if the age analysis were refined further within each 10-year grouping, Mexican rates would be even higher (44). Considering that Mexico experienced the same degree of under-reporting of diabetes as the USA (45) and others (23), the true age-specific prevalence rate would be around 4.6% for the age group 20–74 years. There is evidence suggesting that awareness of the diabetic status in Mexico could be even higher than 50% (44). Further small-scale studies provided age-specific data of the true prevalence (46–48), using WHO criteria (18). All showed rates at least as high as those obtained by doubling the NHS results (42). Mexican NHS age-adjusted rates of diabetes, according to Segi's standard world population and current WHO diagnostic criteria, pointed to a prevalence of 2.8% (self-reported), which is probably close to 6% if the true prevalence had been measured (44). This figure falls within the range of age-adjusted prevalence rates found in European populations (25, 26). The most recent Mexican cross sectional survey (1992), conducted in 933 individuals aged 35–64 years from Mexico City, used 75 g oral GTT and WHO criteria for diagnostic purposes (49). The age-adjusted prevalence rate increased to 8.1% (6.0 and 10.6% for men and women, respectively) in the age group 20–65 years or more. The same study included data obtained in Mexican Americans with comparable socio-economic level (low-income), living in San Antonio. The people had their age-adjusted prevalence of Type 2 diabetes significantly increased (17.8% for men and 23.0% for women). The analysis of such data suggested a role for environmental factors in the expression of the Type 2 diabetes trait. There has been a growing concern that Type 2 diabetes is becoming more common in Mexico. In fact, this disease has represented one of the leading causes for hospital admissions and outpatient visits in health care facilities and one of the main causes of death (50).

Paraguay

The prevalence of Type 2 diabetes was studied in a population sample from Asunción, consisting of 508 men and 1610 women, aged 20–74 years (51).

Diagnosis of diabetes was based on fasting and 2 h after a 75 g glucose load glycemia, using WHO diagnostic criteria (18). An overall prevalence rate of 8.9% was found; 5.3% of subjects previously knew about the diagnosis. Impaired glucose tolerance was detected in 11.1%.

Peru

A prevalence survey in Peru was conducted in the adult population from Lima, including 4113 men and 4089 women. The results were presented at the VIII Latin American Diabetes Association Congress in 1992 in Mar Del Plata, Argentina (52). Prevalence rates of Type 2 diabetes and impaired glucose tolerance were 4.4 and 4.6%, respectively, with male preponderance for both conditions. No information was provided with respect to the population studied and diagnostic criteria.

Trinidad

In 1961–62, a random sample of 24069 subjects, representing the entire population of Trinidad, were screened for diabetes (53). The following criteria were used for diagnosis: (1) post-prandial glycosuria or history of diabetes; (2) venous blood glucose ≥ 9.4 mmol/l, 2 h after 100 g oral glucose in a non-fasting state; or (3) abnormal glucose tolerance test defined as fasting glycemia ≥ 6.1 mmol/l and 2 h 100 g glucose load glycemia ≥ 9.4 mmol/l. A prevalence of 1.9% was found. While diabetes was rare under 20 years of age, the highest rate was observed in the 55–59-year age group, being 8.2% among men and 11.7% among women.

OTHER COUNTRIES IN CENTRAL AND SOUTH AMERICA

West and Kalbfleisch were probably the first to investigate the prevalence of diabetes using standardized criteria for its diagnosis in Latin American countries (54). Almost all subjects over 30 years enrolled in these surveys received oral glucose load and diagnosis was based upon 2 h venous blood glucose ≥ 8.3 mmol/l. The prevalence rates of diabetes for some countries are

Table 11.3 Reported prevalences of diabetes mellitus in some Latin American countries

Country	Prevalence rates (%)
Panama	2.5
El Salvador	3.2
Honduras	4.1
Guatemala	4.2
Nicaragua	5.0
Costa Rica	5.4
Uruguay	6.9
Venezuela	7.0

Data from reference (54) reproduced by permission.

shown in Table 11.3. The differences in prevalence were likely due to the varying degree of obesity, since a marked correlation ($r = 0.89$) was found between the prevalence of diabetes and the mean percentage of standard weight of the populations studied (53–55).

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The Middle East

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INTRODUCTION

Dramatic changes are taking place in the epidemiological pattern of disease in most countries of the Middle East. Declining incidence of infections and undernutrition is associated with a concomitant increase in morbidity and mortality from noncommunicable diseases. Socio-economic development, urbanization and associated lifestyle changes are undoubtedly the underlying causative factors for this accelerated epidemiological transition, since several countries of the region have experienced rapid socio-economic changes in the last few decades. All countries of the WHO Eastern Mediterranean (Middle East) region have experienced an increasing availability of calories for consumption during the last 20 years (1). The few available studies indicate that about one-third of the adults in countries of the region are obese (2), and the prevalence of obesity in children is amongst the highest in the world (3). Obesity is particularly common in women; in a study in Bahrain, 80% of the women were overweight or obese (4). Among the noncommunicable diseases commonly encountered nowadays, diabetes is emerging as a problem of major public health concern.

TYPE 2 DIABETES

Despite the wealth of epidemiological and clinical data published globally on diabetes, there has been a relative lack of accurate information on the exact magnitude of the problem in the Eastern Mediterranean region. Also, the varying methodologies and diagnostic criteria used in the past created considerable discrepancies and made prevalence estimates difficult to compare (Table 12.1). During the last two decades, data on the epidemiology and

clinical characteristics of Type 1 and Type 2 diabetes have been reported from Bahrain, Egypt, Iraq, Jordan, Kuwait, Libya, Oman, Pakistan, Saudi Arabia, Sudan and Tunisia.

One of the earlier epidemiological studies in the region was that performed in 1976 and 1980 on rural and urban samples of the adult Tunisian population aged 20 years and over (5). The age-standardized prevalence, based on fasting samples, using the neocuproine reduction method, was found to be 4.6% in males and 3.5% in females in the urban sample, as compared with 2.3% and 0.6% in rural males and females respectively. Several years later, a further study was carried out in an urban population sample in Tunisia, using a 75 g oral glucose tolerance test (OGTT) and WHO diagnostic criteria (F. Ben Khalifa, personal communication). The prevalence in subjects aged 30 years and over was higher than in the former study—9.2% in males and 9.1% in females.

A study performed in a small village population aged 15 years and above in the south of Iraq, using a 50 g OGTT, revealed an overall prevalence of 4.8% (6). In Saudi Arabia, a prevalence survey on diabetes in a rural population aged 15 years and above used random capillary blood glucose concentration as the initial measurement (7). A value of ≥ 200 mg/dl (11 mmol/l) was the cut-off point used. Those with an initial level ranging between 140 and 199 mg/dl were subjected to a 75 g OGTT and were subsequently classified according to WHO criteria (8). According to this survey, diabetes has a prevalence of 5.9% in females and 2.9% in males, with an overall prevalence of 4.3% among all ages and of 6.6% among subjects ≥ 15 years of age. The same investigators also reported an overall prevalence of diabetes of 5% in an urban sample; and 7.8% in persons aged 15 years and over (9).

Table 12.1 Earlier prevalence studies on Type 2 diabetes in some countries of the Eastern Mediterranean region

Country Author (reference)	Age range (Years)	Diagnostic criteria (mg/dl)	Prevalence (%) Urban	Prevalence (%) Rural
Egypt Arab (12)	10+	WHO	6	4
Iraq Al-Kasab et al. (6)	12+	50 g OGTT		5
Tunisia Papoz et al. (5)	20+	FBG > = 165	5 (men) 4 (women)	2 (men) 1 (women)
Ben Khalifa et al. (personal communication)	30+	WHO	9 (men) 9 (women)	
Saudi Arabia Fatani et al. (7,9)	15+	RBG > = 200	5	4
Saudi Arabia Abu-Zeid et al. (10)	10+	2 hours post-meal > = 200		5

WHO, World Health Organization criteria; OGTT, oral glucose tolerance test; FBG, fasting blood glucose concentration; RBG, random blood glucose concentration.

A few years later, a report from Saudi Arabia describes a prevalence study in semi-urban-rural communities where a cluster of 12 villages was studied and subjects aged 10 years and over were tested (10). Here, the measurement used was the capillary blood glucose concentration 2 hours after the midday meal. Diabetes was diagnosed when this value was ≥ 200 mg/dl (11 mmol/l) and impaired glucose tolerance (IGT) when the level was ≥ 140 mg/dl (7.8 mmol/l) and < 200 mg/dl (11 mmol/l). Using these criteria, the age-adjusted prevalence of diabetes was 4.6%. It was higher among men (5.5%) than among women (3.6%). IGT was diagnosed in 3.7%. Overall prevalence of IGT was 10.6% among those aged 30 years and above (14% in males, 7.4% in females).

The diabetes survey conducted in persons 40 or more years old in the city of Isfahan, Iran, used WHO criteria. The prevalence of diabetes was found to be 7.5% in men and 8% in women (11).

A report from Egypt described prevalence status derived from several surveys based on WHO criteria performed in various geographic areas in the country (12); they estimated the national prevalence of 4.3% for Egypt.

In some areas, high detection rates have been reported. In one of the Saudi Arabian studies, 86% of cases were known to have been diagnosed prior to the survey (10). The earlier Tunisian data indicate a prior detection rate of 60% in the urban population and 46% in the rural area (2). In the later Tunisian study and in Iran, about half the

persons with diabetes had been diagnosed previously (11).

In the last five years, important epidemiological surveys have been reported from Bahrain, Egypt, Jordan, Oman, Pakistan and Saudi Arabia. They employed comparable methodology and diagnostic criteria, and they deliver a consistent and disturbing message: diabetes in these populations is now at least twice as prevalent as it is in Europe and North America (Table 12.2). In Oman, 10% of adults were found to have diabetes, with a similar proportion suffering from IGT (13). Moreover, the high frequency of diabetes was not confined to the urban areas, since all parts of the country showed the same basic pattern in this national study. In Pakistan, 16% of men and 12% of women aged 25 years and above were found to have diabetes, and the prevalence of diabetes and IGT combined was 25% in both sexes (14). This result was all the more remarkable since the survey was conducted in Shikarpur, a relatively traditional town, in an agricultural region of Sindh Province. Similar results were obtained in North West Frontier Province and Beluchistan province in Pakistan (15, 16).

The latest survey of glucose intolerance among Saudi populations in rural and urban communities documents an even greater prevalence of diabetes in subjects 15 or more years old. The age-adjusted prevalence of diabetes was 12% in urban men and 14% in urban women (17). In a survey of cardiovascular disease prevalence in men aged

Table 12.2 Recent prevalence studies of diabetes in Middle Eastern populations using WHO criteria

Location Author (reference)	Year	Age range (Years)	Prevalence (%)			
			Diabetes		IGT	
			M	F	M	F
Oman, National survey Asfour et al. (13)	1991	20+	10	10	8	10
Iran Amini et al. (11)	1993	40+	8	8		
Pakistan, Sindh Province Shera et al. (14)	1994	25+	16	12	8	14
Egypt Herman et al. (19)	1991–94	20+				
Rural			4	6	14	12
Urban, lower SES*			10	18	4	7
Urban, upper SES*			27	16	2	13
Saudi Arabia Al-Nuaim (17)	1995	15+				
Rural			7	8		
Urban			12	14		
Jordan Ajlouni et al. (20)	1994–96	25+	15	13	9	10
Pakistan, NWFP Shera et al. (15)	1995	25+	9	12	10	9
Pakistan, Baluchistan Shera et al. (16)	1995	25+				
Urban			11	11	7	14
Rural			10	5	7	13
Bahrain Al-Mahroos et al. (18)	1995–96	40–49	23	–	17	–
		50–59	29	36	16	19
		60–69	–	37	–	23

* SES socio-economic status

40–59 years and women aged 50–59 years in Bahrain, the age- and sex-standardized prevalence of diabetes was 25% in Jaafari Arabs, 48% in Sunni Arabs, 23% in Iranians and 31% in the unclassified subjects (18).

The survey conducted in Egypt, under the auspices of the US Centers for Disease Control and Prevention (19) demonstrated a wide range in prevalence, from 5% of adults in rural areas, to 20% in the upper socio-economic urban residents. This illustrates the importance of environmental factors, as well as the potential for primary prevention. The authors estimate the prevalence of diabetes in the total Egyptian population over the age of 20 years to be 10%.

A study of four semi-urban communities in Jordan showed a prevalence of 13.4% for diabetes and 9.8% for IGT (20). In Israel, the prevalence of

diabetes in a large sample of the working population was found to be 6.4%, and the authors extrapolated a prevalence of 10% in persons older than 40 years (21).

Based on the available studies, a recent WHO report estimates the total number of persons with diabetes in the Middle East to be 22 million in the year 2000. If current trends in population growth and urbanization continue, there will be 53 million adult persons with diabetes living in countries of the Middle East in the year 2025, the majority of them being in the middle age range. Between 1995 and 2025 the prevalence will have increased by 30%, from 6.3 to 8.2%. There will be a considerable excess of diabetes in urban areas, and similar numbers of males and females with diabetes. Pakistan and Egypt will be amongst the ten countries with the greatest number of adults with diabetes in the world (22).

In high prevalence populations, diabetes also tends to develop at a relatively early age. The age-specific data from Oman indicate that approximately 9% of females aged 20–29 years have diabetes or IGT (13). Comparable figures were obtained in Pakistan (14). This indicates the importance of glucose intolerance as a complication of pregnancy in such susceptible populations. In Oman and Pakistan alike, prevalence of diabetes rose to 30% in subjects in the older age groups. Thus, we can now assume that one-third of all persons in these countries may expect to develop diabetes, unless they die prematurely of something else.

These alarming figures fit convincingly with the hypothesis that populations in formerly harsh environmental conditions, such as living in the deserts which cover much of the Middle East, have developed an efficient metabolism in order to survive (23,24). This former advantage (the so-called thrifty genotype) proves detrimental once a modern lifestyle, characterized by a high-energy diet and low levels of habitual physical activity, is adopted; hence the recent emergence of diabetes and associated disorders as a major threat to the health of the developing world.

TYPE 1 DIABETES

The incidence of this form of diabetes is increasingly well documented worldwide (25). Again, there is great geographical and ethnic variation, and it would be interesting to study the pattern in the Eastern Mediterranean region, where distinct ethnic groups live in various geographical conditions. Although information is unavailable for a large part of the region, the available data suggest differences in the frequency of Type 1 diabetes within the region.

The first report on Type 1 diabetes in this region came from Kuwait. The incidence of diabetes among Kuwaiti subjects 0–29 years of age during 1980–1981 was found to be 22 per 100 000 person-years. Of these, 80% were in the age group 20–29 years and the majority did not need insulin therapy. The observed incidence of 5.6 per 100 000 in the 0–19 year age range was considerably lower than that reported from Europe and North America (26). However, a later study in Kuwait, conducted in 1992 and 1993, reported a

much higher incidence rate in children less than 15 years of age (15.4 per 100 000 person-years), thus indicating a possible increase in a short period of time (27). A hospital-based study in Saudi Arabia estimated the incidence of Type 1 diabetes in children to be 7 per 100 000 person-years during 1980–1982. The study also demonstrated an increase over the 3-year period (28). In Israel, the incidence of Type 1 diabetes in children 0–17 years old also appears to be on the increase, from 5.9 per 100 000 during 1989–1993, to 7.7 per 100 000 in 1997, the incidence being consistently higher in Jewish than in Arab children (29,30). To determine the epidemiology of Type 1 diabetes in Sudan, the prevalence of this disease was determined in 43 000 school children aged 7–14 years. The overall crude prevalence was 0.95 per 1000 (31). The incidence was studied over a 4-year period, utilizing the hospital registry for diabetic children 0–14 years of age, and was reported to be 5.9 per 100 000 person-years in 1987, and 10.1 per 100 000 person-years in 1990. A recent study in Jordan found a low incidence of Type 1 diabetes in children 0–14 years old during 1992–1996. However, the incidence showed a slight but steady increase, from 2.8 per 100 000 in 1992 to 3.6 per 100 000 in 1996 (32). Contrary to these reports, studies from North Africa, using similar methodology and covering the same time period, do not show an increase in the incidence of Type 1 diabetes in children. In Tunisia the average annual incidence was 6.8 per 100 000 person-years during 1990–1995 (33), in Libya it was 8.1 per 100 000 during the same period (34), and in Algeria it was the same during 1980–1989 (25).

Green et al. recently estimated that there are about 6000 new patients who develop Type 1 diabetes annually in the Middle East, and about half of them are older than 15 years (35). The epidemiological model developed by Green et al. estimates the prevalence of Type 1 diabetes in the Middle East at 0.65 per 1000 inhabitants in 1995 and predicts a modest increase to 0.75 per 1000 inhabitants in the year 2025, assuming an unchanged incidence and survival (35).

LONG-TERM COMPLICATIONS

The only population-based study of chronic complications of diabetes in the Middle East was

a survey of diabetes conducted in the urban and rural population of Egypt during 1991–1994 (36). Thus, like for most other regions of the world, the information we have is mainly based on studies of patients attending a clinic. The results of these few studies are not easily comparable because of different methodologies. In Egypt, retinopathy was more common in previously diagnosed than in previously nondiagnosed diabetic patients (42% vs. 16%). Neuropathy was also more common in the previously diagnosed persons (22% vs. 14%), while albuminuria, defined as an albumin-to-creatinine ratio ≥ 100 mg/g was equally prevalent (21% vs. 22%). Although albuminuria was more prevalent in Egyptian diabetics than in a clinic-based sample of patients in Saudi Arabia (21% vs. 10%), the prevalence of clinical nephropathy (albumin-to-creatinine ratio >300 mg/g) in Saudi Arabia was 13% and only 7% in Egypt, possibly due to selection bias, differences in genetic susceptibility or shorter survival of persons with nephropathy (37). Similarly, overt clinical nephropathy was not common in a clinic-based sample of subjects with Type 2 diabetes in Israel (38). In this study, about one-third of the patients had retinopathy, a frequently seen finding (36, 37, 38), and one-quarter had peripheral neuropathy (38). Peripheral neuropathy, measured through vibration perception, seems to be quite common in diabetic patients in the Middle East, the prevalence ranging from 14% in newly diagnosed Egyptian patients to 46% in Libya (36, 38, 39, 40). However, the prevalence of foot ulcers was found to be rather low (36, 39). Some authors attribute this to appropriate footwear (39). As is the case with overt nephropathy, whether this low prevalence of foot ulcers and amputation can be attributed to a lower incidence or a shorter survival of affected patients, has yet to be studied. Except for diabetic patients in Bahrain and insulin-treated patients in Sudan amongst whom 38% and 44% respectively had diastolic hypertension (41, 42), hypertension, as defined by the formerly recommended cut-off point of 160/95 mmHg, seems to affect less than 15% of Arab diabetic patients, which is relatively low compared to patients of European origin (39, 43, 44). Again, this could affect the incidence and progression of other complications, but could also simply reflect a survival effect because all these studies are cross-sectional. Prospective studies would be more informative on the risk of

chronic complications in the diabetic population of the Middle East.

CONCLUSION

Type 2 diabetes represents one of the most serious public health threats to the populations of the Middle East and the situation may be expected to worsen in the near future due to population growth, ageing and rapid urbanization. Concerted measures aimed at both primary and secondary prevention are required at a regional level. Type 1 diabetes has generally been reported to be rarer than in European populations, but incidence may have been underestimated.

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Africa

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INTRODUCTION

Traditionally, Type 2 diabetes mellitus has been regarded as a disease of urbanization and industrialization and one that is still rare or unknown in rural Africa (1). Perhaps one of the most significant advances in diabetes epidemiology was the promulgation of standardized diagnostic criteria for glucose tolerance by the National Diabetes Data Group (NDDG) (2) and World Health Organization (WHO) (3, 4). Based on 1985 WHO criteria and age-standardized estimates from data on 75 communities in 32 countries King et al. (5) showed that diabetes in adults is now a global problem and that populations of developing countries, minority groups and disadvantaged communities in industrialized countries face the greatest risk.

Amos et al. (6), using the WHO database for current and projected global estimates for the years 2000–10, suggested that the prevalence of Type 2 diabetes mellitus will rise from 115 million in 1995 to >200 million by 2010. This was confirmed in a recent report on the global burden of diabetes which showed that the prevalence of diabetes in adults will rise from 135 million in 1995 to 300 million in 2025 and that the major increase will be in developing countries, which will contribute to >75% of the world's diabetic population (7).

From as early as the turn of the twentieth century and up to the early 1960s, diabetes was considered to be rare in sub-Saharan Africa (1).

In recent years, however, non-communicable diseases such as diabetes are attracting increased attention in developing areas of the world such as Africa; today few major African hospitals are without a diabetes clinic.

Despite the explosion of epidemiology data from other continents, data on the impact of diabetes in Africa using standardized (WHO) criteria are, at best, scanty. This is the case despite the fact that Africa is the second largest continent, with an estimated population of 642 million living in about 50 countries and consisting of 3000 distinct ethnic groups and over 1000 languages.

This is a report on the impact of Type 2 diabetes mellitus in non-pregnant adults in continental Africa with respect to the prevalence in different communities and the factors associated with its development.

PREVALENCE

Prior to the introduction of standardized WHO criteria for glucose tolerance (3, 4) and since the early 1960s several studies examined the prevalence of diabetes in Africa. However, those studies involved differing study populations, methodologies and criteria for the diagnosis of diabetes. Despite these limitations, such studies showed prevalence rates ranging between 0.0 and 1.0%. Only six studies reported prevalence rates >1.0%; of these, three studies were those from the same country, i.e. South Africa (Table 13.1).

Over the past 20 years and after the introduction of the WHO criteria (3, 4), there have been several reports from West Africa (8–14), East Africa (15, 16), North Africa (17–20) and South Africa (21–23) (Table 13.2).

Prevalence rates range from an absence of diabetes mellitus in Togo to higher and moderate rates in Cape Town in South Africa (8%) and Egypt in North Africa (9.3%).

Table 13.1 Prevalence of diabetes mellitus in Africa: studies done before 1980/1985 WHO criteria *

Country	Author	Year	Urban/ rural**	Study population	Sample size	Detection method	Prevalence (%)
Ethiopia	Peters	1983	U/R	Community ⁺	2381	Urine	0.3
Ghana	Dodu	1958	U	Outpatients	4000	Urine	0.4
	Dodu & de Heer	1964	U	Community ⁺	5537	Urine	0.2
Ivory Coast	Zmirou	1979	U/R	Community	5000	Blood	5.7
Lesotho	Politzer et al.	1960	R	Outpatients	3000	Urine	0.2
Malawi	Davidson	1963	U/R	Outpatients	4725	Urine	0.1
Mali	Imperato et al.	1976	U/R	Community ⁺	297	Blood	1.4
South Africa	Seftel & Abrams	1960	U	Outpatients	2122	Urine	1.3
	Politzer & Schneider	1962	U	Outpatients	3121	Urine	0.6
	Goldberg et al.	1969	U	Community	882	Urine/blood	2.7
	Goldberg et al.	1969	U	Community	2015	Urine	2.9
	Marine et al.	1969	U	Community	1029	Urine/blood	3.6
Uganda	Tulloch	1964	U/R	Outpatients	7164	Urine	0.2
Zambia	Davidson et al.	1969	R	Community	369	Blood	1.1
Zimbabwe	Corr & Gelfand	1961	U	Community	107	Urine	0.1
	Wicks et al.	1973	U	Community	1078	Urine	0.3
	Guidotti & Gelfand	1976	R	Community	5456	Urine	0.0

* Adapted from McLarty et al. (1).

** U = urban; R = rural

⁺ Selected community: Ethiopia: Schools/factories,
 Ghana: Males >15 yr;
 Mali: police/farmers/students

In sub-Saharan Africa, the prevalence of diabetes is low in both rural and urban communities in countries in West Africa and in Tanzania in East Africa. By contrast, moderate rates (5–8%) have been reported from South Africa, in a semi-urban community in the Orange Free State (OFS) (4.8%) and in urban groups in OFS (6%), Durban (Zulu) (5.3%) and Cape Town (Xhosa) (8.0%).

Studies from North Africa indicate moderate prevalence rates in Sudan and Tunisia (3.4–8.3%). In an Egyptian study, overall prevalence was 9.3% and high rates (13.5%, 20%) were reported in urban populations in Cairo. It is important to note that there were differences in the methodology in the various studies in terms of age group studied, the use of fasting blood glucose (FPG) alone, and the use of reflectance meters as opposed to formal laboratory blood glucose estimations.

From the evidence to date, it would appear that in sub-Saharan Africa north of the Limpopo River, diabetes prevalence is low in both urban and rural communities. However, in South Africa and North Africa, moderate and high rates are found and do not differ significantly from rates found in developed countries; urban Egyptians in fact show a high prevalence. Moreover, there appears to be a difference in urban and rural

prevalence. What is also highlighted is the relative paucity of information on diabetes epidemiology in Africa and the need for further studies, both urban and rural.

IMPAIRED GLUCOSE TOLERANCE; TOTAL GLUCOSE INTOLERANCE; EPIDEMICITY INDEX

The combined prevalence of diabetes (D) and impaired glucose tolerance (IGT), i.e. total glucose intolerance (TGI), may serve as a useful measure of the public health impact of glucose intolerance in a given population (5, 24). This is because IGT may indicate a high risk of subsequent diabetes development. Moreover, it has been suggested that the percentage of TGI made up by IGT, i.e. 'Epidemicity Index' or the ratio of IGT to Diabetes (IGT:D) or TGI (IGT:TGI), may have some predictive value in determining the stage of an epidemic of glucose intolerance in a given population, i.e. a high IGT prevalence in the face of a low prevalence of diabetes (high IGT:D ratio) may indicate an early stage of a diabetes epidemic.

Table 13.3 shows the prevalence of IGT and total glucose intolerance (TGI) (diabetes and IGT)

Table 13.2 Prevalence of diabetes mellitus (D) and impaired glucose tolerance (IGT) in Africa: studies published after introduction of 1980/1985 WHO criteria

Country locality	Authors	Year	Urban (U) rural (R)	Age group (yr)	n	Prevalence (%)	
						D	IGT
Tanzania	Ahrén &	1984	U + R	≥20	3145	0.7	–
Kahalanga	Corrigan (15)		R		996	0.5	–
Ndolage			R		1141	2.5	–
Mwanza			U		1008	1.9	–
Mali	Fisch et al. (8)	1987	R	>15	7472	0.9	–
Togo	Teuscher et al. (9)	1987	R	>1	1381	0.0	–
Nigeria	Ohwovoriole et al. (10)	1988	U		1627	1.7	–
	Erasmus et al. (11)	1989	U + R		2800	2.4	–
Tunisia	Papoz et al. (17)	1988		≥20	5613		
Tunis			U		3826	3.8	–
Siliana			R		1787	1.3	–
Tanzania	McLarty et al. (916)	1989	R	≥15	6097	0.9	7.8
						1.1*	8.4*
South Africa							
Cape Town	Levitt et al. (22)	1993	U	>30	729	6.3	5.9
						8.0*	7.0*
Durban	Omar et al. (21)	1993	U	>15	479	4.2	6.9
						5.3*	7.7*
Orange Free State	Mollentze et al. (23)	1995		≥25			
Mangaung			U		758	6.0*	12.2*
Qwa-Qwa			R		853	4.8*	10.7*
Egypt	Herman et al. (18)	1995	U + R	≥20	1451	9.3	9.6
Cairo			U-h**		213	20.0	8.6
			U-l**		734	13.5	5.4
Kaliubia			R		504	4.9	13.1
Mauritania	Ducorps et al. (13)	1996	U + R	>17	744	1.88	–
Cameroon	Mbanya et al. (14)	1997	U + R	24–74	1767	1.1	2.7
Yaounde			U		1048	1.3	1.8
Evodoula			R		719	0.8	3.9
Sudan	Elbagir et al. (19)	1996	U + R	≥25	1284	3.4	2.9
			U		826	3.9	3.3
			R		458	2.6	2.2
Nigeria							
Sudan	Cooper et al. (12)	1997	R	25–74	247	2.8	–
	Elbagir et al. (20)	1988	U + R	≥25	724	8.3	7.9
						10.4*	9.8*
			U		461	9.6	8.0
			R		263	6.1	7.6

* Age-adjusted rates.

** U-h = urban, high socio-economic status; U-l = urban, low socio-economic status.

in the eight studies in which it was examined. IGT prevalence ranges from 2.2% in rural Sudan to 13.1% in rural Egypt, and TGI from 4.8% in rural Sudan to 28.6% in urban Egyptians from a high socio-economic status group.

It is apparent that in Africa, as in the rest of the world, where the prevalence of diabetes is low (>0% <3%), the IGT rates are higher. This is shown in rural Tanzanians in whom the prevalence of diabetes and IGT is 1.1 and 8.4%, respectively

(16). By contrast, in high diabetes prevalence (>10%) populations, the IGT rates are lower, e.g. in urban Egyptians in whom the prevalence of diabetes and IGT is 20.6% and 8.6%, respectively (18).

The Epidemicity Index (percentage of TGI made up by IGT) decreases as the diabetes prevalence increases. This is exemplified in the low (<3%) diabetes prevalence among rural Tanzanians, in whom the Epidemicity Index is 88.4% (prevalence

Table 13.3 Prevalence of impaired glucose tolerance (IGT) and total glucose intolerance (TGI) and Epidemicity Index in Africa

Country* locality	Authors	Year	Prevalence (%)			Epidemicity Index (IGT/TGI) (%)
			D	IGT	TGI	
Tanzania (R)	McLarty et al. (16)	1989	1.1	8.4	9.5	88.4
South Africa						
Orange Free State	Mollentze et al. (23)	1995				
Qwa-Qwa (R)			4.8	10.7	15.5	69.0
Mangaung (U)			6.0	12.2	18.2	67.0
Durban (U)	Omar et al. (21)	1993	5.3	7.7	13.0	59.2
Cape Town (U)	Levitt et al. (22)	1993	8.0	7.0	15.0	46.7
Sudan** (U+R)	Elbagir et al. (19)	1996	3.4	2.9	6.3	46.0
U			3.9	3.3	7.2	45.8
R			2.6	2.2	4.8	45.8
Egypt** (U+R)	Herman et al. (18)	1995	9.3	9.6	18.9	50.8
Kaliubia (R)			4.9	13.1	18.0	72.8
Cairo† (U-h)			20.0	8.6	28.6	30.1
(U-l)			13.5	5.4	18.9	28.6
Cameroon (U+R)	Mbanya et al. (14)	1997	1.1	2.7	3.8	71.1
Yaounda (U)			1.3	1.8	3.1	58.1
Evodoula (R)			0.8	3.9	4.7	83.0

* U = urban; R = rural

** crude rates.

† U-h = urban, high socio-economic status; U-l = urban, low socio-economic status.

of diabetes, IGT and TGI are 1.1, 8.4 and 9.5%, respectively), indicating possibly an early stage of an epidemic of glucose intolerance (16). By contrast, in urban Egyptians with a high (>10%) diabetes prevalence (20.6%), the Epidemicity Index is 30% (18).

Clearly, there is a need for further studies in Africa to evaluate the significance of IGT with respect to its natural history and its usefulness as a marker of diabetes epidemicity in different populations.

URBAN/RURAL DIFFERENCES

The prevalence of diabetes in rural and urban communities in the same country has been examined in a few studies (Tables 13.2, 13.3) (17, 15, 19, 20, 23, 18, 14).

In all but one country, the prevalence was higher in urban communities. The difference was most striking in the Egyptian study in which the urban prevalence rates (13.5%; 20%) were 2–4-fold higher than rural rates (4.9%) (18). The results from the Tanzanian study were conflicting; when compared with the urban prevalence (1.9%), the rate was lower in the rural Sukuma tribe (0.5%) but higher in the rural Haya tribe (2.5%). The

possible reasons for the differences between the two rural groups include varying age and gender distribution, genetic and lifestyle factors. In South Africa, Sudan and Cameroon, although the diabetes frequency was higher in urban groups, the difference was not marked. In South Africa, this might be accounted for by the fact that in recent years, urbanization and industrialization have affected even the so-called 'rural' areas; it has been estimated that in the new millennium, >75% of the country's population will be urbanized (23).

The effect of urbanization as a risk factor for diabetes was examined in studies from South Africa and Sudan (2, 19, 20). While urbanization was not a risk factor in the Sudanese studies, in urban Xhosas in Cape Town, South Africa, urbanization as judged by the proportion of life spent in the city (cutoff level >40%) was a significant risk factor. However, the definition and measurement of urbanization is under considerable debate.

ETHNIC DIFFERENCES

Ethnic differences were examined in Tanzania and South Africa (25, 21, 26). In both countries,

diabetes prevalence was lower in the indigent African population than in the migrant Asian group (African vs Asian; 5.3 vs 13% in South Africa, 1.1 vs 9.1% in Tanzania).

Regarding IGT, in South Africa, rates were higher in Africans (7.7%) than in Asians (6.9%); by contrast, in Tanzania, the prevalence was lower in Africans (8.4%) than in Asians (16.2%).

PREVALENCE OF KNOWN DIABETES

The proportion of subjects with known diabetes was lowest in studies in Tanzania; this applied even to the study which included an urban sample (15, 16) (Table 13.4).

By contrast, >50% were known to have diabetes in studies from Tunisia (17, 18), Egypt (18) and South Africa (22, 21) which compares with findings in developed countries (5); moreover, these figures may reflect the better access to health care facilities and therefore greater opportunistic screening in these countries. In Tunisia and Egypt,

this was true also for the rural population in which >45% were known to have the disorder. In earlier studies from South Africa, the proportion of African subjects with known diabetes ranged from 28 to 33% and compared with that found in the Europid population in that country (1).

GENDER DISTRIBUTION

The ratio of the diabetes prevalence in men and women varies within and between populations, with no obvious trend. A male preponderance is reported from studies in Tanzanians (rural), Tunisians, Sudanese (urban), Egyptians (urban) and Cameroon (rural) (16, 17, 20, 18, 14).

A female excess was found in studies from South Africa (Durban), Mauritania, Mali, Cameroon (urban), Sudan (rural), Egypt (rural, urban) and Tanzania (rural) (21, 13, 8, 14, 20, 18, 15).

An equal gender distribution was observed in South Africa (Cape Town), Tanzania (urban) and Sudan (22, 15, 19).

Table 13.4 Prevalence of known and newly discovered subjects with diabetes mellitus from population-based studies in Africa

Country* locality	Authors	Year	Diabetes mellitus		
			Total <i>n</i>	Known %(<i>n</i>)	Discovered % (<i>n</i>)
Tanzania (U + R)	Ahrén & Corrigan (15)	1984	22	4.6 (1)	95.4 (21)
(R)	McLarty et al. (16)	1989	53	13.2 (7)	86.8 (46)
Tunisia	Papog et al. (17)	1988			
Tunis (U)			144	59.7 (86)	40.3 (54)
Siliana (R)			24	45.8 (11)	54.2 (13)
South Africa					
Durban (U)	Omar et al. (21)	1993	20	60.0 (12)	40.0 (8)
Cape Town (U)	Levitt et al. (22)	1993	46	52.2 (24)	47.8 (22)
Sudan (U+R)	Elbagir et al. (19)	1996	44	36.4 (16)	63.6 (28)
(U)			32	37.5 (12)	52.5 (20)
(R)			12	33.3 (4)	6.7 (8)
Sudan (U+R)	Elbagir et al. (20)	1998	60	38.3 (23)	61.7 (37)
U			44	34.1 (15)	65.9 (29)
R			16	50.0 (8)	50.0 (8)
Egypt	Herman et al. (18)	1995			
Kaliubia (R)					
Cairo (U-h)**					
(U-l)**					
Cameroon (U+R)	Mbanya et al. (14)	1997	20	40.0 (8)	60.0 (12)
Yaounde (U)			14	42.9 (6)	57.1 (8)
Evodoula (R)			6	33.3 (2)	66.7 (4)

* U = urban; R = rural

** U-h = urban, high socio-economic status; U-l = urban, low socio-economic status.

The lack of discernible trend in gender distribution accords with findings from global estimates (5). However, in that report the apparent male preponderance in Africa is probably accounted for by the fact that only the Tunisian and Tanzanian data were included.

IMPACT OF AGE

As in other regions of the world, using age-specific rates, the prevalence of diabetes in Africa increases with age, both in men and women.

From global estimates, King et al. (5) report that in moderate–high risk populations (diabetes prevalence >3%), peak prevalence occurs in the sixth decade with a decline in the seventh decade, probably because of greater mortality amongst diabetes subjects. But, in most African studies which report moderate diabetes prevalence, the peak prevalence is in the seventh decade (17, 19, 22, 21); this was true even for studies in Tanzanians and Mauritanians in whom there is a low diabetes prevalence (15, 16, 13). A sixth decade peak was observed in Durban, South Africa (women), OFS, South Africa (urban men) and Sudan (men and women) (21, 23, 20).

When compared with other known risk factors, age was found to be a significant risk factor for diabetes in Cape Town, South Africa and Sudan (22, 19, 20).

BODY MASS INDEX AND WAIST–HIP RATIO

In most studies, associations, albeit variable, have been found between body mass index (BMI) and diabetes prevalence. However, the lack of standardized reporting methods makes comparison between studies difficult. In the main, though, the four aspects which have been examined include BMI-specific diabetes prevalence, mean BMI and obesity prevalence in different glucose tolerance categories and BMI/obesity as risk factors for diabetes.

Using BMI-specific rates, it has been shown that diabetes prevalence increases with BMI in rural populations in Mali, Tanzania and Nigeria (8, 16, 12).

When compared with non-diabetic subjects, the mean BMI was higher in diabetes subjects in Mali, Tunisia, Sudan, Egypt and Durban, South Africa (8, 17, 19, 18, 21).

The prevalence of obesity was higher in diabetic than in non-diabetic subjects in studies from Tanzania, Sudan and Durban, South Africa (15, 19, 21). Obesity was reported in 9.1% of diabetes subjects in Tanzania and in 65% of such subjects in the urban South African Zulu population in Durban (15, 21). Of interest, was that in the latter group, obesity was prevalent even in women with normal glucose tolerance (31.8%); it is therefore possible that the higher obesity prevalence in women could account for the female diabetes preponderance in this group. However, this was not borne out by the results in urban Xhosas in Cape Town, South Africa, where although the mean BMI of the study women was high (30.9 kg/m²) and higher than in men (24.2 kg/m²), there was no female preponderance (22).

BMI (23, 19, 20, 12) and obesity (22) were found to be significant risk factors for diabetes in all the studies in which they were examined.

Waist–hip ratio (WHR) and upper segment fat distribution (USFD) have been examined in four studies (22, 23, 12, 18). The prevalence of diabetes increased with WHR in the small rural Nigerian group and in the urban Cape Town Study in South Africa.

In the Egyptian study, mean WHR was higher with worsening of glucose tolerance (D > IGT > NGT).

USFD was found to be a significant risk factor for diabetes in two studies from South Africa (Cape Town, Orange Free State) (22, 23).

PHYSICAL ACTIVITY

This has only been examined in two studies (22, 18). In the South African study from Cape Town, physical activity was not found to be a significant risk factor for diabetes. By contrast, in the Egyptian study, the prevalence of diabetes was inversely related to physical activity.

FAMILY HISTORY

The impact of family history of diabetes has been reported in studies from South Africa and Sudan

(22, 19, 20). A positive family history was not a risk factor for diabetes in urban Xhosas in Cape Town, South Africa. In two Sudanese studies, a positive family history was more frequent in diabetes subjects and was found to be a significant risk factor for diabetes.

IS THE PREVALENCE OF DIABETES INCREASING IN AFRICA?

The paucity of data from earlier studies in the same population as well as different diagnostic criteria employed make it difficult to answer such a question. Notwithstanding these limitations, studies in urban Xhosas in Cape Town, South Africa, suggest that the prevalence of diabetes has increased over the last 15 years.

Using 1985 WHO criteria in subjects >30 years, the crude prevalence of diabetes is 6.3% and of IGT 5.9% (total glucose intolerance 12.2%) (22). In 1969, Marine et al. (see [1]) used less stringent criteria which probably included IGT as well ('diabetes' was diagnosed if two of three of the following were increased: fasting blood glucose >6.6 mM; 1 h post-glucose value >11.1 mM; 2 h post-glucose value >7.6 mM); in that study, the crude prevalence of 'diabetes' in subjects >15 years was 3.6% and in subjects >35 years was 7%. Therefore the prevalence of abnormal glucose tolerance appears to have almost doubled in 20 years. Whether the difference could be explained solely by the degree of urbanization is unclear.

LONGITUDINAL STUDIES

To date, there are no reports of longitudinal studies which have examined the incidence of diabetes or the natural history of intermediate stages of glucose intolerance (IGT, IFG) in Africa.

CONCLUSION/SUMMARY

Data on the epidemiology of Type 2 diabetes mellitus in Africa are limited. However, contrary to a commonly held belief, diabetes is not rare in this continent. Although the prevalence is low in some rural populations, in other countries, moderate rates have been found in both urban and rural

communities and are comparable with those in developed countries; in yet others alarmingly high rates are reported. The moderate-to-high prevalence of impaired glucose tolerance (IGT), especially in populations with a low diabetes prevalence, is a possible indicator of the early stage of diabetes epidemic. Diabetes prevalence is higher in urban populations; the putative role of urbanization and industrialization needs to be established. Although there is evidence for a significant association with modifiable risk factors, there is a dearth of data on the impact of such variables as dietary and genetic factors and the role of insulin. Thus there is a need for further studies which use standardized criteria and reporting methods.

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South East Asia

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INTRODUCTION

South East Asia geographically consists of Myanmar, Thailand, Cambodia, Laos, Vietnam, the Philippines, Indonesia, Malaysia, Singapore, Brunei, the nations that surround the South China Sea and the nations in the Indian subcontinent. The three major forms of diabetes described from South East Asia are Type 1 diabetes mellitus, Type 2 diabetes mellitus and malnutrition-related diabetes mellitus (MRDM). The prevalence of Type 1 diabetes is lower compared to several European countries. Type 2 diabetes constitutes over 90% of the diabetic population. MRDM, especially the fibrocalculous variety, is seen in some parts of India. In this chapter, we shall discuss the epidemiology of Type 1 and Type 2 diabetes in South East Asia, as MRDM is described in detail in chapter 18.

The prevalence of Type 2 diabetes varies in different geographic regions and in different ethnic groups (1). The WHO Ad Hoc Diabetes Report published in 1993 showed that the age-standardized prevalence ratio of diabetes within a chosen age range was low (<3%) or absent in certain traditional communities in developing countries, about 3–10% in European populations, and as high as 14–20% in migrant Asian Indians, Chinese and Hispanic American populations. In rural Papua New Guinea (Pacific region) Type 2 diabetes was virtually unknown (2).

Epidemiological studies during the last two decades have shown that the prevalence of diabetes is steadily increasing in populations in South East Asia. In this chapter, we will examine the data accumulated so far to substantiate this.

EPIDEMIOLOGY OF TYPE 2 DIABETES

A review of the literature available in 1987 showed the estimated prevalence of diabetes in the South East Asian region to be about 2–5% (3, 4). The earliest recorded studies in Malaysia, Singapore and Indonesia showed similar low estimates for Malays and Indonesians, about 1–2% for Malays in Malaysia in the 1960s, 1.4% for Malays in Singapore in 1945 and 1.5% in Indonesians in 1976. These low estimates may, however, be methodological due to the small numbers of subjects tested and the use of urine testing.

The first authentic data on the prevalence of diabetes in India came from the multicentric study conducted by the Indian Council of Medical Research (ICMR) in the early seventies. This study reported a prevalence of 2.3% in the urban and 1.5% in the rural areas. The criteria used in this study were different from those presently set by the WHO Expert Committee on Diabetes Mellitus.

Indian migrants settled in different parts of the world had been shown to have high prevalence of Type 2 diabetes (6) which was believed to be due to greater affluence and a change to a more sedentary lifestyle as compared to the native Indian population (Table 14.1). However, the local host populations living in an identical environment in these countries still had only a low prevalence rate of diabetes. Assuming that Indians as an ethnic group have a high degree of genetic predisposition to develop diabetes, one could expect higher prevalence of diabetes among the native urban populations with a comparable affluent lifestyle.

Table 14.1 Prevalence of diabetes in migrant Indians and other ethnic groups

Year	Author	Country	Prevalence (%)						
			Europeans	Africans	Melanesians	Malays	Chinese	Creoles	Indians
1958	Wright et al.	Trinidad		1.4					1.7
1986	Beckles et al.	Trinidad	10.2	14.8					21.6
1967	Cassidy	Fiji			0.6				5.7
1983	Zimmet et al.	Fiji			7.1 (U)	1.2 (R)			11.0 (U) 11.3 (R)
1969	Marine et al.	South Africa		3.6		6.6			10.4
1975	Cheah et al.	Singapore				2.4	1.6		6.1
1988	McKeigue et al.	East London	4.0						23.0
1989	Simmons et al.	Coventry, UK	2.8						11.2
1989	Dowse et al.	Mauritius					11.5	10.3	12.5
1989	Swai et al.	Tanzania		1.9					7.1
1992	Cheah and Thai	Singapore				9.3	8.0		12.8
		Malaysia				3.0	4.9		16.0

U = urban; R = rural.

Rising prevalence of Type 2 diabetes has been noted in Indians since 1986. Studies by Verma et al. in 1986 (7), using a questionnaire method, reported a prevalence of 3.1% in an affluent area in Darya Ganji, New Delhi. Over the same period, Ramachandran et al., in a series of cross-sectional surveys in Southern India, noted a rising trend in the prevalence of Type 2 diabetes. In 1983 (8), the prevalence of Type 2 diabetes in adults was 5% in an urban township, and it rose to 8.2% in 1988 (9). In a more recent survey in the same urban area, the prevalence has increased to 12%, thus highlighting the rising trend in the prevalence of Type 2 diabetes in urban India (10). The prevalence is comparable to that in migrant Indians.

Cheah and Thai reported an increasing prevalence of Type 2 diabetes in Singapore, the overall prevalence rising 1.99% in 1975 to 4.7% in 1984 with a further increase to 8.6% in 1992 (11). The rise in prevalence occurred in Chinese (4% in 1984 to 8% in 1992), Malays (7.6% in 1984 to 9.3% in 1992) and Indians; but the most predominant change was in the Indians who had a 44% rise, i.e. from 8.9% in 1984 to 12.8% in 1992. The changes were attributed to the rising affluence, change in lifestyle with increasing obesity, and the migration of rural people to urban areas. In Kuala Lumpur, migrant Indians had a prevalence of 4.2% in 1966, 6.1% in 1975 and 16% in 1988 (12).

The first nationwide survey of diabetes mellitus in Thailand was conducted in 1971 by the Diabetic Association of Thailand. Of the 322 953 people

screened, the prevalence of diabetes was estimated to be 2.5% (13). There were several studies in communities later on which showed an increasing prevalence of diabetes (14). Surveys of government savings bank employees (age 30–60 yr) revealed that prevalence of diabetes increased from 2.5% in 1978 to 3.3% in 1983 and 4.6% in 1986.

A study on 3495 employees (age 35–54 yr) of the Electric general authority of Thailand (EGAT) revealed a prevalence of 6.0% in 1986. These people represented the middle income class in Bangkok. The prevalence of diabetes in the lower socio-economic community was studied in 1990 (15). At Klong Toey port area in Bangkok, the prevalence was 4.5 and 5.9% among slum residents and apartment house residents aged 30 years or over respectively.

URBAN-RURAL DIFFERENCES

If environmental factors do have a significant role in unmasking diabetes, one would expect a lower prevalence in the rural areas where the populations follow a conventional lifestyle. Such an urban–rural difference in the prevalence rates was found in a survey conducted in several countries. In Madras, in Southern India, two populations belonging to different socio-economic status showed wide differences in the prevalence of diabetes (8.2% in the urban and 2.4% in the rural populations) (9).

A study from Orissa state, India (16), and the multicentric study by the ICMR have also shown that the prevalence of diabetes is higher in urban areas compared to the rural areas (6). Only in Fiji did rural and urban Indians have similar prevalence of diabetes (13.1 vs. 12.9% for men, 11.3 vs. 11.0% for women) (17). All these studies clearly indicate that the prevalence of Type 2 diabetes is high among Indians in the urban areas. Recently, Rao et al. conducted a comparative study of native rural Indians and migrant Indians in Malaysia and Guyana aged ≥ 24 years (18). The overall prevalence of diabetes in the three groups was 2.8, 13.41 and 13.84% respectively, age-specific prevalence between 45 and 64 years was 4.69% in rural India, 23.39% in Malaysia and 23.63% in Guyana.

A study of Kodali and Alberti reports on the transrural migration of native Indians (19). Improved socio-economic status with association of risk factors such as age, changes in dietary pattern, obesity and sedentary activity produced a higher prevalence of diabetes in the migrants (9.1%) vs. the local population (2.2%).

Zimmerman's study among Indians in Fiji showed the absence of rural-urban difference in Indians which further substantiates the genetic susceptibility. Migrant Asian Indians in Fiji had a very high prevalence rate of diabetes. This was similar in both urban and rural populations and was attributed to similar dietary habits and the sedentary lifestyles in these two populations (17).

The prevalence of diabetes in the rural population in Thailand was not low compared with the urban as previously thought. A study on 13 rural villages of Phon district in Khon Khaen (about 500 km northeast of Bangkok), using the WHO criteria revealed a prevalence of 6.7% (20). Aging, increased body mass index (BMI) and decreased physical activity were associated with diabetes in this study.

Similar findings were also made in Malaysia. Recently, a survey of the rural community in Malaysia was repeated to compare the prevalence to the original survey of 1984 which recorded a prevalence of 3.9%. This survey in 1994 showed a crude prevalence of 14.6% which, when adjusted for age, was 12.2%. Thus, there had been an increase of 21.2% over 10 years, greater than that seen for Singapore (21). The prevalence of diabetes in Vietnam is still relatively low, being 2.5% in Ho

Table 14.2 Prevalence of Type 2 diabetes in South East Asia

	Year	Urban (%)	Rural (%)	Reference no.
India	1972	2.3		6
	1979	3.0	1.3	4
	1988	5.0		8
	1992	8.2	2.4	9
Singapore				
Chinese	1984	4.0		10
	1992	8.0		
Malays	1984	7.6		10
	1992	9.3		
Migrant	1984	8.9		10
Indians	1992	12.8		
Philippines	1992	8.4-12.0	3.8-9.7	10
Malaysia			7.4	
	1988	6.6		
	1994		14.6	
Thailand	1971	2.5		12
	1986	6.0	6.0	
	1989		6.7	
Vietnam		2.5	1.4	Mai Theh Trach
Sri Lanka	M	5.1		2
	W	2.4		

Chi Minh City, 1.4% in Hanoi, and 0.55% in rural areas of Vietnam. The prevalence in ethnic Vietnamese is 2.5% and in ethnic Chinese is 2.8% (personal communication, Professor Mai Theh Trach, Vietnam). There are no data on the prevalence amongst the other indigenous groups such as the Dayaks and Kadazans of Borneo. Table 14.2 summarizes the findings on the prevalence of Type 2 diabetes in South East Asia.

PREVALENCE OF IGT

A number of epidemiological studies both in Asia and among the migrant south Asians have consistently documented high prevalence of impaired glucose tolerance (IGT) among south Asians and Indians (Tanzania, Mauritius, Fiji, Madras) (2). Studies in Madras were significant in this respect because the urban-rural difference in Type 2 diabetes in Southern India was conspicuous by its absence in the prevalence of IGT (9). Similar uniform high prevalences of IGT have been reported among Fiji Indians. Previous studies have shown a high conversion rate of IGT to diabetes (35% in 5 years) in Southern India. Therefore high rates of IGT, especially in rural

populations having low rates of diabetes, furnish evidence of a large potential diabetes pool for future (2).

In Malaysia, Osman et al. (22) found prevalence of IGT to be inversely correlated to socio-economic status and to the prevalence of diabetes. In very rural villages, the prevalence of IGT was 15.0%, diabetes 2.7%; in a land resettlement scheme, IGT was 8.5%, diabetes 7.4%, and in urban Kuala Lumpur, IGT was 7%, diabetes 8.2%. In the aboriginal Orang Asli, however, with prevalence of diabetes 0.3%, IGT was only 4.7%, implying less risk of IGT and diabetes in this racial group (22). In their latest study in rural villages in 1994, the crude prevalence of diabetes was 14.6% and IGT 11.5%, implying higher risk of diabetes and IGT in rural Malays (21). This is in contrast to the finding of the urban survey in 1988 where prevalence of diabetes was 6.6% but IGT was only 1.9%.

In Thailand, in the Khon Khaen study, 9.3% and 12.6% of men and women were found to have an abnormal oral glucose tolerance test. The figures from the Klong Toey study were 6.1 and 4.4% for the slum and apartment house residents respectively. A study on the patterns of glucose tolerance after 2 years of diagnosis of IGT revealed that 16.3% of the subjects had become diabetic and 4% reverted to normal when they were retested (23).

RISK FACTORS FOR TYPE 2 DIABETES AMONG SOUTH ASIANS

Due to its rapid industrialization and economic growth, South East Asia is facing a Westernization of lifestyles and food habits, and increased rural to urban migration. There are also better health facilities and thus earlier detection of diseases much as diabetes.

FAMILIAL AGGREGATION IN TYPE 2 DIABETES

There are a number of epidemiological factors to indicate a strong genetic component in the causation of Type 2 diabetes. Recent studies in Madras showed that parental diabetes was present in 54% of Type 2 diabetes patients, with no maternal or paternal excess (24). A growing risk of

diabetes with increasing familial aggregation has been shown by the development of diabetes in the offspring two decades earlier than their parents. Several communities in India have a high rate of consanguinity and inbreeding. This is probably also a factor contributing to the high prevalence of diabetes in the Tamil Indian community in South Africa (25). Prevalence of diabetes was found to be high in Parsees in north-western India and in tribal populations in Orissa, India, providing evidence for higher genetic susceptibility in inbred populations (25).

OBESITY

Recent studies have highlighted that in addition to general obesity, the regional distribution of body fat is significantly associated with diabetes and cardiovascular disease. Central adiposity as indicated by waist:hip ratio measurement has been associated with high risk of diabetes. Studies in Southern India showed that even in the non-obese population, this association holds true (9). McKeigue's studies in London, comparing south Asians and Europeans, showed that the Asians have high prevalence of diabetes as well as coronary heart disease and its risk factors. Interestingly, for a given BMI, the Asian subjects had a higher waist : hip ratio compared to the Europeans (26).

Obesity is becoming more common in urban Thailand. Body mass index of 25–29.9 (overweight) was reported in 23.3% of Thai men employed in the Electric General Authority aged 35–54 years (27). The corresponding figure in women was 18.4%. In rural Thais in the Khon Khaen study, 17.0% subjects were found to be overweight. Of interest was the much higher prevalence of obese (BMI > 30) subjects in the lower socio-economic classes in Klong Toey port areas being 10 and 11% in the slum and apartment house residents respectively. The prevalences of overweight and obese patients with Type 2 diabetes in Thailand were 32.1% and 14.2% respectively (14).

In Kuala Lumpur, the prevalence of diabetes was 7.3% in obese and 1.6% in non-obese subjects (22). The community-based studies done in three different socio-economic locations in Malaysia clearly showed a positive correlation with economic status,

educational attainment, family income and location (22). The prevalence was only 2.8% in rural villages, 6.7% in the higher socio-economic location of a land resettlement scheme, and 8.2% in urban Kuala Lumpur. The prevalence was also associated with light physical activity and obesity. In the 1985 Singapore survey, the mean BMI in diabetics was 25.8 compared to 22.7 in non-diabetics. In Malaysia, diabetics had BMI of 28.3 compared to non-diabetic 23.7.

EPIDEMIOLOGY OF TYPE 1 DIABETES

It is generally believed that Type 1 diabetes is less common in the tropical regions, especially in South East Asian countries. Genetic as well as environmental factors may be involved in this. Recent studies in the UK interestingly showed that the incidence of Type 1 diabetes in Asian children is not significantly low compared to European children (28). Accurate information on the prevalence and incidence of Type 1 diabetes is not presently available from most of the Asian countries. There have been attempts to set up Type 1 diabetes registries to collect data in many cities.

A recent population-based study of prevalence of Type 1 diabetes in Madras, in Southern India, showed that the prevalence was 0.26/1000 in children in the age group of 0–15 years. This suggested that Type 1 diabetes was not rare in urban India and is an even higher rate than that reported from many other Asian countries (29). Nevertheless, it is much lower than the prevalence reported from North Europe (2.1/1000) and 1.54/1000).

Type 1 diabetes affected 0.08% of children aged 0–15 years in Thailand. The annual incidence has been reported to be 0.14 and 0.19 per 100 000 in 1984 and 1985 respectively (30). The peak age of onset was later than in the European children. More than 60% of the patients developed Type 1 diabetes at the age of 11–15 years.

In Singapore, the prevalence of Type 1 diabetes in Chinese children of age range 6–16 years was estimated to be 0.15 per 1000 (Prof. A.C. Thai, personal communication) and in Ho Chi Minh City, Vietnam, prevalence was 0.31% (Prof. Mai Theh Trach). The incidence of Type 1 diabetes has been estimated recently in Karachi by Staines et al.

as 0.06/100 000 per year (31). More data are needed from the South East Asian countries on the incidence and prevalence of Type 1 diabetes.

CONCLUSION

The available epidemiological data show that the prevalence of Type 2 diabetes is rapidly increasing in all ethnic groups and nationalities in South East Asia. With the present rate of high economic growth in this region a further increase in the prevalence of Type 2 diabetes is expected in the near future.

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Pacific Island Populations

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Recently published global estimates of diabetes suggest that around 110–135 million people, or about 2–2.5% of the total population, have Type 2 diabetes (1–4). Furthermore, these reports project that the number of people with Type 2 diabetes worldwide may double within the next 10–25 years, with the greatest increases expected in developing or newly industrialized countries (1, 3–4).

As with the pathogenesis of Type 2 diabetes, the environmental and genetic factors underpinning this global epidemic on the population level are complex. Part of the epidemic will likely be due to the ‘demographic transition’: increasing longevity, shifts in population age structures towards older age groups and rising urbanization. The ‘epidemiological transition’ (5), or changes in disease morbidity and mortality patterns from communicable to non-communicable disease associated with improved nutrition, hygiene and access to health care, will also be a contributing factor. Finally, continued global economic development and modernization will mean that more people will be adopting Westernized lifestyles which, along with many benefits, also include the characteristics of high-fat, energy-dense diets and decreased levels of physical activity, important risk factors for the development of obesity and Type 2 diabetes. The corresponding burden of complications and premature mortality resulting from diabetes will constitute a serious and growing public health problem for most countries.

Arguably, the studies which have most clearly shown the association of lifestyle change with obesity and diabetes have been conducted in Pacific Island populations over the past 25 years (7–24). Most of the Pacific Island populations have undergone dramatic demographic and epidemiologic changes in recent decades. In this chapter

we review available epidemiological prevalence and diabetes risk factor data for Pacific Island populations.

TYPE 2 DIABETES PREVALENCE IN THE PACIFIC

The prevalence of Type 2 diabetes varies tremendously in Pacific Island populations, from none to very few cases in Papua New Guinea (PNG) highlanders (11) to between 40 and 45% in the urbanized Koki of PNG (13) and in Nauruans (16) (Figure 15.1). Some of the highest rates ever reported were found in Melanesian, Micronesian and Polynesian populations.

Some of this variation in diabetes rates reflects minor differences in the age range of the subjects studied, sample sizes and the criteria used to classify diabetes (25–27). It appears that much of the variation in Type 2 diabetes prevalence relates to the degree of development (or Westernization) of the population studied, as evidenced by consistently higher rates in urban than rural areas and the exceptionally high rates in the most developed countries (6).

Type 2 diabetes is also a significant problem in Australian Aborigine and Torres Strait Islander communities (7, 8, 28). Although the heterogeneity of these populations prohibit the calculation of a summary prevalence estimate, available data suggest that Type 2 diabetes prevalence is between 10 and 30% in adults (28).

Diabetes prevalence appears to have increased dramatically in Pacific Island countries, as evidenced by repeated cross-sectional surveys conducted in PNG (11–13) and Western Samoa (23–24). However in Nauru, where the population has experienced many years of Westernization, data suggest that the

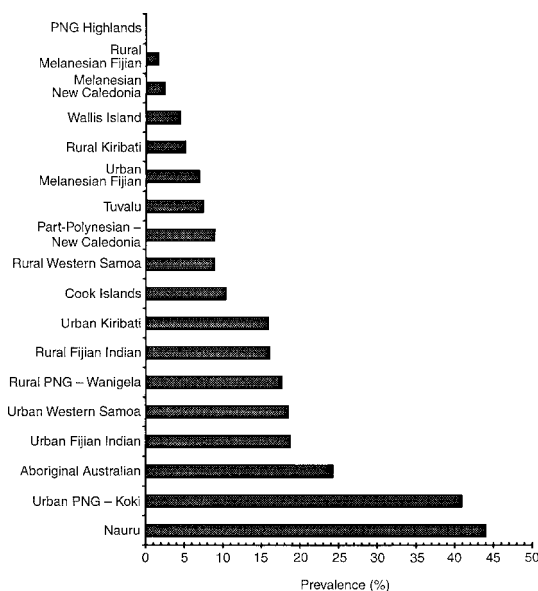


Figure 15.1 Type 2 diabetes prevalence in Pacific Island populations. All values are age-standardized to Segi's world population (29) for the age group 35–64 years

prevalence of diabetes may have reached a plateau (16–18).

Observations within countries suggest large differences in prevalence between urban and rural areas. Without exception, urban rates of diabetes exceed those of the corresponding rural areas, supporting the notion that increasing urbanization is associated with an increasing prevalence of lifestyle-related diseases such as diabetes.

The studies in PNG (11–13) illustrate quite clearly the increasing diabetes prevalence over time, the urban/rural variation in rates and differing genetic susceptibility among subgroups of the population. However, the two rural PNG populations most recently surveyed have a 6-fold difference in diabetes prevalence (2% vs 12.4%), suggesting that diabetes prevalence and factors determining the patterns of diabetes in these countries are very complex (13).

Comparison of diabetes rates between males and females in the Pacific Islands generally shows little variation (data not shown). Exceptions to this include Ouvéa (10) and Tuvalu (20) where the majority of newly diagnosed subjects with diabetes were women. In contrast, in rural PNG (12) all cases identified were men. Differences in levels of physical activity and of obesity between males and

females in these regions may explain the variation in the male:female ratio of diabetes cases in these studies.

Figure 15.1 shows the age-standardized prevalence of Type 2 diabetes in the Pacific region for people aged 35–64 years. The individual rates were standardized to Segi's World Population (29) to allow direct comparison between the countries. Some of these studies were conducted a number of years ago. Therefore it is likely that the data presented are underestimates of the current rates of diabetes in those countries that have experienced modernization with concomitant increases in lifestyle-related non-communicable diseases.

Impaired Glucose Tolerance (IGT)

The prevalence of impaired glucose tolerance (IGT) is thought to be a useful indicator of diabetes potential as a person with IGT is at increased risk of developing diabetes in comparison to those with normal glucose tolerance (30). In many Pacific Island and migrant Asian populations IGT levels are often lower than the diabetes rates, particularly in urban areas. Therefore, one could expect that the prevalence of diabetes is closer to its maximum level in these populations (30).

Undiagnosed Diabetes

Evidence suggests that the majority of Pacific Islanders with diabetes are likely to be undiagnosed, which indicates a serious potential for severe complications and premature mortality resulting from extended periods of poor glycaemic control. The prevalence of undiagnosed diabetes in Pacific Island populations is generally quite high with 80–100% of classified cases not having a previous diabetes diagnosis in some communities (Table 15.1).

ENVIRONMENTAL RISK FACTORS FOR TYPE 2 DIABETES

Genetic susceptibility to Type 2 diabetes is clearly important, but there is also strong evidence that the disease is unmasked by environmental factors

Table 15.1 Prevalence of IGT and diabetes in Pacific Island populations

Ethnic group/country	Investigator/ Year Published	Sample size (n)	Age range (years)	Diabetes classification *	IGT (%)	Newly diagnosed (%)	Previously diagnosed (%)	Total crude prevalence diabetes (%)
Aboriginal Australian *								
Bourke	Cameron et al. 1986 (7)	294	≥20	a	2.4	39.1	60.1	15.6
Central Australia	O'Dea et al. 1993 (8)	245	≤35	c	4.7	—	—	5.3
		108	>35		14.8	—	—	29.6
Indian								
Fiji	Zimmet et al. 1983 (9)		≥20	b		54.4	45.6	
Rural		846			10.4			13.1
Urban		452			10.6			12.8
Melanesian								
Fiji	Zimmet et al. 1983 (9)		≥20	b				
Rural		477			8.2	62.5	37.5	1.7
Urban		863			11.1	64.9	35.1	6.6
New Caledonia	Zimmet et al. 1982 (10)		≥20	a				
Touhu		172			5.8	66.7	33.3	1.7
Ouvea		535			5.0	91.7	8.3	2.2
Papua New Guinea								
NAN—Highlands	King et al. 1984 (11)	308	≥20	b	2.3	—	—	0.0
	King et al. 1989 (12)		≥20	c				
NAN—Highlands		257			1.9	—	—	0.0
AN—Rural		269			0.0	100.0	0.0	0.7
AN—Periurban		273			0.7	72.7	27.3	4.0
AN	Dowse et al. 1994 (13)		≥25	c				
Kalo—Rural		541			4.1	—	—	2.0
Wanigela—Rural		197			18.5	26.9	73.1	12.4
Koki—Urban		664			21.1	63.0	37.0	30.1
Vanuatu	Taylor et al. 1991 (14)		≥20	a				
Mid. Bush Tanna—Rural		397			2.4	—	—	1.0
Nguna—Semi-Rural		544			2.3	—	—	1.5
Vila civil Servants—Urban		632			2.3	—	—	5.1
Micronesian								
Kiribati	King et al. 1984 (15)		≥20	b				
Rural		1031			13.5	83.8	16.2	3.6
Urban		1880			16.0	80.0	20.0	7.7
Nauru	Zimmet et al. 1977 (16)	221	≥20	d	11.3	69.7	30.3	34.4
	Zimmet et al. 1984 (17)	1583	≥20	b	18.4	40.9	50.1	24.2
	Dowse et al. 1991 (18)	1213	≥20	c	11.4	26.9	73.1	27.9
	Dowse et al. 1994 (13)	1404	25–74	c	16.2	—	—	28.1
Part Polynesian								
New Caledonia								
Ouvea	Zimmet et al. 1982 (10)	401	≥20	a	8.0	85.7	14.3	7.0
Polynesian								
New Caledonia								
Noumea—Wallis Isl. migrants	Taylor et al. 1985 (19)	564	20–64	b	8.7	—	—	11.9
Tuvalu								
Funafuti	Zimmet et al. 1977 (20)	397	≥20	d	13.6	70.6	29.4	4.3
Wallis Island								
Rural	Taylor et al. 1983 (21)	549	≥20	b	5.5	73.3	26.7	2.6
Western Samoa	Zimmet et al. 1981 (22)		≥20	e				
Rural		745			3.9	44.0	56.0	3.4
Urban		744			8.3	60.0	40.0	8.7
	Collins et al. 1994 (23)		≥20	c				
Poutasi—Rural		463			8.2	60.0	40.0	6.5
Tuasivi—Rural		524			5.3	46.8	53.2	9.0
Apia—Urban		785			9.6	49.2	50.8	16.0
Cook Islands	King et al. 1986 (24)		≥20	c				
Rarotonga		1102			9.6	50.0	50.0	6.7
Niue		1128			6.9	49.4	50.6	7.4

AN = Austronesian (coastal) ancestry, NAN = non-Austronesian (highland) ancestry.

*Selected studies: a WHO, 1980 (25); b WHO 1980 and NDDG 1979 (27); c WHO, 1986 (28); d 75 g OGTT; DM = 2 h-PG ≥ 160 mg/ml; e NDDG.

(31, 32). The most recognised environmental determinants of Type 2 diabetes (i.e. changing diet, physical inactivity and obesity), can be assessed as targets for intervention and prevention of this disease.

Changing Diet

Although no specific nutrients have been identified which directly affect insulin resistance, dietary intake is recognized as an important risk factor for Type 2 diabetes through its role in obesity. Increased intake of refined carbohydrate and saturated fats and decreased intake of dietary fibre have been demonstrated to decrease insulin sensitivity and lead to abnormal glucose tolerance by promoting obesity (33, 34). Alleviation of diseases associated with poverty and undernutrition has been particularly evident in Asia/Pacific countries in recent years, but the scales may have tipped too far with an overabundance of unhealthy foods (35). This phenomenon is common to the developing countries of the Asia/Pacific region.

Epidemic Obesity

An epidemic of obesity in the Pacific has contributed to the rise of non-communicable diseases, Type 2 diabetes in particular (36). The patterns of obesity mirror those of Type 2 diabetes prevalence, with a larger proportion of obesity in urban than rural areas and an even greater prevalence in migrant populations in more Westernized countries.

The body mass index (BMI) is widely used as a reference measure for body mass with values forming a continuum from underweight to obese. The BMI criterion used to classify obesity differs between studies and ethnic groups and it is argued that a lower threshold for obesity should be applied in Asian populations. The prevalence of overall obesity (BMI >30 kg/m²) in the Pacific Islands ranges from a low of 3.3% (men) and 2.2% (women) in the rural PNG highlands to 77.3% (men) and 77.1% (women) in Nauru (36). In general, women tend to have a higher prevalence of obesity than men, with often more than a 2-fold difference. This pattern is not mirrored in diabetes prevalence, with similar rates for males and females.

In Asian and Pacific populations, it is thought that central (abdominal) fat distribution, measured with the waist-hip ratio, is an important risk factor for diabetes which acts independently of overall obesity (37-41).

Obesity in Polynesian and Micronesian societies has been valued as a symbol of status and prosperity for many centuries (42-43). The cultural value placed on obesity may provide a challenging barrier to intervention with weight loss as the target. Food culture, beliefs and knowledge must be taken into account when planning any lifestyle intervention to decrease the prevalence of diseases such as diabetes.

Decreasing Physical Activity

Physical activity has been reported to increase insulin sensitivity and improve glucose tolerance (44). The protective effect of exercise was illustrated in a study in the USA whereby a decreased incidence of diabetes was observed following an increase in physical activity levels (45).

Lifestyle changes associated with urbanization in Asia and the Pacific have led to a reduction in physical activity, due in part to a reduced dependence on intensive manual labour to maintain subsistence. Several studies in Asian and Pacific Island populations have supported the notion that a significant association exists between the level of physical activity and glucose tolerance (18, 46, 47). When comparing urban and rural populations, people residing in rural areas have higher levels of physical activity than their urban counterparts and a correspondingly lower prevalence of diabetes (48).

The association between physical activity and diabetes remains even after adjusting for obesity, hypertension and family history of Type 2 diabetes (45). Increasing physical activity should be an important component of strategies aimed at the prevention of diabetes and improvement of insulin sensitivity in affected individuals (49).

THRIFTY GENOTYPE, THRIFTY PHENOTYPE OR BOTH?

The high prevalence of diabetes and obesity in many developing nations has been described as

'arising from a collision of our hunter-gatherer genes with our new twentieth-century lifestyle' (50). In 1961, Neel proposed a 'thrifty genotype' to explain this phenomenon (51). He suggested that optimal energy storage during times of plenty offered a survival advantage in times of nutritional hardship. With modernization, people have greater access to high-energy, low-fibre refined food and generally decrease their traditional activity levels. The survival mechanism for times of nutritional hardship may act as a disadvantage in times of nutritional plenty through the promotion of selective tissue insulin resistance and high basal and stimulated insulin concentrations. This could then eventually lead to obesity and lifestyle-related non-communicable diseases (51). Lifestyle changes and increasing longevity combined with thrifty genes may form the foundation of the epidemic of Type 2 diabetes which is currently occurring in the Pacific region.

CONCLUSION

The magnitude of the diabetes epidemic in the Pacific region coupled with the significant morbidity and mortality associated with diabetic complications heralds the need for increased attention and resources to primary prevention of diabetes. The fact that the strongest environmental risk factors are potentially modifiable, points to lifestyle intervention, with the incorporation of a healthy diet and increased physical activity, as a means of curbing the impact of this epidemic in the Pacific region. Promotion of healthy lifestyles, while respecting local culture, poses an enormous challenge but is essential to optimize health for all Pacific Islanders.

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China

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INTRODUCTION

The prevalence of diabetes in China has generally been regarded to be low by most observers. Nevertheless, it is estimated that there are presently some 18.6 million persons with diabetes, a number greater than in any other country except India (1). China currently has a population of some 860 million aged 20 years and over and this number will increase to about 1200 million by AD 2025.

TYPE 1 DIABETES

Until recently, information about the occurrence of type 1 diabetes in China was sparse. As part of the WHO DIAMOND Project a registry for Type 1 diabetes was established in 22 centers to determine the incidence of the disease (2). New cases of diabetes, diagnosed and placed on insulin treatment before their 15th birthday, residing in defined registration areas, were identified. New cases were ascertained among 20.7 million children from many different geographical areas over a period ranging from 1985 to 1994. The overall annual incidence was estimated to be 0.51/100 000, an extremely low rate (2).

There was, however, considerable geographic variation, with the higher rates in the North and Northeast and lower ones in the South of the country (Table 16.1). The majority (95%) of the population monitored were Han Chinese, but six other minority populations were represented in the study. The majority of these had rates higher than those seen in the Han population.

Whenever unusually low rates of Type 1 diabetes are found there is always concern about the

completeness of ascertainment of cases. In this study a two-stage capture-recapture method was employed from which it was estimated that 94% of the diagnosed cases had been identified. The incidence rates reported are corrected for under-ascertainment. The study authors also believe that few cases were missed because of failure to diagnose the disease.

The incidence rate of Type 1 diabetes in the mainland of China is only one-quarter that reported among Chinese in Singapore and Hong Kong, which also have a low rate by Western standards. Even though the genetic susceptibility of Chinese children to develop the disease may be low, the lower incidence in mainland Chinese children suggests that environmental factors play a major role in determining if the disease develops. The precipitating or protective factors remain to be elucidated.

On the basis of this multicenter study the authors estimate that in China approximately 9750 children aged 10–14 years develop the disease each year.

TYPE 2 DIABETES

Earlier studies of the prevalence of Type 2 diabetes were conducted in Shanghai in 1978, and in Beijing between 1979 and 1981 (3, 4). An overall prevalence of 1.01% was found in Shanghai and in Beijing 0.75%. Subsequently a nationwide survey of 314 895 subjects from 14 provinces and cities was performed (5). Among those under 40 years of age screening for glycosuria was performed, and in subjects aged 40 years and over, venous plasma glucose concentrations were determined before and after breakfast or lunch. Those with glycosuria and

Table 16.1 Ascertainment-corrected annual incidence rates of Type 1 diabetes in six regions of China

Region	Centers	Population	Observed cases	Estimated cases	Estimated rate/ 100 000 (95% CI)
Northeast	7	4 894 818	177	180	0.55(0.53–0.56)
North middle	4	4 129 795	196	218	0.79(0.73–0.85)
Northwest	2	862 761	20	20	0.41(0.39–0.43)
Southeast	2	2 640 947	77	90	0.68(0.57–0.80)
South middle	3	5 031 456	67	70	0.23(0.21–0.26)
Southwest	4	3 075 203	55	60	0.36(0.31–0.41)

Source: Adapted from reference (2).

those with plasma glucose values of >7.77 mmol/l post-prandially received a 100 g OGTT, unless their fasting plasma value was >7.22 (130 mg/dl) or the post-prandial was ≥ 11.1 mmol/l (100 mg/dl) in which case they were assumed to have diabetes.

Overall, the prevalence of diabetes was 0.67%. However, the design of the study and the criteria employed for diagnosis make comparison with other populations difficult. Nevertheless, rates of diabetes were similar in men and women, increased with age, and were higher among the overweight. There were appreciable differences among the provinces with rates being higher in Beijing and in the southern coastal provinces, than elsewhere. More recently, studies using the 1985 WHO criteria for the diagnosis of diabetes and impaired glucose tolerance have been carried out.

DaQing

To determine the prevalence of Type 2 diabetes and impaired glucose tolerance (IGT) and incidence of Type 2 diabetes among the Chinese, and to determine the effect of intervention therapy on IGT, a 10-year prospective study (1986–1996) was initiated in June 1986 in DaQing City (6).

DaQing City is a new industrial city with a population of 500 000 in Heilongjiang Province in the north of China. This city is a petroleum production base. People in DaQing were gathered from all parts of China after 1960. There were 281 589 people with an age range of 25–74 years in DaQing in 1986. All of them receive health care in assigned local clinics throughout the city. In the 1986 prevalence survey half of these clinics were randomly chosen. They provided medical care to

126 715 people in the age range of 25–74 years. There were 110 660 subjects (87.3%) in the selected population; 55 391 men and 55 269 women who took part in the study. Of these, 190 had previously known diabetes, and the remainder were screened by measuring the 2 hour post-breakfast plasma glucose concentrations after taking about 100 g of steamed bread (equal to 80 g of carbohydrate); 4209 subjects had a 2 hour post-breakfast plasma glucose >6.67 mmol/l (120 mg/dl), and 3,956 of them (94% of 4,209) received a 75 g OGTT.

The prevalence of diabetes by WHO (1985) criteria in 1986 was similar in men and women. When standardized to the Chinese population (1982), the prevalence of diabetes was 1.25% (CI = 1.2–1.33) and of IGT 0.77% (95% CI 0.71–0.82%).

NATIONAL PREVALENCE SURVEY, 1994

In 1994 the methods used in DaQing were then extended to survey populations in 19 of the 32 provinces and areas that comprise mainland China Table 16.2 (7). Capillary finger blood glucose concentrations were measured 2 hours after a breakfast containing at least 80 g carbohydrate. A total of 223 251 subjects aged 25 and over participated in the study. ($\approx 89\%$ of the study population) of whom 213 515 were aged 25–64 years and of these 21 851 had a 2 hour capillary blood glucose value ≥ 6.67 mmol/l (120 mg/dl). Those who were already taking insulin or oral hypoglycemic agents and those whose post-breakfast capillary blood glucose level was ≥ 11.1 mmol/l (200 mg/dl) were taken to have

Table 16.2 The prevalence (%) of diabetes (previously and newly diagnosed) in 1994 National Survey

Age	Men				Women			
	With diabetes				With diabetes			
	Sample N	Known N	New N	Prev	Sample N	Known N	New N	Prev
25–34	36 446	15	89	0.29	36 114	12	102	0.32
35–44	33 610	114	392	1.51	34 404	95	361	1.33
45–54	24 932	257	639	3.59	19 243	248	496	3.87
55–64	18 014	417	771	6.59	10 752	285	571	7.96
Total	113 002	803	1891	2.38	100 513	640	1530	2.16
Standardized rate (95% CI)		Men 2.21 (2.12–2.30)	Women 2.40 (2.31–2.49)		TOTAL 2.28 (2.22–2.34)			

Adapted from reference (7).

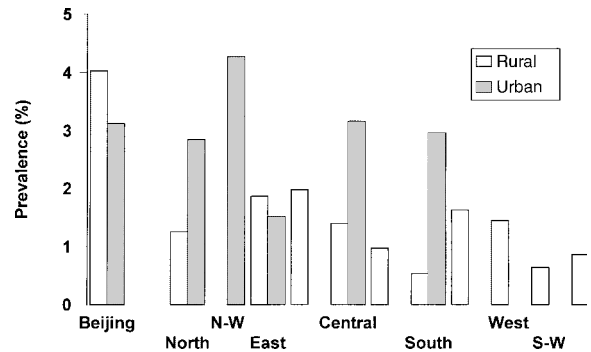
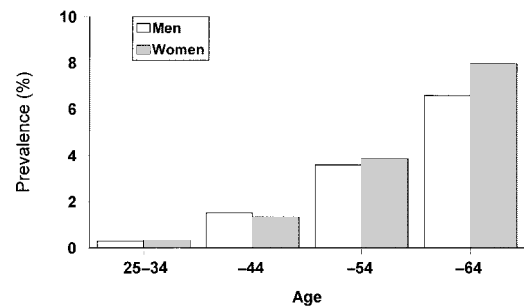
diabetes. Those not currently taking either insulin or oral hypoglycemic agents and whose 2 hour glucose level was <11.1 mmol/l received a 75 g OGTT.

The prevalence of diabetes is shown in Table 16.2 and Figure 16.1. Some 2.3% of the 25–64-year-old population had previously or newly diagnosed diabetes, and 2.1% had IGT. Rates of diabetes increased with age, but the frequencies in men and women did not differ significantly (Figure 16.1).

To determine the prevalence of persons who had diabetes or IGT whose 2 hour post-breakfast capillary glucose values were <6.67 mmol (120 mg/dl), a sample of 1626 subjects with levels of 6.1–6.6 mmol/l ($\geq 110 < 120$ mg/dl) also received a 75 g OGTT. Among them 3.5% had diabetes and 15.7% had IGT. These results were used to estimate the proportion of the population in which diabetes and IGT had not been detected. (0.23 and 1.11%, respectively). Consequently the estimated overall prevalence was 2.51% for diabetes, and 3.23% for IGT.

The prevalence of diabetes in mainland China in 1994 was still low compared to that in developed countries. The total of people with diabetes in China at that time was estimated to be 15 million, of whom about 75% had undiagnosed diabetes.

Prevalence rates tended to be higher in the north, and in urban areas that were more affluent (Figure 16.2). Persons with diabetes had higher income, greater body mass index and waist/hip

**Figure 16.1** Prevalence of diabetes by 1985 WHO criteria in Nationwide Survey of Diabetes in China conducted in 1994**Figure 16.2** Prevalence of diabetes in various regions in China. Rates are higher in Beijing and other urban areas than in the rural areas, and decrease from the north to south

Source: Data from 1994 Nationwide Survey

Table 16.3 Comparison of prevalence of diabetes in China in 1980 and 1994

Year	Area	<i>n</i>	Age (years)	Diabetes (%)
1980	12 provinces	107 954	≥30	0.9
1994	19 provinces	213 515	25–64	2.51

Source: Adapted from reference (7).

ratio, had less education and were less physically active than those with normal glucose tolerance (7).

CHANGING PREVALENCE

Prevalence rates from the earlier 1980 and the 1994 nationwide surveys are compared in Table 16.3. While the age groups and survey methods are not identical, it appears that the prevalence of diabetes had increased approximately 3-fold over the 14-year interval. Thus, the prevalence of diabetes in China appears to be changing rapidly.

In 1994 a second prevalence study was performed in DaQing as part of the National Study. The remainder of the population, the half that did not take part in the 1986 study, was examined. Using the same methods, the prevalence in DaQing in 1994 was 3.51% in the 25–64 year age group compared to the earlier standardized rate of 1.04%. Thus, in this community the prevalence was 3.4 times higher 8 years later, again indicating a rapid increase in the prevalence of the disease over a short time interval.

On the basis of changes in the demography, in particular the expanding population and the concomitant migration from rural to urban areas,

it is estimated that the number of persons with diabetes in China will increase from some 16 million in 1995 to 18.6 million in 2000, and to 37.6 million in 2025 (1).

IMPAIRED GLUCOSE TOLERANCE AND EFFECTS OF INTERVENTION

Impaired glucose tolerance (IGT) is a state in which the risk of developing Type 2 diabetes is substantial and is a stage at which the development of diabetes may potentially be delayed or prevented. In 1986, in DaQing, a randomized controlled clinical trial was initiated to determine if exercise, dietary intervention or a combination of the two would reduce the incidence of Type 2 diabetes (8) in persons with IGT.

Some 577 subjects with IGT, identified during the diabetes prevalence study in 1986, were randomized to a control group and three active intervention groups—diet, exercise, or diet plus exercise. The subjects were followed by glucose tolerance testing every 2 years for a total of 6 years. Subjects were randomized to the groups on the basis of which clinics they attended. The results of the study are shown in Table 16.4.

In each of the active intervention groups the incidence of diabetes was significantly reduced compared with the control group. On the other hand, there were no significant differences among the active intervention groups. Interventions were equally effective in both more and less obese subjects although, as might have been expected, the incidence of diabetes was greater in the more obese (BMI ≥25 kg/m²) and among those with higher glucose levels at the beginning of the study.

Table 16.4 Incidence of diabetes and fasting hyperglycemia over a six-year period in DaQing in subjects with IGT participation in the intervention study

	Intervention			
	Control	Diet	Exercise	Diet + Exercise
No. of subjects	133	130	141	126
6-year follow-up				
No. with diabetes by WHO criteria	90	57	58	58
Incidence/100 person-years	15.7	10.0	8.3	9.6
No. with FPG ≥7.8 mmol/l	55	21	37	33
Incidence/100 person-years	9.6	3.7	5.3	5.5

THE FUTURE

Investigations of the occurrence of diabetes in China have shown that the country still has relatively low rates of diabetes compared to many Western countries, but the rates are increasing at an alarming rate. On the basis of incidence rates calculated from the DaQing Study, it is estimated that about 700 000 new cases of diabetes per year occur in China at the present time (6).

Elsewhere the rates of diabetes in people of Chinese origin are considerably higher than in mainland China. Rates in Singapore, Mauritius and in the island of Taiwan are appreciably higher. In Mauritius, for example, the prevalence of diabetes in the 30–64-year-old age group is 16% in men and 10% in women, and in Singapore 7 and 8%, respectively (9). These much higher rates are almost certainly the result of differences in lifestyle resulting from greater affluence, increased obesity, lower levels of physical activity, and possibly dietary changes. With rapid economic development it is likely that these risk factors will increase among the mainland Chinese population. If so, the projections about the prevalence of diabetes, based on demographic changes, will greatly underestimate the magnitude of diabetes in China. Before this happens, perhaps preventive measures can be implemented that may alleviate the magnitude of the projected epidemic of diabetes in China in the next millennium.

APPRECIATION

This chapter is dedicated to Professor Pan Xiaoren, who initiated and carried out much of the work described in this chapter. Professor Pan died in July 1997, shortly after providing much of

the data included in it. He had agreed to co-author the chapter, but sadly was unable to see it materialize. His life was devoted to understanding the nature and causes of diabetes in the hope that preventive strategies could reduce the burden of the diabetes, especially in his homeland.

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Japan

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INTRODUCTION

A rapid economic recovery after World War II westernized Japanese diet and made people's life-style more sedentary. These two factors form a hotbed for developing Type 2 diabetes and its prevalence has increased dramatically. At present, the total number of individuals with diabetes mellitus, including unknown diabetics, is estimated to be more than 7 million people. Moreover, it is assumed that the number of patients with advanced diabetic micro- and macrocomplications is increasing, which threatens an economic problem of healthcare in the society. It is critical to have ongoing accurate incidence/prevalence data which provide the core information for the prevention of this disease. Mortality studies are another important aspect of diabetes epidemiology. It is essential to investigate the risk factors for dying of diabetes and to prevent unnecessary deaths from the illness.

The Japanese government has seriously considered the situation, and the Ministry of Health and Welfare, Government of Japan, organized and sponsored the Diabetes Study Group in 1989. The data obtained from this study group have been accumulated and have contributed greatly to the understanding of the epidemiology of diabetes in Japan. This chapter describes the most recent observation of diabetes epidemiology in Japan.

INCIDENCE AND PREVALENCE STUDY

Type 1 Diabetes

Overall and Age-specific Incidence

Type 1 diabetes is one of the most important chronic diseases among children, yet its nation-

wide incidence has not been clarified until the past decade. The most reliable data were reported from three areas including Hokkaido, Tokyo and Kagoshima, with a total population of 3.6 million (1). The degree of case ascertainment was more than 95% and demonstrated that the overall incidence rates for children 0–14 years of age during 1985–89 were 2.07, 1.65 and 1.78 per 100 000, respectively, with peak incidence being seen in the 10–14 year age group with a predominance of females developing Type 1 diabetes (WF ratio: 0.7) (Table 17.1). The diabetes Study Group of the Ministry of Health and Welfare reported a similar figure of the mean incidence rate as 1.5/100 000 for nine areas with no discernible pattern from the north to the south (2). The rates are quite low compared with those in Caucasian children. There have been no published data which demonstrate the secular increase of Type 1 diabetes after 1980.

Prevalence

Type 1 diabetes prevalence in Japan was first reported by Hososako et al. in 1964 (3). They conducted a survey on childhood diabetes among the families of a large industrial company in Kitakyushu-city and found 4 Type 1 diabetes cases among 40 000 children aged 0–14 years. Since then, several studies mainly using a questionnaire survey to schools have been performed and the prevalence data of Type 1 diabetes have been accumulated (4, 5). The data obtained are quite consistent with approximately 10 per 100 000 population.

The annual number of newly registered diabetic children of 0–17 years old for the Central Registry

Table 17.1 Annual Type 1 diabetes incidence rates per 100 000 and 95% CI

Age group (yr)	Hokkaido	Tokyo	Kagoshima
0–4	0.74(0.39–1.26)	1.16(0.72–1.78)	1.48(0.88–2.33)
5–9	1.43(0.96–2.06)	1.68(1.14–2.37)	1.76(1.11–2.63)
10–14	3.65(3.29–4.56)	2.01(1.46–2.67)	2.07(1.39–2.98)
0–14	2.07(1.73–2.48)	1.65(1.35–2.01)	1.78(1.40–2.26)

The dates of the study in Kagoshima was 1980–89.

for Free Medical Care, launched in 1974 and sponsored by the Ministry of Health and Welfare, Government of Japan, is another good source for estimating the prevalence of Type 1 diabetes. Because of the nature of this system, the degree of case ascertainment is estimated to be more than 95%. Through the spread of this system, the number of patients receiving its benefit has increased gradually and the calculated prevalence is reported to be 2.38 per 10 000 in 1994 (6). The prevalence rate obtained from the registry is almost twice as high as that seen in the previous studies; however, it should be read with caution due to the possible inclusion of Type 2 diabetes among children, which will be discussed later in this chapter.

Clinical Characteristics at Diagnosis of Type 1 Diabetes

Japanese children may develop Type 1 diabetes gradually. It has been reported that a large number of patients have been diagnosed as having Type 1 diabetes by urine glucose screening at school without showing distinct symptoms. At Nihon University Hospital, Tokyo, out of 88 Type 1 diabetes children diagnosed during 1974–91, 55 had abrupt onset with severe clinical symptoms but 33 had minimal or no clinical symptoms at diagnosis. Neither group is obese but the clinical features are different. Figures for Type 1 diabetes with abrupt onset are: (1) mean onset age: 8.8 ± 4.5 years old; (2) male/female: 28/27; (3) HbA_{1c} level: $9.88 \pm 3.66\%$; and (4) high ICA positively at onset (83%) with rapid decline. Whereas Type 1 diabetes patients with slow onset show: (1) older mean onset age: 11.9 ± 3.1 years old ($p < 0.05$); (2) male/female: 9/24; (3) HbA_{1c} level: $7.05 \pm 1.49\%$ ($p < 0.05$); and (4) lower ICA positively at onset (62%, $p < 0.05$) with gradual

decline. Moreover, Type 1 diabetes with abrupt onset has significantly lower 2 hour post-prandial C-peptide levels and higher daily insulin dosage for at least 10 years after the onset (7).

The genetic background between the two is slightly different. HLA DRW9 and DR4 are significantly more common in the abrupt onset group than in the slow onset group (8). Therefore, two different Type 1 diabetes groups seen among Japanese children cannot be explained by the different timing of diagnosis, e.g. appearance of slow onset Type 1 diabetes due to early detection of Type 1 diabetes by urine glucose screening at school. A similar group of Type 1 diabetes is also seen in adults, Kobayashi et al. demonstrating that slowly progressive Type 1 diabetes is characterized by slow progression of beta-cell failure with persistent positive low-titer ICA, frequent involvement of exocrine pancreas, positive family history of Type 2 diabetes, association with HLA-DQA1*0301–DQB1*0401, and a lack of association with HLA-A24 (9), which indicates the complete destruction of the pancreatic beta-cell (10).

Type 1 Diabetes Incidence/Prevalence in Adults

Little information is available regarding the incidence and prevalence of Type 1 diabetes after the age of 20 years. An attempt to estimate the prevalence of Type 1 diabetes using the capture–recapture method was first conducted in Kakogawa City with a 234 249 adult population (11). Several independent sources such as hospital records, lists of the diabetic patients at the local diabetes association, and personal health data on the medical information network system were used for the capture–recapture method and the accuracy of diagnosis was confirmed by physicians.

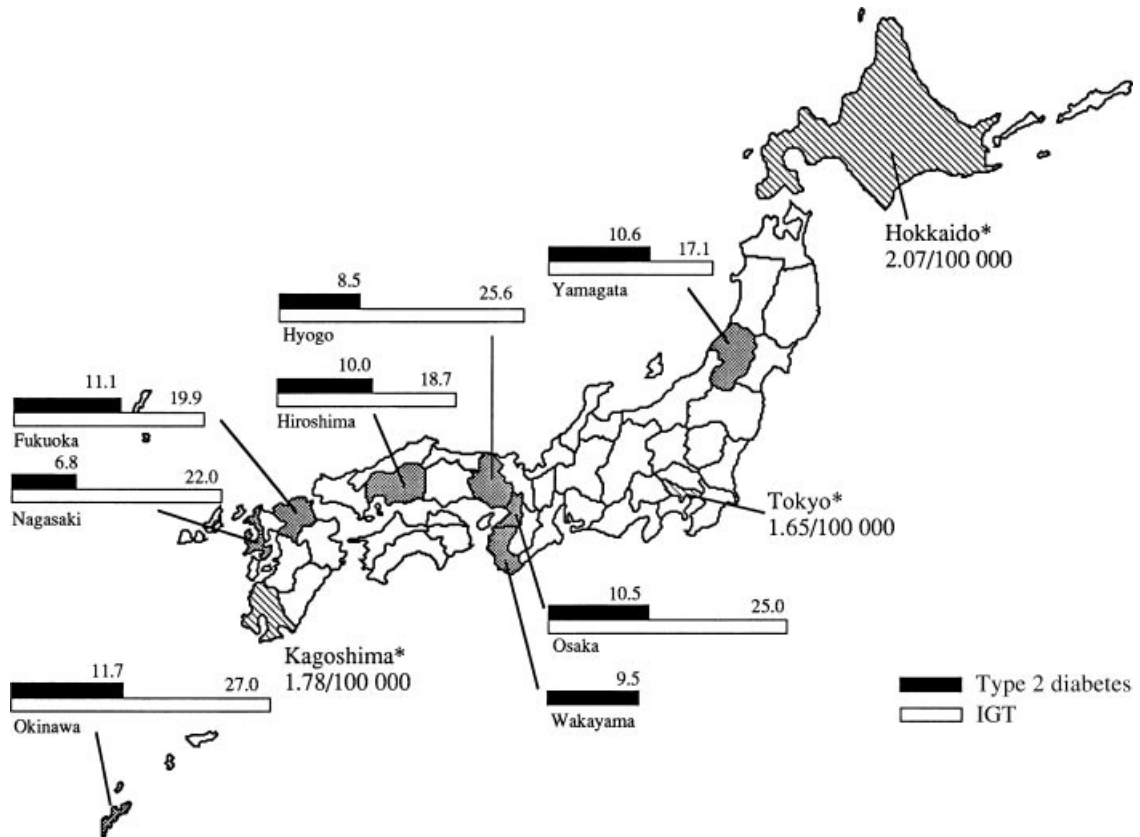


Figure 17.1 Annual Type 1 diabetes incidence (per 100 000, 0–14 yrs) and Type 2 diabetes/IGT prevalence (% 40–80 yrs) in various areas in Japan

Obtained prevalence of Type 1 diabetes in 1994 was estimated to be 1.75 per 10 000. As the sample size is small and the data are still premature, nationwide further study is warranted.

Type 2 Diabetes

Prevalence

Population-based studies on Type 2 diabetes prevalence have been conducted in Japan since the early 1960s. They have provided invaluable information on the extent of diabetes, however, in the early studies, people were first screened by urine glucose tests and then further evaluated by oral glucose load. The prevalence of Type 2 diabetes in the population aged 40 years or older is reported to be 1.3–4.7% in those studies (12).

After 1985, a Type 2 diabetes prevalence study using WHO criteria became popular and the figures obtained were 6.8–11.7%, much higher than that seen in earlier literature (2) (Table 17.2). In the population-based settings, the report from Funagata-machi, Yamagata prefecture demonstrated that the prevalence rate in 1991–92 was 10.5% for males, and 12.9% for females (13). Similarly, the age-adjusted Type 2 diabetes prevalence rates in males and females reported from Hisayama-machi, Fukuoka, prefecture in 1988 were 12.79 and 8.4%, respectively (14). Under the assumption that these prevalence rates can be extrapolated to the general Japanese population, the number of people with Type 2 diabetes, including those who have not yet been diagnosed, increased to over 5 million in Japan. The prevalence of IGT ranged from 17.1 to 27% (2). It can easily be assumed that the increase in Type 2

Table 17.2 Prevalence of IGT and diabetes in selected populations aged 40–80 years in males and females in Japan

Area (prefecture)	Prevalence		Reporter (year)
	IGT (%)	Diabetes (%)	
Yamagata	17.1	10.6	Sekigawa (1991, 92)
Osaka	25.8	10.8	Konishi (1990)
	24.5	11.1	Sasaki (1990)
	24.7	9.6	Seino (1990)
	25.6	8.5	Doi (1992)
Hyogo	—	9.5	Nanjo (1992)
Wakayama	18.7	10.0	Takashina (1992)
Hiroshima	19.9	11.1	Omura (1988)
Fukuoka			
(Hisayama cho)	22.0	6.8	Nagai (1991)
Nagasaki			
(Ojika-jima)	27.0	11.7	Mimura (1992)
Okinawa			

diabetes patients will result in an increase in patients with macro- and microvascular diseases and an explosion of medical care costs, leading to a burden on society. From the public health and epidemiological perspective, an intervention in the population with IGT as well as those with Type 2 diabetes is urgently needed for the primary and secondary prevention of diabetes and its complications.

Epidemiology of Type 2 Diabetes Among Children

The annual change in the incidence rates of childhood Type 2 diabetes for the years 1975–90 in the Tokyo area has been reported (7). It is calculated using urine screening data of primary and junior high school children in the age range of 6–15 years old. The case ascertainment is almost 100%. It appears that an approximately 1.5-fold increase of Type 2 diabetes was observed during 1976–1981, which is associated with the increase in the prevalence of obesity among school children. Until 1977, the rate was much the same as that of Type 1 diabetes; however, it increased gradually with year-to-year fluctuation and reached approximately 8 per 100 000. The incidence rates of Type 1 diabetes and Type 2 diabetes cannot be directly compared because of the different methods of case ascertainment. The data, however, obviously demonstrate a larger

number of children with Type 2 diabetes existing in Japan than children with Type 1 diabetes. Westernization of their diet, a decrease in physical activity, and mental stress which has occurred in the society appear to have influenced the disease structure of Japanese children.

Characteristics of Type 2 Diabetes Children at Onset

During 1974–95, a urine glucose screening test was conducted for 220 000–380 000 school children aged 6–15 years in some areas in Tokyo and a total of 215 new diabetic children was detected. Among those, 180 were diagnosed as having Type 2 diabetes. Owada et al. (15) have examined the clinical features of those 180 with Type 2 diabetes and found that 67 or 87% were diagnosed after 12 years of age. The youngest child was age 6 and was mentally retarded. Other characteristics of Type 2 diabetes can be summarized as: (1) the prevalence rate increases according to age, (2) the male/female ratio is 0.75; (3) obesity over ideal body-weight of more than 140% is 68.8% in males and 34.9% in females, (4) hyper insulinemia; and (5) a high prevalence of family history of diabetes. As the majority of the cases with Type 2 diabetes are asymptomatic, compliance is poor and resulted in a high rate of drop-outs. They often returned to hospital with advanced complications. Early detection and constant care for Type 2 diabetes children, therefore, is a critical problem.

Risk Factors for Developing Type 2 Diabetes

Nutritional factors are perceived as a potent risk factor playing a predominant role in the increase of Type 2 diabetes in Japan. Indirect evidence has been provided by studies on the Japanese American population where the prevalence of Type 2 diabetes is almost twice as high as that seen in Japanese in Japan (16,17). Hara et al. demonstrated that the total caloric intake in these two populations was similar; however, consumption of animal fat and refined carbohydrate was at least twice as high in Hawaiian Japanese as in Hiroshima Japanese. An estimated level of physical activity was significantly reduced in Hawaiian subjects when compared to their counterparts in

Hiroshima. Westernized diet coupled with reduced physical activity may foster the development of obesity and insulin resistance (18) and could be partially responsible for the higher prevalence of diabetes among Japanese-nisei in the US. Such dietary and physical factors may also operate within Japan and should be taken into account as possible causative factors implicated in the increase of Type 2 diabetes in Japan.

Besides dietary factors, a family history of diabetes, a plasma glucose level of more than 180 mg/dl at 120 min after 75 g oral glucose load, the low initial response of insulin during OGTT (19,20) the sum of insulin concentration during OGTT, serum triglycerides, body mass index, waist-hip ratio, and blood pressure levels (21) are the possible risk factors for Type 2 diabetes among Japanese.

MORTALITY STUDY

Type 1 Diabetes

Long-term Mortality

Diabetes remains a major risk factor for premature death among children. The Diabetes Epidemiology Research International (DERI) Mortality Study was initiated in 1986 to compare the Type 1 diabetes mortality in four countries—Japan, Allegheny County, US, Finland and Israel—with diverse differences in environmental surroundings and genetic backgrounds (22,23). The subjects of this study were diagnosed (1) as having diabetes between 1965 and 1979, and (2) as having developed diabetes before 18 years of age. The subjects in the countries other than Japan were taken on population-based registry, that is on ongoing incidence surveys. In contrast, there was no Type 1 diabetes registry in Japan; therefore, the study subjects were recruited from the two nationwide prevalence surveys conducted in 1970 and 1981.

The latest results of the DERI Mortality Study up to the 1990 follow-up, including a total number of 8123 individuals with Type 1 diabetes, were reported in 1991 (24), and indicated that Japanese children had a much higher risk of death; compared to the other countries. Study population size and the number of deceased cases are

summarized in Table 17.2. The age-adjusted mortality rates per 100 000 person-years for the four populations were 760 (Japan), 408 (Allegheny County), 250 (Finland) and 158 (Israel). Life-table analysis revealed that over 16% of the Type 1 diabetes cases were deceased after 20 years of duration in Japan, which was significantly worse than that of the other three countries. The standardized mortality ratio (SMR) for Japan was also extremely high, indicating that individuals with Type 1 diabetes appeared to be almost 13 times more likely to die compared with age- and sex-matched controls of the general population.

Causes of Death

Causes of death of 90 deceased cases were determined using the standardized procedure of the DERI mortality classification committee, which consisted of five international members. On the basis of information collected through hospital records, death certificates and direct family contact, (1) the underlying cause of death and contributory conditions, (2) pattern of death, and (3) the contribution of Type 1 diabetes to the death were examined (23). The main reason for the high death rate in Japan was the high mortality caused by diabetic renal disease and acute complications such as ketoacidosis and hypoglycemia (Table 17.3).

Risk Factors for Premature Death

The next step in the DERI Mortality Study consisted of two components. One was to identify the risk

Table 17.3 Underlying cause of death

Cause of death	No. of deaths	%
Diabetic renal	28	31.1
Acute complications	24	26.7
Accident/Suicide	13	14.5
Cardiovascular	7	7.8
Infection	11	12.2
Cancer	0	0
Other, non-diabetes	4	4.4
Other, diabetes	1	1.1
Unknown	2	2.2

factors for premature deaths among Japanese Type 1 diabetes children by an ecological study in order to build the hypotheses regarding risk factors for death, and a case-control study to test the hypotheses. Another component was the study to clarify the reasons why Japanese with Type 1 diabetes were more likely to die from diabetic renal disease compared to other countries. In the DERI ecological studies, area-specific mortality in Japan was associated with the availability of diabetologists, indicating a possible contribution of supervision by specialists to the prognosis of individuals with Type 1 diabetes (25).

A case-control study for testing the hypothesis was conducted to identify the risk factors for premature deaths (26). The study was based on 90 cases who died during follow-up and 90 living controls, selected from the rest of the cohort, who were matched for sex, birth year, year of diagnosis and duration of diabetes. Socio-economic and behavioral status were surveyed through a questionnaire. Conditional logistic regression analyses revealed that the better educated patients, who retained the same physician (number of times a patient changed physician) and who attended a clinic specializing in diabetes (attendance at university hospital clinic), injecting insulin several times a day (number of insulin injections) and more frequently attending the clinic, were at substantially lower risk of death.

To elucidate the reasons why Japanese with Type 1 diabetes are more likely to die from renal disease, the DERI Mortality Study compared the incidence of end-stage renal disease (ESRD) between Japanese and the US DERI cohorts (27,28). It was reported that Japanese with Type 1 diabetes were 2.4-fold more likely to develop ESRD. Moreover, 10 of the 36 renal-failure-related deaths in the Japanese cohort had never been treated by dialysis, while all renal-failure-related deaths in the US cohort had been treated by dialysis. The data suggested that a greater frequency of diabetic ESRD and reduced access/acceptance to dialysis underlie much of the excess of diabetic renal deaths in Japan. Recently, the high mortality in the Japanese DERI cohort has been improved to the same level as in the other three countries (29). This is probably the result of the establishment of a medical care system, such as free access to medical care for young-onset diabetic patients. However, Japanese Type 1 diabetes patients in the DERI Mortality Study

are still approximately 2-fold more likely to die compared to the general population of the same age as the patients ($SMR = 2$), which means that half of the deaths can potentially be prevented.

Type 2 Diabetes

Mortality Rate

To our knowledge, there have been no population-based follow-up studies regarding the mortality for individuals with Type 2 diabetes in Japan. Two reports in the hospital-based setting have been published, demonstrating the increased risk of 1.5–1.7 of death among Type 2 diabetes patients compared to that in the general population (30,31). Such an observation of mortality among people with Type 2 diabetes is the same as that in the reports for the Caucasian population.

A Changing Pattern of Causes of Death

It is of interest, however, that the constitution of causes of death in people with Type 2 diabetes differs between Japanese and Caucasian (32–34). A report from England and Wales (1975–77) (32) demonstrated that deaths due to disease of the heart, of the cerebrovascular system, of renal disease and malignant neoplasm were 31.6, 14.7, 0.7 and 7.2% respectively, whereas in Osaka (1975–79), corresponding figures were 12.5, 13.9, 1.2 and 7.8% (33). The difference in causes of deaths between Japanese and Caucasians, i.e., the lower risk for cardiovascular deaths and higher risk for renal deaths in the Japanese with Type 2 diabetes, may be attributed to genetic and environmental factors such as dietary characteristics. In Japan, dietary habits changed from the conventional diet including low-protein and low-fat intake, with low calories to the Westernized diet with high-fat and high-calorie rates after World War II. With this change, Japanese with Type 2 diabetes have been more likely to die from coronary artery disease (34). Only 8.9% of those who developed diabetes during 1960–74 die of coronary artery disease, whereas 15.3% of those who developed diabetes during 1980–84 died of the disease (35). As described, the characteristics of causes of death in Japan may get close to those in

Europe and the USA in the near future. In terms of diabetes care, the risk factors for cardiovascular disease should be granted much more attention by Japanese with Type 2 diabetes. Further investigation, especially a population-based follow-up study for Type 2 diabetes, is essential in order to conduct an unbiased evaluation of the prognosis and its risk factors.

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Part IV

Associated Risk Factors and Complications

Malnutrition-related Diabetes Mellitus: Myth or Reality?

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INTRODUCTION

In 1985 a World Health Organization Study Group recognized malnutrition-related diabetes (MRDM) as a major class of diabetes mostly in tropical developing countries (1). Two important components of MRDM were described: the protein-deficient diabetes (PPDM) and fibro-calculous pancreatic diabetes (FCPD) subtypes. The recent American Diabetes Association classification of diabetes (2) does not mention at all the existence of MRDM as a separate entity. Furthermore, in the last provisional report of a WHO Consultation on diabetes mellitus, MRDM has been deleted (3). This chapter intends to discuss the controversy surrounding MRDM and review the evidence behind its non-recognition as a major type of diabetes by both ADA and WHO (2, 3).

HISTORICAL BACKGROUND

In some tropical areas of the world, an apparently unique form of diabetes occurs which is seemingly associated with malnutrition. Two major forms of this type of diabetes, designated as malnutrition-related diabetes mellitus (MRDM) (1), were probably already recognized in 1955 by Hugh-Jones in Jamaica (4) and in 1959 by Zuidema in Indonesia (5). Hugh-Jones found that 13 out of his 215 diabetic patients in Jamaica did not fit into the typical Type 1 or Type 2 classes, and he called them 'J-type' (Jamaican type). These patients were young, lean, insulin-resistant and not prone to ketosis (Table 18.1). 'Z-type' or Zuidema syndrome, or tropical pancreatic diabetes, comes from Indonesia where it was described for the first time

by Zuidema (5). In this form of diabetes, in addition to the features seen in the Jamaican type, i.e. insulin resistance and malnutrition, patients show evidence of chronic pancreatitis with pancreatic calcification and fibrosis and an invariable history of childhood malnutrition (Table 18.1).

Since 1955, numerous descriptive studies have been published on this type of diabetes in tropical countries. It has been differently termed according to people and places and this has created even more confusion about the real nature of the condition. In 1978, the late Dr K.M. West reviewed the available epidemiological data and the clinical features of diabetes in the malnourished (6). He emphasized that there was a need for additional studies to clearly define this syndrome and determine its incidence and prevalence.

The lack of definition of the condition is probably due to the lack of a clear distinction from Type 1 and Type 2 as pointed out by Abu-Bakare et al. in their review (7). Follow-up of the original Jamaican cases showed that some could be controlled by oral agents, and that some mimicked Type 1 diabetes as they became ketoacidotic on insulin withdrawal. In 1980, the second WHO Expert Committee on Diabetes Mellitus (8) recognized the lack of a precise definition of this syndrome and concluded that 'it is not clear whether the malnutrition-related diabetes mellitus syndrome (MRDM) of severe non-ketotic diabetes in children in the tropics is a peculiar manifestation of ordinary childhood-onset diabetes or whether it is aetiologically distinct'.

Five years after this statement, the most important change from the previous WHO classification of the diabetes mellitus syndrome is the appearance of MRDM as a major clinical subclass,

Table 18.1 Clinical features of malnutrition-related diabetes mellitus (MRDM)

Feature	PDPD or PDDM	FCPD
Age at onset of diabetes (years)	10–40 often before 35	15–35
Sex predominance (M/F)	Variable: 3 : 1 Asia 2–3 : 1 Africa 1 : 1 West Indies 1 : 1	
Family history	Negative	Negative
History of childhood malnutrition	++	++
History of cassava consumption	?	Common
Alcohol consumption	Negative	Negative
Extreme poverty	Common	Common
Abdominal pain	Rare	Common
Underweight	Common	Common
Hepatomegaly	++	+
Bilateral parotid enlargement	++	+
Malnutrition signs and symptoms	++	++
Exocrine function disturbance	Rare	Common
Pancreatic calcification	Absent	Common
Pancreatic fibrosis	++	+
Ketosis	Absent	Variable
Insulin requirement	>60 units/day	Moderate to high
Endogenous insulin secretion	Present	Present
ICA	?	?
HLA association	?	?
Long-term complications (mostly neuropathy)	Common	Common

Adapted from reference (1).

Characteristics of the two major subtypes: Protein-deficient pancreatic diabetes (PDPD or 'J-type').

Protein-deficient diabetes mellitus (PDDM)

Fibro-calculous pancreatic diabetes (FCPD or 'Z-type').

M = male; F = female; ICA = islet cell antibodies.

+ = often present; ++ = very common

ranking with Type 1 and Type 2 diabetes (1). The Study Group reviewed the available literature on MRDM and suggested, for future research purposes, the recognition of at least two subclasses of MRDM: fibro-calculous pancreatic diabetes (FCPD) and protein-deficient pancreatic diabetes (PDPD). The Study Group insisted on the fact that the distinction should be viewed as a basic research tool that might replace the former myriad names given to this condition and facilitate communication and comprehensive comparisons between interested investigators. Previously known as 'tropical diabetes', 'tropical pancreatic diabetes', 'pancreatic diabetes', 'J-type diabetes', 'ketosis resistant diabetes', 'juvenile tropical pancreatitis syndrome' and 'Z-type diabetes', MRDM became an entity distinct from Type 1 and Type 2 diabetes. However, there are still crucial unanswered questions. What has happened since the latest recognition of MRDM as a major type of diabetes by WHO (1)?

FIBROCALCULOUS PANCREATIC DIABETES (FCPD)

Geography of FCPD

FCPD is an identifiable syndrome when the features of pancreatic disease, including recurrent episodes of abdominal pain, pancreatic lithiasis, and malabsorption and diabetes mellitus, are present in individuals in tropical and semi-tropical areas. FCPD without pancreatic lithiasis may be suggested by epidemiological association and a history of episodes of abdominal pain (1, 7, 9–11). In 1959, Zuidema from Indonesia was the first to describe cases of pancreatic calculi in association with diabetes. FCPD was therefore recognized as equivalent to the 'Z-type' described in Indonesia by Zuidema (5). It has been reported in several countries including Brazil, Ghana, India, Indonesia, Jamaica, Madagascar, Sri Lanka, Thailand,

Uganda, Congo, Bangladesh, Singapore, New Guinea, Nigeria, Cameroon, the Ivory Coast, Togo, Benin, South Africa, Zambia, Zimbabwe and Kenya (1, 7, 9–11).

Prevalence and Incidence of FCPD

Precise estimates are totally unknown. Most of the reported prevalence rates are not population-based. One population-based study has been reported on the prevalence of tropical chronic pancreatitis in India (12). A population of 28 507 was interviewed and 518 subjects identified who had one of the following characteristics: abdominal pain suggestive of pancreatitis; diabetes mellitus; or a history of weight loss (malnutrition). One in 1020 subjects had chronic calcific (calcifications visualized using abdominal X-ray, ultrasound) pancreatitis (0.09%). The reported prevalence of FCPD in diabetic clinic populations varies widely. Studies from Africa showed that in Zimbabwe 1% of diabetic patients had FCPD (13) and in Nigeria 8.6% of patients had FCPD (14). In South Africa, FCPD was found to be rare (15). In Thailand, 14 of 253 (5.5%) of young diabetic patients, defined as those with age at diagnosis below 30 years, had FCPD (16). Another 16 patients had signs of malnutrition but did not have pancreatic calculi. In Kerala, FCPD constituted 29.3% of the total diabetic cases registered and 1.3% of all inpatient admissions at the Kottayam Medical College in 1964 (16). At the Diabetes Research Centre, Madras, 50–60 new patients with FCPD are currently registered every year, which represents about 1% of all diabetics and 4% of 'young' diabetics, defined as those with age at diagnosis below 30 years (17). Although these reports suffer from a selection bias, FCPD does not seem to be a rare medical condition in tropical countries.

Clinical Features of FCPD

Diagnosis is based upon the characteristic clinical features summarized in Table 18.1. Many are common to FCPD and PDPD or PDDM (as well as some biochemical findings that will be discussed later on in this chapter) despite the differing ethnic groups of the patients. High blood glucose levels,

dehydration and signs and symptoms of severe undernutrition have been reported mostly in Asian patients (7). Severe infections such as florid tuberculosis are often present. Patients belong to the lower socio-economic class. A history of childhood malnutrition is common as well as a history of recurrent abdominal pain. Abdominal X-rays show calculi in the pancreatic duct in most of the cases. Ultrasonography may indicate obstruction, dilatation and calcification of the pancreatic ducts. These findings correspond to the pathological features that have been reported in some cases. The pancreas has been described as being firm, fibrosed with multiple calcium carbonate and calcium phosphate stones present in the major ducts (1, 10, 11). Destruction of islet tissue is variable and ranges from total absence to almost normal islet structure with areas of atrophy (1, 10, 11).

Geevarghese and associates in Kerala, South India, have made major contributions to the understanding of FCPD (6, 18). In Kerala over 90% of those with the onset of DMS under age 30 had pancreatic lithiasis; in Trivandrum and ottayam FCPD accounted for approximately 15% of all with diabetes (6, 18). Bajaj (19) summarized data on 970 patients with FCPD reported from India. Pancreatic calculi were noted in 72%. In 24% there was a 'typical history' (episodic abdominal pain) but no detectable pancreatic calculi. About 3% had pancreatic calculi without diabetes mellitus. These findings are similar to those reported from Indonesia, including Zuidema's 1955 report, and Nigeria. Thus, FCPD diabetes is secondary to chronic pancreatic disease; a similar form of secondary diabetes occurs in the West, most commonly in chronic alcoholics with chronic pancreatitis.

The Diabetes Component of FCPD

The diabetes component of FCPD varies in intensity, and in its advanced state approaches an insulinopenic state requiring insulin. Studies of 33 patients with FCPD indicated the heterogeneity of FCPD (20). They showed that 5 of 33 patients with FCPD had very low plasma C-peptide concentrations with no increase following glucose stimulation. These patients developed ketoacidosis without insulin therapy. Another 17 patients had

low plasma C-peptide concentrations with a minimal increase after stimulation. These patients were not ketotic without insulin. The other 11 of the 33 showed higher basal and stimulated plasma C-peptide concentrations and were treated with oral hyperglycemic agents. This study is significant in that age and sex matched non-diabetics and patients with Type 2 diabetes were included. The onset of FCPD was on average at age 25 and the average duration of diabetes in the patients studied was 7 years. The body mass index (BMI) of the FCPD group was 17 with overt protein caloric malnutrition (PCM) described in 25%. Significantly there was no history of cassava ingestion. A family of diabetes was described in 51% of those with Type 2 diabetes, in 12% with FCPD and none in the control group. Details of food intake and nutritional status throughout life were not included and, in fact, would be difficult to determine retrospectively (21). Rao et al. (22) have reported on the suppressible glucagon secretion in FCPD. They found that fasting glucagon levels were similarly elevated in both Type 1 subjects and FCPD patients compared with non-obese non-diabetic controls. After glucose administration, glucagon responses were strikingly different in the two groups. In Type 1 subjects, glucagon levels rose paradoxically during OGTT while in FCPD individuals they fell after a glucose load. Rao et al. concluded that postprandial glucagon suppressibility may be responsible for the ketosis resistance seen in FCPD in combination probably with a residual insulin secretion. In the pathogenesis of FCPD, there is an impaired glucose tolerance phase that will ultimately lead to overt severe diabetes. This profile is quite similar to what has been observed in the pathogenesis of chronic pancreatitis in developed countries.

FCPD: Possible Causative Factors

The pathogenesis of FCPD is unknown. The sequence appears to be repeated pancreatic injury, which, over years, produces chronic pancreatitis with large ductal calculi and progressive destruction of islet and acinar cells (21). The most favored theories about the etiology of MRDM implicate malnutrition alone or combined with cassava consumption. Chronic alcoholism and biliary tract disease, the two main causative factors of pan-

creatic disease in Western countries, do not seem to play an important role in the causation of FCPD in the tropics. However, alcohol consumption has been reported to be related to pancreatic calcification and diabetes in some countries in Africa (23–25). We will review the evidence relating FCPD to some possible causative factors.

Malnutrition

Evidence that malnutrition or protein-calorie undernutrition may induce diabetes comes from various clinical and experimental observations. Abnormal glucose tolerance and a decreased insulin response are found in children with kwashiorkor (26–28), in adults with protein-calorie malnutrition and in monkeys subjected to protein deprivation (29). These abnormalities can persist for several months or even permanently (28, 30, 31). The exocrine and endocrine pancreas can be damaged by experimental protein-calorie malnutrition (32–36). This finding supports the notion that protein-calorie malnutrition might be implicated in the etiology of MRDM. On the other hand, the protein-energy malnutrition in FCPD could well be the effect rather than the cause in that chronic pancreatitis. Consequent maldigestion and malabsorption could itself lead to protein-energy malnutrition. The absence of FCPD in places where malnutrition is rife suggests that malnutrition by itself is unlikely to have an etiological role (9, 37). It is also possible that subclinical malnutrition may contribute to pancreatic tissue damage in FCPD. It is of interest that the Kerala State, which exhibits the highest literacy rate and the lowest infant mortality rate, has the highest prevalence of FCPD in India (38). The exact role of malnutrition in the pathogenesis of FCPD is thus far from clear.

Cassava Consumption and MRDM

The 'cassava hypothesis' has been put forward to explain the occurrence of FCPD (39). Cassava (or manioc or tapioca) is the staple food in places where FCPD occurs. It is consumed by more than 400 million people living in tropical countries (9, 11). It has been suggested that this tropical root, together with malnutrition, is the major cause of

FCPD. The geographic distribution of this form of diabetes coincides with areas where cassava is ingested associated with poor dietary protein intake. For instance, in Kerala (India) where both malnutrition and MRDM (mostly FCPD) are endemic, cassava is the staple food (40, 41). More than 70% of the total carbohydrate and 50% of the protein intake are derived from cassava in some areas, and the prevalence of FCPD is highest in the regions where most cassava is grown.

Cassava root contains 0.4% protein, 95% starch and cyanogenic glycosides, linamarin and lotaustralin. These glycosides, on hydrolysis, release hydrocyanic acid. The hydrocyanic acid is ingested and normally inactivated by conversion to thiocyanate. This chemical conversion requires conjugation with SH radicals derived from amino acid sources (methionine, cystine and cysteine) to form thiocyanate which is excreted in the urine. In protein-calorie malnutrition, there is a deficiency of these amino acids and accumulation of hydrocyanic acid may cause pancreatic damage. Animal experiments have demonstrated that cyanide can produce pancreatic damage and diabetes. McMillan and Geevarghese (42) have shown a marked reduction in urinary thiocyanate excretion in the rat when protein intake was lowered (especially during growth). They could produce marked hyperglycemia in the same animal with either parenteral or oral cyanide. It was therefore concluded that cyanide played a part in the pathogenesis of FCPD. However, none of the rats in these experiments developed permanent diabetes. Furthermore the effects were seen only with potassium cyanide and not with cassava.

The relevance of these experiments to the human situation is far from clear. The demonstration of hyperglycemia in young rats after intraperitoneal KCN is of interest but this acute effect differs from the chronic sequence of pancreatic injury in FCPD. Uncertainty regarding the cassava hypothesis is also raised by a study in which rats fed on a diet containing cassava did not show significant pancreatic damage, irrespective of whether they were malnourished or not (43). Two other studies are contrary to the hypothesis: a study from the Ivory Coast (44) has shown that the chronic pancreatitis seen in that region was not related to either kwashiorkor or cassava ingestion. A study in a rural area of Tanzania where nerve damage secondary to cassava consumption is endemic has

brought important new information. The prevalence of diabetes and IGT was low and not different from other parts of the country despite high plasma cyanide and thiocyanate levels (45). Finally, although the cassava hypothesis might explain the occurrence of FCPD in areas where the tuber is consumed, it does not explain its occurrence in other areas (e.g. Madras) where it is not (10). The possibility exists that other foodstuffs such as sorghum, ragi, jowar or certain varieties of peas may contain cyanide. Among other dietary factors, a low fat intake could be another factor responsible for the occurrence of FCPD (10).

Familial and Genetic Factors

The first report on a large series of familial cases of FCPD was published by Pitchumoni (46). Familial aggregation has also been noted by Geevarghese (47) and Balakrishnan (48). Familial occurrence suggests a hereditary etiology for FCPD. One study on gene markers using the restriction fragment length polymorphism technique suggests a genetic predisposition hypothesis for FCPD. It was found that FCPD shares susceptibility genes in common with Type 2 (class 3 of the insulin gene) and Type 1 patients (HLA-DQ β gene). More studies are needed to firmly establish a genetic basis for FCPD if any. It must however, be noted that FCPD can also occur in individuals bearing the susceptibility genes for Type 1 or Type 2 diabetes.

FCPD: Some Unresolved Questions

1. What environmental factor(s) causes the pancreatic injury? Is there a widely confirmed genetic susceptibility? Why do such a small number with apparently similar diets and nutrition develop chronic pancreatitis and diabetes?
2. What is the natural history? Of those with initial pancreatic injury, as suggested by episodes of abdominal pain in endemic areas, how many recover or how many have repeated attacks and progress to chronic pancreatitis?
3. What are the prevalence and incidence—and trends—among populations affected? Methods

exist to examine this important question in areas with a high prevalence.

4. What is the explanation for the occurrence of FCPD among the minority of non-poor and well nourished?
5. Could a more complete understanding of the pathogenetic sequence provide a basis for primary, secondary and tertiary therapeutic intervention? To the extent that environmental factors dominate, the answer is yes. However, if more money and more food is the answer there should be no illusions about the difficulty of making changes in these basic areas. Cultural and social practices are other features which are difficult to change.

Protein-deficient Pancreatic Diabetes or Protein-deficient Diabetes Mellitus (PDPD, PDDM)

The delineation of this syndrome has been largely by clinical and descriptive criteria which lack specificity (Table 18.1). The available reports neither establish nor disprove the existence of PDPD as a distinct syndrome. The reasons for this relate to the difficulty of quantitative assessment of nutrition, pancreatic function and the diabetes mellitus syndrome. It may be helpful to examine some reports on PDPD. Studies tend to be from hospital-based patients at a single point in time and few have included immunologic or genetic markers. PDPD is similar to the 'J-type' described by Hugh-Jones in Jamaica (4). It has been reported from the Ivory Coast, Ghana, Benin, Togo, Nigeria, Cameroon, Congo, Uganda, South Africa, Malawi, Tanzania, Kenya, India, Sri Lanka, Bangladesh, Thailand, Brunei, Papua, New Guinea and Fiji (1, 9, 11). Its world distribution is quite similar to that of FCPD. Its clinical features are shown in Table 18.1. The absence of recurrent bouts of abdominal pain, of intraductal pancreatic calculi and of steatorrhea differentiates PDPD from FCPD. This is, however largely arbitrary.

Ethiopia: Much Malnutrition, No PDPD?

Lester, in Addis Ababa, Ethiopia, has reported careful and longitudinal observations in 849 patients cared for in a hospital setting (49).

Malnutrition or undernutrition was widespread. BMI was less than 18 in 13% of the 849; 202 had onset before age 30; diabetic ketoacidosis was frequent, being noted in 70% of 24 patients with onset under age 10, in 27% of 40 patients with onset between age 11 and 20 and in 14% of 106 patients with onset between age 21 and 30. Lester, using the WHO criteria, classified 20% as Type 1 and 80% as Type 2 diabetes. Of the latter, 25% were actually obese. Of the 849 patients 40% 'required' insulin. Lester did not identify any patient as FCPD or PDPD.

In a subsequent study, Lester re-examined 733 consecutive patients who met the WHO criteria for diabetes in an attempt to identify those with FCPD or PCPD (50). Diabetes was diagnosed before age 30 in 202 or 26% of the total. BMI was 18 or less in 33%. No pancreatic calcification was demonstrated in 65 of the 202 patients who had X-rays of the abdomen. Painless parotid enlargement was not observed. Lester identified only 4 patients among the group of 773 with features compatible with PDPD; in none was an adequate follow-up possible. Another 8 patients showed most of the features of PDPD for a variable time period. Over time and with improved nutrition after treatment, the criteria for PDPD did not persist. Two cases showed the progression of the diabetes mellitus syndrome over several years from what appeared to be PDPD to what may be Type 1 diabetes. One case at age 14 presented with the acute diabetes syndrome without ketosis. BMI was 13; symptoms had been present over 6 months; blood glucose concentration was over 400 mg/dl (22.2 mmol/l); ketosis was absent. Insulin treatment included a dosage of 2.2 U/kg. Two years later, after food and insulin, BMI was 20.4 and insulin dosage was 1 U/kg. At age 17 this patient presented in DKA and islet cell antibodies were positive, pointing toward Type 1 diabetes. Another case is similar. This patient had a BMI of 23 before symptoms of 6 months duration led to detection of hyperglycemia without ketosis and a BMI of 13.9. Insulin dosage was 1.5 U/kg. This was compatible with PDPD. Two years later, at age 28, this patient had multiple episodes of DKA and ICA were positive. Thus, when examined longitudinally, Lester found little or no evidence for FCPD or PDPD. In this selected hospital population, information on dietary or environmental factors was limited. It is possible but unlikely that patients with FCPD or

PDPD self-selected not to seek the limited medical care available, mostly in the capital of Addis Ababa. Cassava is not part of the diet in Ethiopia. This important study provides no data on incidence or prevalence of diabetes mellitus syndromes among the people of Ethiopia.

India

In India, there have been numerous reports of PDPD or PDDM (other names have been used). These have been mostly descriptive studies of selected (hospital) patients with the features described being non-specific (Table 18.1). Ahuja's report in 1985 (51) of 15 patients studied at the All India Institute of Medical Sciences in New Delhi is noteworthy. From an unknown population base, he identified 15 patients with onset of diabetes before age 30, with BMI 19 or less, no DKA and stated insulin requirement of over 2 U/kg. Heterogeneity was indicated by pancreatic lithiasis in 4 (hence, FCPD), abnormal d-xylose absorption in 5, protein caloric malnutrition (PCM) in 5 and decreased C-peptide secretion in 9. Ahuja's data did not show the four variables separately for each patient and immunologic (ICA) or genetic markers were not reported. Hence, an accurate classification of those with and especially those without pancreatic lithiasis is difficult.

Diabetes Mellitus Syndrome Prevalence: Increased in Malnutrition?

Is the diabetes mellitus syndrome, regardless of classification, increased in humans with under-nutrition? The answer is not known and it is an important one (6). The study of the Indian Medical Research Council as reported by Gupta in 1982 is noteworthy (52). In this study the prevalence of diabetes was determined in six regions of India. Screening techniques included urine and blood glucose after ingestion of 75 g of glucose. Criteria for diagnosis differed from the present WHO recommendations (8). Yet, among 7000 (half urban, half rural) individuals over age 15 in Ahmodabad tested, the prevalence of diabetes was 14–15% in the overweight, 2–4% in those of normal weight and less than 2% in those underweight. The overall prevalence was

2.1% and was higher in urban (3%) compared to rural (1.3%) dwellers. Gupta reported a slightly increased prevalence in the rural group studied who had an estimated caloric intake of under 1500 calories daily. This difference was not a consistent finding in the other geographic regions of India.

Krishnaswami and colleagues' findings in a rural epidemiologic study in Tail Nadu, South India, are of interest (53). They screened 60% or 10 000 of the entire population of 17,431 under age 14 using qualitative urine testing 1½ hours after a meal, and 46% showed moderate or severe malnutrition. Only one boy had diabetic mellitus and this individual was known to have diabetes and was under irregular treatment. This study is noteworthy in that among a large sample of those under age 14 assessed there was considerable undernutrition and yet virtually no diabetes of any type.

PDPD: Some Unresolved Questions

1. With the available knowledge of nutrition–malnutrition, pancreatic function and the diabetes syndrome can precise, reproducible criteria be developed which will separate PDPD, if it exists, from Type 1, Type 2 and FCPD?
2. What are the prevalence/incidence, and trends, in endemic areas? Whether, even using non-specific criteria, these are increasing or decreasing along with rapid socio-economic and environmental change would be important to know. Epidemiologic techniques and methodologies exist to do this.
3. Longitudinal studies: if PDPD can be reproducibly defined (whether a distinct entity or a subset of Type 2) what is its natural history in terms of the metabolic (progressive, intermittent) and non-metabolic (micro- and macrovascular disease, neuropathy, infections) manifestations? What is the effect of optimal nutrition both acutely and permanently?
4. Can information be obtained to provide the basis for primary, secondary or tertiary intervention? To the extent that environmental factors (as apposed to genetic) dominate, the answer is probably yes.

CONCLUSIONS

In addition to Type 1 and Type 2, more diabetes syndromes have been described in the tropics and developing countries. There are numerous possible interactions between environmental/nutrition factors, heredity and pancreatic disorders and the diabetes mellitus syndrome. The major problem which accounts for the lack of precise definitions of the DMS syndromes in the malnourished is the difficulty in quantitative assessment of nutrition, pancreatic function and the diabetes syndrome in a longitudinal manner in population groups. Pancreatic beta-cell function is reduced in severe undernutrition in humans with kwashiorkor or marasmus (54,55). Limited data suggest that recovery of beta-cell function occurs if those affected do survive (55). Whether less severe undernutrition, with the fluctuations known to occur among those with marginal caloric and protein intake, affects beta-cell function, and to what degree, has not been determined in longitudinal studies. Body mass index (BMI), commonly used to assess nutrition, is an indicator of limited sensitivity, especially in studies at a single time point.

Retrospective dietary assessment is difficult and subject to error. Biochemical markers of nutritional state (plasma albumin, vitamins, liver functions, hemoglobin) which could provide added information have rarely been used. Other environmental factors have received limited consideration. Pancreatic function, both acinar and islet cell, is difficult to assess in the early phase of disease, even with all the available non-invasive and invasive technology. Late phase disease manifested by chronic pancreatitis with pancreatic lithiasis along with diabetes and malabsorption syndromes provides little information on the initial lesion and pathogenetic process.

Equally, the diabetes mellitus syndrome may be difficult to identify and classify. Classic Type 1 diabetes with acute onset with diabetic ketoacidosis along with positive immunologic (ICA+) and genetic (DR3, DR4) markers represents a fairly distinct entity; however, there is heterogeneity in the clinical manifestations and natural history of Type 1 diabetes. In contrast, Type 2 diabetes is far less specific. Even in Europe and North America, patients are encountered who, at one time point, are not easily classified as Type 1 or Type 2. Up to 20% of adults with non-acute Type 2 diabetes are

not overweight and insulin secretion is reduced to a variable degree. Such patients may present with marked hyperglycemia with or without ketosis and insulin treatment is required; with recovery *effective* treatment (as reflected by normal glycated hemoglobin) may be achieved with diet or diet plus oral hypoglycemic agents. Over time and especially with the stress of illness, surgery or pregnancy, insulin may be required. Some become C-peptide negative and require insulin on a permanent basis. These same problems of classification apply to patients in the tropical and developing world where malnutrition has been linked pathogenetically to the DMS.

This chapter examines some of the possible interactions between environmental/nutritional factors, pancreatic disease and the diabetes mellitus syndromes, and indicates some potential research avenues. Malnutrition may influence the expression of several types of diabetes. However, the evidence that diabetes can be caused by malnutrition or protein deficiency *per se* remains largely slim and speculative. This might explain why MRDM has been omitted or deleted in the new classification of the diabetes mellitus syndrome (2,3). The former subtype of MRDM, protein-deficient pancreatic diabetes (PDPD or PDDM) may be considered as a malnutrition modulated or modified form of diabetes mellitus (3). The other former subtype of MRDM, fibrocalculous pancreatic diabetes (FCPD) is now classified as a disease of the exocrine pancreas, fibrocalculous pancreatopathy, which may lead to diabetes mellitus (3). More epidemiological and basic research is needed to firmly establish MRDM as a peculiar entity.

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Type 2 Diabetes and Obesity

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The association between obesity and Type 2 diabetes (non-insulin-dependent diabetes mellitus) has been observed in both cross-sectional (1–13) and prospective studies (5, 14–22). The consistency of the association across populations using different measures of fatness and criteria for diagnosing Type 2 diabetes reflects the strength of the relationship. In fact it is often stated that obesity is the most important risk factor for Type 2 diabetes (23). While there is a continuous increase in risk of Type 2 diabetes associated with rising body mass, the relationship is complicated by the effects of duration of obesity, distribution of body fat, physical activity, ethnicity, family history of Type 2 diabetes, and possibly foetal and early infant growth rate, all of which contribute to the risk of Type 2 diabetes, and modify the effect of fat mass *per se* (24, 25). This review will focus on these confounding factors and how they might modify the obesity–Type 2 diabetes relation.

DURATION AND TIMING OF OBESITY

Although the duration of obesity is considered important in determining the risk of obesity-associated conditions, including Type 2 diabetes, there is little information available to quantify this relationship. Even in most prospective studies the actual onset of obesity is not measured and can only be obtained by recall. Moreover, if weight is changing it is difficult to differentiate between the effects of degree and duration of obesity.

Weight loss associated with the onset of Type 2 diabetes (20, 26) means that the association of obesity with Type 2 diabetes prevalence is generally weaker than its association with incidence. Results from a prospective study in Mauritius

indicate clearly that subjects with newly diagnosed or known diabetes at baseline lost weight over the subsequent 5 years while those with normal or impaired glucose tolerance at baseline gained weight (Figure 19.1a). Although the mean weight loss of around 1 kg in diabetic subjects is small, weight loss may have already occurred in association with hyperglycaemia prior to these measurements being made.

In a study of 2041 Israeli Jews, Modan et al. (22) found that the main determinant of the incidence of Type 2 diabetes over a 10-year study period was the BMI at baseline, rather than the BMI at follow-up when glucose tolerance was measured. Moreover, weight changes had little effect and most of the incident cases of Type 2 diabetes had not changed weight—BMI had been at 27 kg/m² or greater for at least the period of the study. Obesity lasting for less than 10 years was not associated with a major increase in diabetes incidence compared with that found in subjects who had remained slim (BMI < 23 kg/m²), and weight loss from a high level to an intermediate level of BMI did not seem to be beneficial. Incident-impaired glucose tolerance was associated with both concurrent and prior BMI, as would be expected if the weight loss that weakens the association of Type 2 diabetes with concurrent BMI only occurs after glucose tolerance has deteriorated to frank diabetes.

Baseline body mass index was strongly related to the incidence of Type 2 diabetes in a study of 3137 Pima Indians but there was little association between diabetes prevalence and concurrent obesity (27). In a small group of subjects with BMI data from 4 years before diagnosis to 2 years after, there was a clear pattern of weight gain in the 4 years preceding diagnosis, followed by a

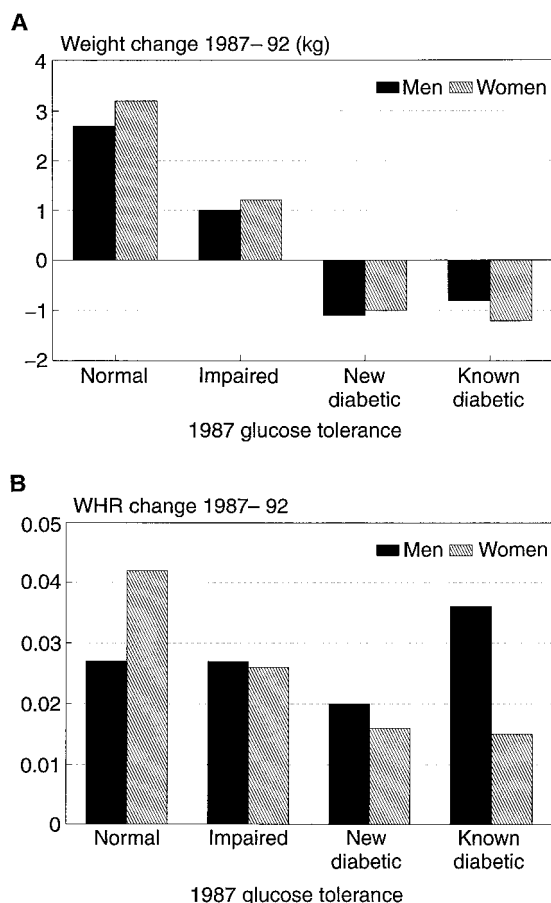


Figure 19.1 (A) Weight change over 5 years by baseline glucose tolerance status in 1987 in the multiethnic population of Mauritius ($n = 1678$ for men and 1917 for women) (B) Waist/hip ratio (WHR) change over 5 years by baseline glucose tolerance status in 1987 in the multiethnic population of Mauritius ($n = 1675$ for men and 1906 for women)

weight loss in the following 2 years, in subjects 25–44 years at time of diagnosis. Older subjects did not show the same weight increase prior to diagnosis, but weight also fell afterwards (27). Older subjects developed diabetes at a lower BMI than younger individuals, suggesting that the age-related deterioration in insulin sensitivity enables the development of diabetes at lower levels of adiposity than that required for the development of diabetes in younger subjects.

In contrast to the results in Pimas, Tai et al. (5), found that BMI was similarly associated with the prevalence or 4-year cumulative incidence of diabetes, with odds ratios of 1.12 and 1.14

respectively for a 1 unit increase in BMI in slim (mean BMI 23 kg/m²) Chinese over the age of 40 years. Weight loss is associated with diabetes in the Pimas (27), and in obese Micronesian Nauruans (26), and is also predicted by initial weight (26, 28). Thus more obese populations may show a greater weight loss in association with Type 2 diabetes. However, diabetes is associated with weight loss in Chinese in Mauritius (28) who are of a similar level of obesity to the population studied by Tai et al. (5). Stronger cross-sectional associations could be expected in populations where diabetes was diagnosed earlier and treated better, so as to minimize hyperglycaemia and weight loss.

Among women of the Nurses' Health Study Cohort, Colditz et al. (18) found a strong association between baseline obesity at 30–55 years of age and self-reported incidence of Type 2 diabetes over 8 years follow-up. Body mass index at age 18 was also related to Type 2 diabetes incidence, but the effect was no longer significant after adjusting for current BMI. However, weight gain after age 18 was an important determinant of Type 2 diabetes risk after adjusting for BMI at age 18. In the short term, weight gain during the first 4 years of the study also increased the risk of incident diabetes in the following 4 years. In a cohort of male health professionals aged 40–75 years at baseline and followed for 5 years, the same strong association between baseline obesity and self-reported Type 2 diabetes incidence was observed. Body mass index at age 21 and weight gain since age 21 were independent predictors of diabetes (19).

Indirect evidence for the importance of duration of obesity on Type 2 diabetes is provided by studies in Israelis and Mauritians. Modan et al. (22) found increased risk of Type 2 diabetes in subjects who had lost weight to reach a specific BMI class relative to those who had remained stable within that class. Those with a stable BMI had in turn a greater risk of Type 2 diabetes than those who had increased their BMI class, indicating that weight gain per se was not associated with increased risk of Type 2 diabetes. Similar results for the multiethnic population of Mauritius are indicated in Figure 19.2. For any level of BMI at follow-up, the greatest prevalence of Type 2 diabetes (newly diagnosed and known) was associated with weight loss since baseline (lost > 1 kg), and the least with weight gain (gained > 1 kg). Subjects who gained weight to reach a specific

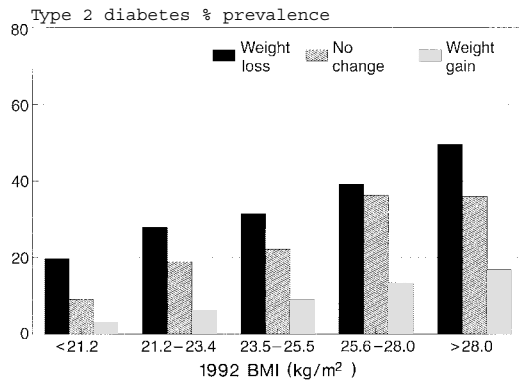


Figure 19.2 1992 prevalence of non-insulin-dependent diabetes mellitus (both newly diagnosed and known) (Type 2 diabetes) by body mass index (BMI) in 1992 and weight change between 1987 and 1992 in the multiethnic population of Mauritius ($n = 3647$)

BMI level would not have been at that level for as long as those who had remained stable at that BMI, so would have a lower risk of Type 2 diabetes. Subjects who had lost weight to reach a specific BMI would have had some duration of an even greater degree of obesity which would contribute to the higher prevalence of Type 2 diabetes in this group compared with the weight maintainers or gainers at the same BMI level.

In one of the few reports to actually examine the levels of glucose tolerance associated with different duration of self-reported obesity (based on percentage of standard weight ranging from 14 to 137% overweight), Ogilvie (29) observed that it took 5–18 years of obesity for glucose intolerance to develop, and 12–38 years for diabetes to occur. In contrast to other studies, the degree of obesity was not associated with glucose tolerance.

Evidence for a specific effect of weight gain on Type 2 diabetes comes from two American studies, where self-reported weight gain throughout adulthood or immediately prior to the study period was associated with increased risk of Type 2 diabetes independent of BMI in early adulthood (18, 19). Harris (30) also indicated that weight gain between 25 and 50 years of age was a risk factor for Type 2 diabetes, and Di Pietro et al. (31) have shown a rapid weight gain between puberty and age 25 years in a cohort of Swedish subjects who were overweight in childhood and went on to develop diabetes. As mentioned earlier, weight gain also preceded Type 2 diabetes in Pima Indians (20, 27).

An association between weight gain and Type 2 diabetes could be explained in a number of ways. It is possible that weight gain in the short-term could lead to β -cell decompensation, glucose intolerance and Type 2 diabetes in already susceptible individuals, with the BMI at which this occurs determined by other factors such as genotype, age or physical activity. Alternatively, weight gain could be a result of the hyperinsulinaemia that precedes Type 2 diabetes (32–34). Thirdly, behavioural factors resulting in weight gain, such as dietary changes or reduced physical activity may also promote the development of Type 2 diabetes.

FAT DISTRIBUTION

Anthropometric measures of body fat distribution (e.g. waist/hip ratio (WHR), subscapular/triceps skinfold ratio (STR), waist/thigh ratio) or computed tomography (CT) scan measures are associated with risk of diabetes, both in longitudinal (14–17) and cross-sectional (2, 6–13) studies. The effects of fat distribution are generally independent of measures of overall fatness (2, 6–8, 10, 11, 13–17), and in many cases fat distribution appears more important (6–11, 20).

Is Fat Distribution More Important than Overall Fatness?

Shelgikar et al. (10) found that WHR was more strongly associated with the prevalence of impaired glucose tolerance and diabetes than was BMI in Asian Indians in India. McKeigue et al. (11) confirmed the greater importance of WHR for prevalence of glucose intolerance in Asian Indian and European men and women in London. Waist/thigh ratio was also more strongly associated with Type 2 diabetes than was BMI in Pima Indians, especially those between 25 and 34 years of age (20). Sosenko et al. (35) examined the usefulness of BMI, WHR, and STR as screening tools for Type 2 diabetes in a group of Mexican American and non-Hispanic white volunteers. Both WHR and STR were better markers of Type 2 diabetes than was BMI. With increasing age, the associations with both WHR and BMI were attenuated.

Longitudinal data are less consistent. Among men of the Normative Aging Study who were

followed over 18 years, fat distribution as measured by the ratio of abdominal circumference/hip breadth was a stronger predictor of both Type 2 diabetes and IGT than was BMI (17), but in prospective studies of Swedish men (14), and women (15), BMI and WHR were of similar importance. The tendency for markers of fat distribution to be more strongly associated with Type 2 diabetes prevalence than is BMI could be explained if a fall in BMI but not WHR was associated with the onset of diabetes. This hypothesis is supported by data from Mauritius. Figure 19.1 (A & B) shows a decrease in BMI but not WHR over 5 years in people with newly diagnosed or known diabetes.

Gender, Fat Distribution and Diabetes

Consideration of the literature as a whole suggests that both overall adiposity and fat distribution are independently important risk factors for Type 2 diabetes, in both men and women (2, 6–8, 10, 11, 13–17). However, some studies suggest gender differences in the relative importance of overall fatness and fat distribution. In a study of Type 2 diabetes prevalence in Mauritius, Dowse et al. (6) found that WHR and BMI were independently associated with Type 2 diabetes, after controlling for age, family history of diabetes and physical activity. The effect of WHR was greater than that of BMI in women, while in men the converse was found. In Brazilian and Chinese adults BMI and WHR were independently associated with Type 2 diabetes in women but only WHR remained significant in multivariable analysis in men (7, 8). Haffner et al. (36) found that overall obesity was independently associated with Type 2 diabetes prevalence in Mexican American and non-Hispanic white men and women, but central obesity (subscapular/triceps skinfold ratio, STR) was only significant in women. This led them to propose a plateau effect of centrality, whereby above a certain level of STR, i.e. that achieved in most men, there was no further increase in rates of Type 2 diabetes.

Fat deposition in men is generally abdominal, thus waist circumference or WHR would be expected to correlate strongly with overall obesity, reducing the chance of both measures being significant in multivariable analyses. In women

there is more variation in fat distribution, so measures such as WHR would be expected to differentiate between higher and lower risk individuals within a given level of overall fat mass, and it is therefore more likely to be independently significant. This is shown in Mauritius where correlation between BMI and WHR was much stronger in men ($r = 0.45$) than in women ($r = 0.28$). Similar results were also found in Nauruans (37). The lack of independent association of Type 2 diabetes prevalence with fat distribution in men may therefore be due to the limited range in abdominal obesity, or its correlation with overall obesity, rather than the higher degree of abdominal obesity.

Interestingly, waist/hip ratio has been observed to be a better indicator of CT measured abdominal fat in men than women (38), suggesting that the association of WHR with metabolic aberrations including Type 2 diabetes, should in fact be stronger in men. However, as discussed above, this does not appear to be the case.

Fat Distribution, Overall Fat Mass and Type 2 Diabetes

Evidence for a greater effect of fat distribution at higher levels of overall obesity is available from a number of sources. In a study of over 15 000 women attending weight loss groups, the self-reported prevalence of diabetes was associated with both WHR and BMI but the increase in prevalence across tertiles of WHR was steeper in the most obese group (12) suggesting an interaction between BMI and WHR. Among the Swedish men followed up by Ohlson et al. (15), the incidence of Type 2 diabetes was higher for each successive tertile of WHR within each tertile of BMI, but the increase in incidence with increasing WHR was only about 6-fold in the lowest BMI tertile compared with a 30-fold increase in the top tertile of BMI. Schmidt et al. (8) found that the association of WHR with Type 2 diabetes prevalence was 1.5 times stronger in obese women compared with lean, while the reverse situation was found in men. In contrast, data from the Pima Indians indicate that the association of Type 2 diabetes with fat distribution weakened with increasing BMI or age (20), while in each of Indian, Creole and Chinese Mauritians there was

no evidence for any interaction between BMI and WHR (6).

The apparently greater effect of WHR in more obese subjects appears in contrast to the results of Busetto et al. (38), who showed that the relationship between WHR and intra abdominal fat area was stronger in lean subjects compared with obese. If WHR is important because it is a marker of intra-abdominal fat, its association with metabolic disturbances might be expected to be stronger in lean subjects, where it is a more precise marker.

In more specific studies Bonora et al. (39) measured glucose tolerance in 18 normal weight and 18 obese women in relation to WHR, STR or visceral/subcutaneous abdominal fat ratio by CT scan. Fasting glucose utilization did not vary between the two groups, but during euglycaemic insulin clamp studies only total body fat was related inversely to glucose utilization in the lean women, while in the obese only fat distribution (inversely), and not total fat was important. Landin et al. (40) also found that the effect of WHR was greater in obese than lean women. Similarly in men, Pouliot et al. (41) found that fat distribution by CT scan was related to glucose and insulin metabolism only in obese men ($n = 58$) and not in lean men ($n = 29$). These results suggest that a reasonably high level of overall obesity is required to facilitate the effects of central obesity. On the other hand, in extremely obese subjects with a tendency to abdominal adipose distribution, increases in adiposity beyond a certain point may result in fat being accumulated in other areas, leading to a proportional reduction in intra-abdominal fat in association with increasing BMI. The risk of Type 2 diabetes may continue to increase as body fat content rises, weakening the association between fat distribution and Type 2 diabetes. Such a scenario could be envisaged in the Pimas and observations in Western Samoans support this hypothesis.

In summary, both overall obesity and fat distribution contribute to the risk of Type 2 diabetes, but their relative importance appears to vary in relation to whether incidence or prevalence of Type 2 diabetes is used, the gender of the individuals examined or their degree of obesity. However, strategies to reduce Type 2 diabetes risk via diet and physical activity can reduce both overall and abdominal obesity and improvements in both should be sought.

GENETIC SUSCEPTIBILITY, OBESITY AND TYPE 2 DIABETES

Genetic susceptibility to Type 2 diabetes can be studied at the population level, where it is believed that certain ethnic groups such as Native Americans and Micronesians (Nauruans) have enhanced susceptibility to Type 2 diabetes (24); or at the personal level where family history of Type 2 diabetes is a well-recognized risk factor (1, 4, 6, 24, 27, 42).

Family History

Fujimoto et al. (43) observed similar levels of both general adiposity and fat distribution across normal and Type 2 diabetes men with a positive family history of diabetes, while in men with no family history of diabetes those with Type 2 diabetes were fatter. This was supported by the findings of Lemieux et al. (44). In this study 104 men were divided first into those with 'normal' or 'altered' insulin and glucose during an oral glucose tolerance test. Among men with 'high' levels of insulin or glucose or both, those with a negative family history of diabetes had a higher BMI at age 20, and a lower current ratio of abdominal/thigh adipose tissue than men with normal glucose metabolism. These two studies suggest that a higher level of obesity is required for the development of diabetes in individuals without a genetic predisposition to Type 2 diabetes. Consistent with this, Kuzuya and Matsuda found that patients with Type 2 diabetes who had a definite history of obesity had a lower prevalence of family history of diabetes than those who had not been obese (45). Similarly, the siblings of lean diabetics had a higher prevalence of Type 2 diabetes than the siblings of obese diabetics in the study of Lee et al. (46), and Hanson et al. (47) observed that the prevalence of Type 2 diabetes in Pimas was higher in relatives of leaner Type 2 diabetes cases than in relatives of more obese cases. In the latter three studies it appears that leaner cases of Type 2 diabetes did not need to accumulate as much adipose tissue as obese diabetics because they had a greater familial predisposition contributing to Type 2 diabetes risk. Among elderly men in the Zutphen study, obesity did not appear to be related to diabetes, irrespective of family history

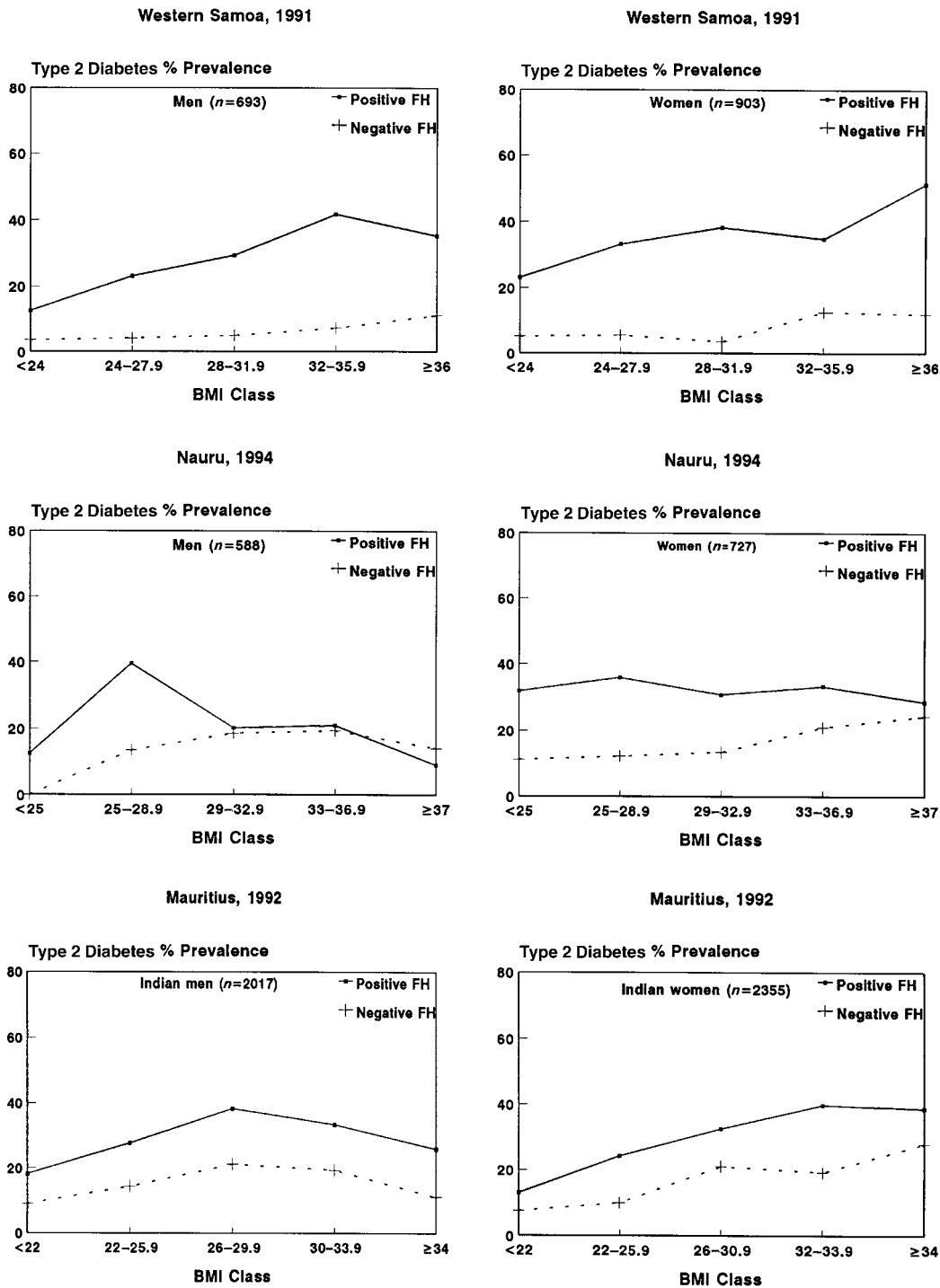


Figure 19.3 Prevalence of Type 2 diabetes (non-insulin-dependent diabetes mellitus) by body mass index (BMI) and family history of Type 2 diabetes, in men and women of three populations at high risk of Type 2 diabetes

(48). However, it is possible that these associations change with age and that other risk factors, such as an age-related deterioration in insulin sensitivity, become more important.

In an earlier study of Pima Indians, a clear interaction was demonstrated between family history and BMI in relation to the incidence of Type 2 diabetes, such that a positive family history enhanced the effect of BMI on Type 2 diabetes risk (27). Such an interaction has not been observed in other populations. Ohlson et al. did not find a significant interaction in Swedish men who were followed for 13.5 years (42), and for data from Western Samoa, Nauru and Mauritius (Figure 19.3), it was only in Nauruan women that the interaction of family history and BMI was significantly ($p = 0.023$) associated with Type 2 diabetes prevalence.

Ethnic Group

Among the biracial population of the San Antonio Heart Study (49), it is clear that the prevalence of Type 2 diabetes is higher in Mexican Americans than in non-Hispanic whites. This difference may be attributed to a number of factors, including the greater degree of obesity among Mexican Americans. However, even within each of three levels of obesity (based on sum of skinfolds in non-Hispanic whites) the prevalence of Type 2 diabetes was higher in Mexican Americans, suggesting increased genetic susceptibility, or increased levels of other risk factors. A more recent study among similar racial groups in Colorado also indicated that the risk of Type 2 diabetes was higher in Hispanics than in non-Hispanic white Americans, independent of BMI and other risk factors (1).

Asian Indians also appear to have an elevated risk of Type 2 diabetes compared to members of other ethnic groups at similar or lower levels of BMI (50–52). When these studies were conducted the measurement of body fat distribution was not as common as it is today, but in Fiji it was observed that although Indians had lower BMI than Melanesians, their triceps skinfold thicknesses were greater, consistent with greater muscularity among Melanesians (52). Shelgikar et al. have since shown that for Asian Indians, WHR is more important than BMI in defining risk of Type 2 diabetes in a cross-sectional study (10). This was confirmed by

McKeigue et al. (11) in a study which also found that Indians had a greater WHR than Europeans for the same level of BMI. Thus the differential distribution of body fat appears to play a role in the increased susceptibility of Asian Indians to Type 2 diabetes and cardiovascular disease (53).

There is evidence to suggest that in some other ethnic groups the risk associated with a central distribution of body fat is relatively low. Among non-Hispanics in Colorado the diabetes risks associated with BMI, triceps and subscapular skinfold thicknesses, family history and income were similar to those found in Hispanics. However, a 1 unit increase in either WHR or STR was associated with a greater risk of Type 2 diabetes among non-Hispanic whites than among Hispanics (1). Similarly, upper body obesity was more closely associated with increased concentration of insulin and glucose in the blood, and reduced insulin sensitivity by the minimal model method, in obese Caucasian compared to African American women (54). This metabolic study, along with the study of Marshall et al. (1) suggest that Caucasians may be more susceptible to the effects of fat distribution than some other ethnic groups.

PHYSICAL ACTIVITY, OBESITY AND TYPE 2 DIABETES

Obesity and physical activity have been found to be independently associated with both prevalence (6, 55) and incidence (56–60) of Type 2 diabetes in men and women. Physical activity may lower Type 2 diabetes risk via reduced total body fat (55, 56, 58–62) and less abdominally distributed fat (55, 58, 61, 62), and/or through its action in improving insulin sensitivity (61, 62). These mechanisms are closely linked, but the independent effects of activity and obesity suggest that physical activity can modify the risk of Type 2 diabetes associated with a given level of obesity.

MECHANISMS LINKING OBESITY AND TYPE 2 DIABETES

Thrifty Genotype

Neel (63, 64) argued that a disease such as diabetes which appears to reduce reproductive rates must

have, in the past, conferred some survival advantage to become so prevalent. Neel's thrifty genotype hypothesis suggests that a metabolism adapted to survival under 'feast or famine' conditions, by efficient storage and utilization of energy, would lead to obesity and Type 2 diabetes under conditions of ample food and lower physical activity (63). The high rates of obesity and Type 2 diabetes among indigenous populations such as American Indians and Pacific Islanders who have undergone rapid modernization, are thought to be consistent with the thrifty genotype hypothesis (65). Hyperinsulinaemia, and/or relative insulin resistance in skeletal muscle may be the basis for obesity and the vicious cycle of increasing insulin resistance and compensatory hyperinsulinaemia that eventually lead to β -cell failure and Type 2 diabetes (65). However, recent studies have shown that low insulin levels and relative insulin sensitivity increase the risk of weight gain (66–69), and that insulin resistance may in fact act to limit weight gain in obese individuals (68). Careful longitudinal studies are required in order to increase our understanding of the metabolic pathways leading to obesity and glucose intolerance in humans (66).

Animal studies have provided evidence for common genetic causes for obesity and glucose intolerance, but the situation in humans is likely to be more complex. Single gene mutations in the *ob/ob* and *db/db* mice lead to early weight gain and glucose intolerance (70). The Israeli sand rat (*Psammomys obesus*) is used as a model of the thrifty genotype. In the wild, sand rats living on a diet of saltbush remain lean and normoglycaemic. However, on a diet of laboratory chow sand rats develop obesity, insulin resistance, glucose intolerance and diabetes (71).

Leptin

Leptin, the product of the *ob* gene, has been shown to reduce energy intake and body weight in *ob/ob* mice (72–75), but not in *db/db* mice (72, 74). A truncated form of leptin is produced by adipose tissue in *ob/ob* mice (76), while *db/db* mice appear to have a defect in the hypothalamic leptin receptor (77, 78) and have relative hyperleptinaemia (78). Obese humans (79–81) and sand rats (82) also have elevated leptin levels, consistent with a

receptor defect. Such a defect could be part of the expression of the thrifty genotype.

CONCLUSION

Obesity is clearly associated with an increased risk of Type 2 diabetes, and the longer the duration and greater the degree of obesity, generally the higher the risk. Prospective studies show a stronger relationship between obesity and Type 2 diabetes than cross-sectional studies because the onset of Type 2 diabetes tends to be associated with weight loss. Waist/hip ratio on the other hand, may remain high after Type 2 diabetes is diagnosed, thereby showing a stronger association than does BMI in cross-sectional studies. Overall body mass and abdominal fatness are more likely to contribute independently to the risk of Type 2 diabetes in women than in men, possibly because the two measures are more strongly correlated in men than in women.

Familial propensity to Type 2 diabetes and obesity are two of the factors that contribute to risk of Type 2 diabetes. Where Type 2 diabetes is associated with a strong family history of diabetes, it may occur at a lower level of obesity. Ethnic groups also differ in the degree of diabetes risk associated with similar levels of obesity, whether due to genetic susceptibility or the presence of other risk factors.

Obesity and Type 2 diabetes may be manifestations of the same thrifty genotype, characterized by insulin resistance and hyperinsulinaemia, but the likelihood of a simple genetic explanation seems low. Single gene defects in the leptin receptor or the leptin molecule appear to cause both obesity and glucose intolerance in animal models. The role, if any, of leptin in producing obesity and Type 2 diabetes in humans remains to be elucidated.

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Epidemiology of the Insulin Resistance Syndrome

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INTRODUCTION

The insulin resistance syndrome, otherwise known as the plurimetabolic syndrome or 'Syndrome X' as formalized by Reaven (1), has provided a unifying hypothesis for the genesis of cardiovascular disease (CVD), essential hypertension and non-insulin-dependent (Type 2) diabetes. Using clinical, experimental and epidemiological evidence, Reaven hypothesized that chronic hyperinsulinaemia was a response to the resistance to insulin-stimulated glucose uptake (1): this hyperinsulinaemia may prevent the frank decompensation of glucose homeostasis, but it is also associated with (perhaps causally), glucose intolerance, dyslipidaemia (in particular hypertriglyceridaemia and hypo-HDL-cholesterolaemia) and elevated blood pressures; these abnormalities constituted Reaven's first definition of 'Syndrome X'. Zimmet and Björntorp

observed that the characteristics of this syndrome were also associated with abdominal adiposity (2, 3). More recently, Reaven extended DeFronzo's 'triumvirate: beta-cell, muscle, liver: collusion responsible for non-insulin dependent diabetes' (4) to include the 'fourth Musketeer'—the adipose tissue (5). Reaven also included additional elements in the syndrome: hyperuricaemia, plasminogen activator inhibitor 1 (PAI-1) and obesity (6). The list of anomalies associated with the syndrome continues to grow: microalbuminuria has been suggested (7), and small dense low-density lipoprotein (LDL) has also been proposed (8).

Reaven's unifying hypothesis created a lot of interest, and provided coherent arguments in agreement with previous observations of researchers such as Himsworth, who proposed that diabetic patients should be classed as either insulin-sensitive or insulin-insensitive (9); Vague, who noted the association between central adiposity, diabetes and atherosclerosis (10); Crepaldi, who described the 'plurimetabolic' syndrome; and Modan, who concluded that insulin resistance and/or hyperinsulinaemia may be the link between hypertension, obesity and glucose intolerance (11).

DEFINITION OF THE INSULIN RESISTANCE SYNDROME

While there is agreement that there is a clustering of abnormalities in the insulin resistance syndrome, the elements included in epidemiological studies describing the syndrome almost always include insulin, glucose, triglycerides, HDL-cholesterol and blood pressures; the other elements differ from study to study.

1988 – Reaven	insulin resistance hyperinsulinemia impaired glucose tolerance hyper VLDL triglycerides hypo HDL-cholesterolemia hypertension
1989 – Zimmet 1990 – Björntorp	central adiposity
1990 – Haffner	microalbuminuria
1993 – Reaven	hyperuricemia plasminogen activator inhibitor 1 (PAI-1) obesity
1995 – Haffner	small dense LDL

Figure 20.1 The insulin resistance syndrome

Further, there is no consensus as to the level at which each of the elements constitutes an abnormality. Often when the syndrome is described, an abnormality for a given element is defined according to the percentiles of the observed distribution or according to threshold values; sometimes these are defined by consensus groups for the treatment of the various diseases such as diabetes, hypertension, dislipidaemia.

When does an individual have the syndrome? This can be defined in a number of ways, for example

- all the constituent elements elevated
- at least two of the elements of the syndrome elevated
- two or three specific elements elevated

Some authors have used a scoring procedure to quantify the syndrome, counting the number of abnormalities—using their own definition of an abnormality and then giving an equal weight to each of the abnormalities (12, 13). The BIGPRO clinical trial aimed to select insulin-resistant but non-diabetic subjects on the basis of central adiposity—a waist/hip ratio of ≥ 0.95 for the men age 35–60 years, and ≥ 0.80 for the women aged 40–65 years (14, 15); these criteria resulted in the selection of subjects who were not only centrally obese but also obese, with an average BMI of 33.1 kg/m^2 , hyperinsulinaemic with a mean fasting insulin of 96 pM , but with mean lipid concentrations and arterial pressures within the normal range (15). The insulin resistance syndrome was evident: 64% of these subjects had hyperinsulinaemia (see definitions in Figure 20.2), 58% had two or more of the five measured abnormalities of the syndrome, only 15% had no abnormality (16).

The final definition of the syndrome will only be established once the pathophysiology is understood.

MEASURING THE ELEMENTS IN THE INSULIN RESISTANCE SYNDROME

Evaluating Insulin Resistance

Insulin resistance is the key element in the syndrome. While the euglycaemic hyperglycaemic clamp has become the gold standard for the measurement of insulin resistance (17), the frequently sampled intravenous glucose tolerance test

(FSIGTT) with minimal model analysis (18) is also used, even if the physiological relevance of these techniques might be disputed (19). While the clamp method may be feasible for explanatory clinical studies, the sophistication and the cost of the technique, as well as the number of subjects often included in epidemiologic studies, make it difficult in practical terms.

The measures of insulin sensitivity provided by these two methods are not identical. Saad, using an insulin modified FSIGTT, found correlation coefficients between the clamp method and the 22 or 12 sample minimal models of 0.53 or 0.53 respectively, in normal glucose-tolerant subjects, and for the impaired glucose tolerant, 0.48 or 0.58 (20, 21). The correlation coefficients were lower in the diabetic subjects, 0.41 and 0.30 respectively.

A number of authors have looked at the question as to which simple index of glucose and insulin concentrations (at fasting and during a 2 hour oral glucose tolerance test) best reflects insulin resistance as measured by the euglycaemic hyperinsulinaemic clamp technique and by frequently sampled intravenous tolerance tests. The literature provides a partial response, although the correlations are far from perfect (Table 20.1).

In non-diabetic subjects, clamp studies have shown correlation coefficients between insulin sensitivity and fasting insulin ranging from -0.25 to -0.68 , with higher coefficients in the normal glucose tolerant than in the impaired glucose-tolerant subjects (Table 20.1). In the one clamp study where the 2 hour insulin concentration was measured, the correlation was a little higher than for fasting insulin, except in the diabetic subjects, where it was halved (22).

Insulin sensitivity was measured by the intravenous tolerance test by Kahn and by Phillips and the correlation coefficients with fasting insulin concentrations were of a similar order to that from studies with the clamp (19, 25). Phillips also gave correlation coefficients with the product of fasting insulin and glucose, an index of insulin resistance derived from the HOMA (Homeostasis Model Analysis) (28) (Table 20.1). For impaired glucose-tolerant subjects, the 2 hour insulin was the most correlated measure.

There was a series of letters in *Lancet* which discussed the 'empirical fasting insulin resistance index' (FIRI): the product of fasting plasma insulin and glucose normalized to have means values of 5

Table 20.1 Pearson correlation coefficients between measures of insulin sensitivity and various parameters from a 2 hour oral glucose tolerance test, using insulin and glucose concentrations at fasting, 60 min and 120 min (I0, I60, I120, G0, G120)

	I0	I60	I120	G0	G120	I0 × G0	I0/G0	Method to determine sensitivity
Normal glucose-tolerant								
Laakso, * 1993 (22)	−0.68	−0.58	−0.74					Hyperinsulinaemic euglycaemic clamp
Saad, 1994 (20)	−0.61							Hyperinsulinaemic euglycaemic clamp
Phillips, * 1994 (19)	−0.57		−0.39	−0.46	−0.38	−0.61	−0.51	% decline in glucose per min, 3–15 min after a short intravenous insulin tolerance test
Anderson, 1995 (21)	−0.53							Hyperinsulinaemic euglycaemic clamp
Cleland, * 1996 (23)						FIRI ** = −0.67	−0.56	Hyperinsulinaemic euglycaemic clamp
Impaired glucose-tolerant								
Laakso, * 1993 (22)	−0.47	−0.60	−0.54					Hyperinsulinaemic euglycaemic clamp
Saad, 1994 (20)	−0.31							Hyperinsulinaemic euglycaemic clamp
Phillips, * 1994 (19)	−0.37		−0.62	−0.39	−0.40	−0.42	−0.29	% decline in glucose per min, 3–15 min after a short intravenous insulin tolerance test
Anderson, 1995 (21)	−0.25						−0.27	Hyperinsulinaemic euglycaemic clamp
Non-diabetic subjects								
Bogardus, 1989 (24)	−0.66							Hyperinsulinaemic euglycaemic clamp
Kahn, * 1993 (25)	−0.73							Intravenous glucose tolerance test, Bergman minimal model
Duncan, 1995 (26)						FIRI = −0.79		Intravenous glucose tolerance test, Bergman minimal model
Del Prato, 1996 (27)						FIRI = 0.035		Hyperinsulinaemic euglycaemic clamp
Non-insulin dependent diabetes								
Laakso, * 1993 (22)	−0.56	−0.27	−0.23					Hyperinsulinaemic euglycaemic clamp
Saad, 1994 (20)	−0.54							Hyperinsulinaemic euglycaemic clamp
Anderson, 1995 (21)	−0.55						−0.59	Hyperinsulinaemic euglycaemic clamp

* Laakso and Phillips: logarithms of insulin and glucose.

Kahn: logarithms of both insulin and the insensitivity sensitivity index.

Cleland: logarithm of FIRI.

** FIRI = empirical fasting insulin resistance index = $I_{0 \times G0} / 25$, I0: $\mu\text{U/ml}$, G0: mM both normalized to have mean values of 5.

mU/l and 5 mM respectively, with a reference range centred around unity: $\text{FIRI} = (G0 \times I0) / 25$ (23, 26, 27). Duncan found in normal glucose-tolerant subjects a correlation of -0.79 with insulin sensitivity, estimated from the minimal model (26). However, using a 120 min euglycaemic, hyperinsulinaemic clamp methodology, Del Prato found a correlation of only 0.035 (27). In contrast, Cleland, using a 180 min euglycaemic, hyperinsulinaemic clamp, found a correlation of -0.67 , using the logarithm of the index (23). The difference between these two latter studies may be because of the length of the clamp and the fact that Del Prato did not take logarithms for the correlation coefficient.

An additional problem is the assay method for insulin concentrations—it is not always clear whether the above studies used an assay specific for insulin. Phillips assayed insulin, split proinsulin and proinsulin (19); while insulin correlated well with insulin sensitivity, $r = -0.57$ and $r = -0.37$ respectively for normal and impaired glucose-tolerant subjects, split proinsulin ($r = -0.50$,

-0.62 respectively) had higher correlations than proinsulin ($r = -0.36$, -0.25). Thus, while split proinsulin might be a useful additional parameter to evaluate insulin resistance in impaired glucose-tolerant subjects, in normal subjects the correlation with insulin was equally good.

In summary, fasting insulin is a surrogate measure of insulin resistance in the normo-glucose-tolerant subject, but it does not perform as well in either the impaired glucose-tolerant or in non-insulin-dependent diabetic subjects (29). The FIRI measure requires further investigation.

Even if it were possible to perform the clamp or the intravenous glucose tolerance test methodology in epidemiological studies, there is no agreed limit for 'insulin insensitivity'.

Hyperinsulinaemia

For insulin, the variability between assays would render the definition of a universal threshold

difficult (30). However, for a given study, the laboratory quality control should ensure that the values are internally consistent. The nonspecificity of the great majority of insulin assays has been called into question. Haffner (31) showed that in non-diabetic Mexican Americans and non-Hispanic whites, the ratio of pro-insulin to insulin was 7% in normal glucose-tolerant subjects, in impaired glucose-tolerant subjects 9%, and much higher in the diabetic subjects (31%). Given the great variability in insulin assays between sites, this would appear to be of minor importance in the non-diabetic subjects. Wherever fasting insulin concentrations or those following an oral glucose tolerance test (and at what time interval) were used has not been mentioned in the definition of the syndrome, it has usually been assumed that the basal or fasting rate is to be used.

Impaired Glucose Tolerance

The biological assays for glucose may be sufficiently standardized now, so that glucose levels can be compared across studies. The World Health Organization definition for 'Impaired glucose tolerance', namely a 2 hour plasma glucose concentration ≥ 7.8 mM (140 mg/dl) following a 75 g oral glucose tolerance test (32), is presumably the reference intended by Reaven. Given that about 30% of subjects with impaired glucose tolerance may eventually progress to diabetes (33), perhaps the criteria for this element could be lower. Recent data from the Hoorn Study gave a very high annual progression rate from impaired glucose tolerance to diabetes, of 14% per year in 50–75-year-old subjects (34); there was a marked increase in the incidence for baseline 2 hour glucose concentrations above 9.4 mM (170 mg/dl), with a conversion rate of almost 30%. This high progression rate may be in part due to the fact that the impaired glucose-tolerant subjects were those identified following two oral glucose tolerance tests—thus the subjects are likely to be at a higher risk. In middle-aged men from the Paris Prospective Study the risk of diabetes increased exponentially with increasing 2 hour glucose greater than 6.1 mM (110 mg/dl) (35), see Figure 20.2, even though the conversion rates were not high.

Two hour glucose concentrations following an oral glucose tolerance test are not always available from epidemiologic studies. If the diagnosis of diabetes is based on the specific complications of diabetes, retinopathy and nephropathy, then fasting glucose, 2 hour glucose and HbA1c have been shown to be equally predictive of the progression of non-diabetic subjects to these diabetic complications in Pima Indians (36). In the Paris Prospective Study the risk of diabetes would appear to increase at a faster rate for fasting than for 2 hour glucose (35, 37).

Criteria for fasting rather than post-load glucose concentrations need to be agreed for the definition of diabetes, 'pre-diabetes' and for the inclusion of fasting glucose in the definition of the insulin resistance syndrome. The American Diabetes Association proposed recommendations in June 1996 were, for fasting glucose, diabetes: ≥ 7.0 mM (125 mg/dl), and 'hyperglycemia': 5.8 to 6.9 mM (105–124 mg/dl) (38).

While in individual studies, HbA1c levels may be predictive of decompensation to diabetes, and so to an insulin-resistant state, the assays for HbA1c are not as yet sufficiently standardized to be able to give a universal definition.

Hypertriglyceridaemia, Hypo-HDL-cholesterolaemia

Dyslipidaemia is not a disease, but a risk factor for cardiovascular disease and so any available threshold values are for treatment for the prevention of cardiovascular disease. However, while the evidence for HDL-cholesterol as a cardiovascular risk factor is not disputed, it is debated whether triglycerides are a risk factor, and whether it is only a risk factor when the HDL-cholesterol concentration is low (39).

Triglyceride concentrations are subject to a high biological variation, even in the fasting state. It is recommended that fasting should be for a period of 9–12 hours, and blood drawn after the subject has been seated for 5 minutes (40). For the treatment of hypertriglyceridaemia the European guideline (41) for both hypertriglyceridaemia and for mixed dyslipidaemia was a triglycerides concentration >2.3 mM (200 mg/dl). In the United States the NIH classified 2.8–5.6 mM (250–500 mg/dl) as borderline, and subjects with ≥ 5.6 mM (500 mg/dl)

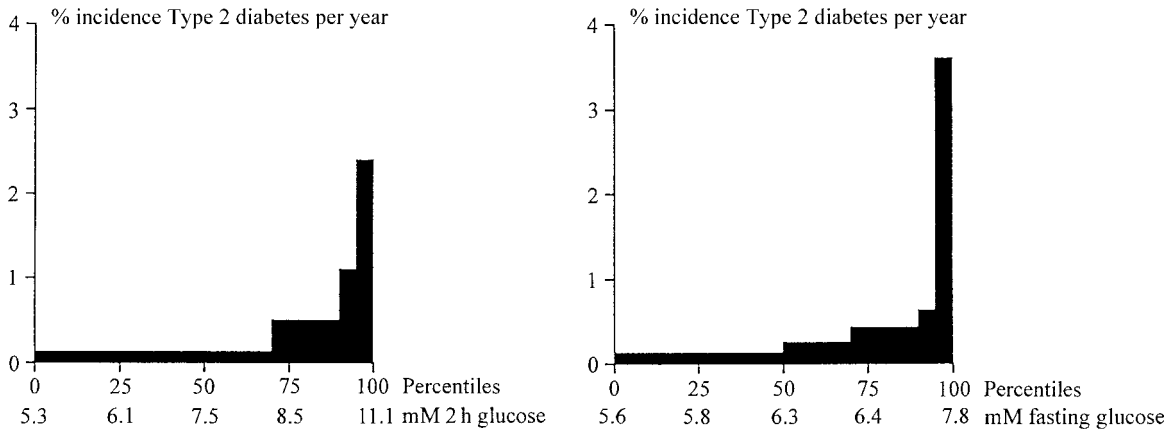


Figure 20.2 Incidence of diabetes according to fasting and 2 hr glucose concentrations. The Paris Prospective Study

as having definite hypertriglyceridaemia (40), while the Adult Treatment Panel of the National Cholesterol Education Program (NCEP) used 2.3–4.6 mM (200–400 mg/dl) as borderline, and >4.6 mM (200 mg/dl) as high or very high triglycerides (40). While the thresholds for treatment of dyslipidaemia are for fasting concentrations, post-prandial values may be equally predictive as a risk factor for cardiovascular disease, but a standardized meal would be necessary (42).

The criteria for treatment for HDL-cholesterol from the American NCEP Expert Panel (43) were <0.9 mM (35 mg/dl) and from the European Atherosclerosis Society <0.9 mM (35 mg/dl) in men and <1.1 mM (42 mg/dl) in women (41).

It may be more appropriate to give criteria for dyslipoproteinaemia in terms of the apoproteins, rather than the lipoprotein lipids (44), given that the measurement of ApoB and ApoA1 has been standardized. In fact the French consensus statement gave the following bounds for treatment: ApoA1 <1.20 g/l, ApoB >1.30 g/l (45), in the case where the cholesterol concentration is over 6.5 mM (200 mg/dl).

Hypertension

For measuring blood pressures, the recommendations of the WHO should be used (46): the subject should be seated for several minutes in a quiet room, and a cuff of suitable size applied to the upper arm at heart level.

The World Health Organization criteria for hypertension, a disease in its own right, were given in a 1978 technical report (47), as a systolic pressure ≥ 160 mmHg and/or a diastolic pressure ≥ 95 mmHg; the definition of normal adult pressures was ≤ 140 and 90 mmHg. The 1993 guidelines were for the management of mild hypertension; normotension was redefined as <140 and <90 mmHg, mild hypertension by 140–180 and/or 90–105; borderline hypertension 140–160 and/or 90–95 mmHg and finally moderate and severe hypertension as ≥ 180 and/or ≥ 105 mmHg (46). In fact these 1993 criteria are not mutually exclusive, and further hypertension *per se* has not been defined at all. Most epidemiological studies use the 1978 criteria, and also include as hypertensive those subjects treated by anti-hypertensive drugs. Given that cardiovascular risk increases in a linear fashion with increasing arterial blood pressure (48), lower limits such as ≥ 140 and ≥ 90 mmHg may be appropriate.

Central Adiposity, Obesity

Central adiposity and obesity are risk factors for cardiovascular disease and for diabetes (29, 49–55).

The most commonly used measure of central adiposity is the waist hip/ratio, easy to perform in epidemiological studies or in clinical practice. This is a surrogate measure of visceral fat, which can be more precisely measured by methods such

as computerized tomography and magnetic resonance imaging (56). The methods for measuring the circumferences are not completely standardized between studies, particularly for the waist circumference; the WHO definition is to measure the circumference midway between the lower rib margin and the iliac crest (57), but some studies use the smallest circumference (58), others at the level of the umbilicus (59). Other simple anthropometric measures correlated with visceral fat are the waist circumference, the sagittal waist diameter (60) and the conicity index (61). Skinfold thicknesses, such as the triceps subscapular skinfolds, also provide measures of fat distribution; however, they are more prone to measurement error (59).

There are no well-defined limits for an 'abnormal' waist/hip ratio. In the BIGPRO clinical trial the limits of ≥ 0.95 in men and ≥ 0.80 in women were used; a high percentage of the population so selected had two or more of the abnormalities of the insulin resistance syndrome (14, 15). In fact these limits are close to the upper quartiles in a population of French men and women within these age ranges (58).

For obesity, the body mass index is universally accepted as the quantity to be measured, but the limits used to define obesity vary between studies. A classification endorsed by the World Health Organization (57) gives moderately obese as BMI within 25.0–29.9 kg/m², severe overweight/obese within 30.0–39.9 kg/m², morbidly obese ≥ 40 kg/m² (62). These definitions are independent of sex. One of these thresholds may be appropriate for the precise definition of obesity for the insulin resistance syndrome.

Plasminogen Activator Inhibitor 1 (PAI–1), Hyperuricaemia

Plasminogen activator inhibitor 1 (PAI–1) and hyperuricaemia were included as possible additional elements in the syndrome because of their association with the other abnormalities, and with the diseases associated with the syndrome (5).

As for PAI–1, the main regulator of the fibrinolytic system, it is a risk factor for cardiovascular disease and is correlated with the elements of the syndrome (63–66). High fibrinogen concentrations enhance the deposition of fibrin; the fibrinolysis depends on the activity of tissue plasminogen

activator (tPA), which is released from the vessel wall upon injury, but is inhibited by PAI–1. Given that PAI–1 activity increases and tPA activity decreases with increasing triglycerides concentration, VLDL along with insulin have been proposed as triggering factors for PAI–1 (66, 67).

While uric acid concentrations tend to be higher in men than in women, only the mortality in women in the NHANES I study was significantly associated with a uric acid concentration, with a threshold of 6 mg/dl (68). The uric acid concentrations were more closely related in women than in men to the other elements of the insulin resistance syndrome (68, 69).

EVIDENCE FOR THE INSULIN RESISTANCE SYNDROME

The correlations between the abnormalities in this syndrome have been discussed by a number of authors, some long before Reaven provided his unifying hypothesis. These statistical relations cannot be disputed, but the mechanisms underlying the clustering of abnormalities in this syndrome are still controversial. We present some of the studies which demonstrate this clustering of abnormalities.

Following the description of the insulin assay (70), the correlates of insulin were studied, and following Reaven's description of 'Syndrome X' (1), they continue to be studied. One of the first articles was by Welborn, who showed that subjects with hypertension or with peripheral vascular disease had hyperinsulinaemia (71). The hypertensio-hyperinsulinaemia association was confirmed by Modan in 1985 (11) and in 1987 Ferrannini used the euglycaemic insulin clamp technique and showed that whole body glucose utilization was impaired in hypertensive normal weight subjects, in comparison to matched control subjects (72).

A second early analysis came from the Busselton study; the insulin response one hour after an oral glucose load was correlated most closely with the one hour blood glucose and age ($r = 0.32$ and 0.29 respectively), followed by the systolic blood pressure ($r = 0.23$) and the mid-triceps fatfold ($r = 0.21$) (73) (Table 20.2)

Orchard, in 1983, provided data from non-diabetic subjects, on the correlations between

Table 20.2 Associations between insulin concentrations and the various parameters associated with the insulin resistance syndrome

	Study population	BMI	Abdominal obesity	Blood pressure		Glucose	Cholesterol		Triglyc.	Other parameters with correl. >0.20 or $p < 0.001$	Comments
				Syst.	Diast.		Total	HDL			
Buselton Webborn, 1969 (73)	>21 yrs 1770 M&W population sample			0.23	0.08	0.32	0.12			Age: $r = 0.29$	Log (fasting insulin) Pearson correlation
Pennsylvania Orchard, 1983 (74)	19–66 yrs 100 M 19–57 yrs 110 W non-DM relatives of IDDM patients	0.42 0.42					0.19 0.23	-0.38 -0.27	0.36 0.38		Log: fasting insulin, chol, trig Pearson correlations
Parma Zavaroni, 1989 (75)	mean: 39 yrs 44 M, 20 W			$p < 0.05$	$p < 0.01$	ns	ns	$p < 0.05$	$p < 0.05$		High fasting insulin (mean: 140 pM) vs normal (mean: 70 pM) t-Test comparison of means Pearson correlations
The European Fat Distribution Study Cigolini, 1991, (76)	38 years 452 W volunteers from random samples in 5 European centres	0.30	0.20	0.12	0.17		0.22	-0.20	0.36	Waist: $r = 0.35$ Hip: $r = 0.31$ Thigh: $r = 0.24$ Waist/thigh: $r = 0.21$ Triep:skinf.: $r = 0.31$ Subs skinf.: $r = 0.31$	
Paris Prospective Casassus, 1992 (54)	43–54 yrs 7152 M free of CHD	0.30	0.18	0.21			0.10				2 hr insulin Pearson correlation
ECAT Study Juhon-Vague, 1993 (65)	all ages 1281 M, 203 W suspected coronary artery disease	$p < 0.001$		$p < 0.001$			$p = 0.14$		$p < 0.001$	PAI-1 ag: $r = 0.42$ PAI act: $r = 0.44$ TPAI ag: $r = 0.36$	Ln (fasting insulin) Analysis of covariance(adjusted) Pearson correlations
Kaiser Permanente Edwards, 1994, (77)	mean: 50 years 281 W		0.59	0.19		0.43		-0.26	0.33		Fasting insulin Pearson correlations, age-adjusted
Zutphen Elderly Feskens, 1994 (78)	70–89 yrs, 389 M non-diabetic			0.08	0.10	0.38	-0.01	-0.34	0.32	Creatinine: $r = 0.22$ Uric Acid: $r = 0.26$	Fasting insulin Spearman correlations
Rancho-Bernardo Ferrara, 1994 (79)	50–89 years 538 M 705 W	0.35 0.36	0.19 0.21	0.03 0.06	0.08 0.01	0.15 0.21		-0.22 -0.23	0.36 0.28		Log (fasting insulin) Pearson correlations, age-adjusted
Kuopio Kuusisto, 1995 (80)	born: 1912–21 396 M, 673 W non-diabetic mean: 63 yrs	0.44	0.25	0.04	0.04	0.36	-0.05	-0.32	0.42		Log(fasting insulin) Pearson correlations
Normative ageing Lee, 1995 (81)	mean: 63 yrs 886 M	0.35	0.32								Log (2 hr insulin) Pearson correlations
Honolulu Burchfiel, 1995 (82)	71–93 years 3741 M Japanese Americans mean: 58 years	0.50	0.33	0.05	0.08	0.38		-0.41	0.43	Waist circum: $r = 0.50$ Subs skinf.: $r = 0.44$ Triep: $r = 0.31$ Hematocrit: $r = 0.24$	Spearman coefficients Log (mean of fasting, 2 hr insulin)
Hospitalized French Canadian Solymoss, 1995 (83)	322 W potential coronary heart disease	$p < 0.001$ $p < 0.001$	$p < 0.001$ $p < 0.001$	ns $p < 0.002$	ns ns	$p < 0.001$ $p < 0.001$	$p < 0.01$ $p < 0.1$	$p < 0.002$ $p < 0.001$	$p < 0.001$ $p < 0.001$	Uric acid: $p < 0.001$ Uric acid: $p < 0.001$	Kruskal Wallis tests by fasting insulin quartile
Jichi Medical School Cohort	30–90 years 1028 M,	$p < 0.001$		$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$	Factor VII act: $p < 0.001$	ANOVA tertile 1 vs tertiles (2 + 3) for fasting insulin
Kario, 1996 (84)	1399 W 5 rural communities 25–64 years	$p < 0.001$	0.42	$p < 0.001$	$p < 0.001$	$p < 0.001$	ns	$p < 0.001$	$p < 0.001$	Factor VII act: $p < 0.001$	
Northern Sweden		0.53		0.29	0.33		0.14	-0.26	0.42	PAI-1 act: $r = 0.54$	Pearson correlation fasting insulin
MONICA Study Lindahl, 1996 (67)	353 M 403 W random population sample	0.57	0.49	0.38	0.20		0.27	-0.30	0.53	tPA act: $r = -0.42$ fibrinogen: $r = 0.15$ PAI-1 act: $r = 0.49$ tPA act: $r = -0.32$ fibrinogen: $r = 0.35$	

insulin concentrations during a 4 hour oral glucose tolerance test, and triglycerides, total, LDL- and HDL-cholesterol concentrations (74). The correlations with HDL-cholesterol were high and similar to those with triglycerides.

Following the description of the insulin resistance syndrome, there have been numerous studies, correlating insulin concentrations with biologic, clinic and anthropometric factors (54, 65, 73–84) (Table 20.2). Where BMI was analysed, it had a higher correlation coefficient than the other variables.

There have been few multivariate analyses of the insulin resistance syndrome. In a cross-sectional study of the baseline characteristics of participants in the BIGPRO clinical trial (14, 15), using a hierarchical graphical model (Figure 20.3), hypertension was found to be independent of hyperinsulinaemia, after conditioning on hyperglycaemia; further, hypertriglyceridaemia was also independent of hyperinsulinaemia after conditioning on hypo-HDL cholesterolaemia (16). In contrast, the links with central adiposity, hyperglycaemia and hypo-HDL cholesterolaemia were independent of the other factors. Thus, there were three axes defined by this modelling, all directly related to hyperinsulinaemia: central adiposity, lipids and glucose/hypertension.

Edwards et al. presented a multivariate analysis of the various parameters involved in the syndrome, in middle-aged women from the Kaiser Permanente Women Twins Study (77). Using factor analysis, they showed there to be three principal factors—body mass/fat distribution, insulin/glucose/systolic blood pressure and lipids. Thus, the conclusions from these two multivariate modelling techniques are consistent.

While there have been many studies of the factors predictive of diabetes (29) and several studies of hypertension (85–87), there have been few prospective studies of all the elements of the insulin resistance syndrome. Haffner, with an 8-year follow-up in the San Antonio study showed that hyperinsulinaemia was predictive of hypertension, low HDL-cholesterol and high triglyceride concentrations and Type 2 diabetes in univariate analyses, not taking into account the baseline status (85). After adjustment for the body mass index and central adiposity, hyperinsulinaemia was no longer predictive of hypertension.

PREVALENCE, INCIDENCE AND RISK FACTORS OF THE INSULIN RESISTANCE SYNDROME

Given that the syndrome is not yet defined in quantitative terms, it is difficult to evaluate its prevalence or incidence, or to compare its prevalence between study populations. Reaven estimated the prevalence to be close to 25% in non-obese glucose-tolerant adults (1).

A lower bound on the prevalence of the syndrome would be the prevalence of treatment for, or passing the treatment thresholds for, at least one hypertension, dyslipidaemia or diabetes. In a population study of French men and women aged 30–64 years, median age 44 years (88, 89), the prevalences of the syndrome so defined were 28% for men and 16% for women (Table 20.3). For two of the other elements of the syndrome, insulin and the waist/hip ratio, the median values increased with the number of abnormalities. As might be expected, the prevalence of the syndrome increased with age (Figure 20.4), and almost doubled between 30–39 and 60–64 years.

The risk factors for the insulin resistance syndrome are in fact the risk factors for the

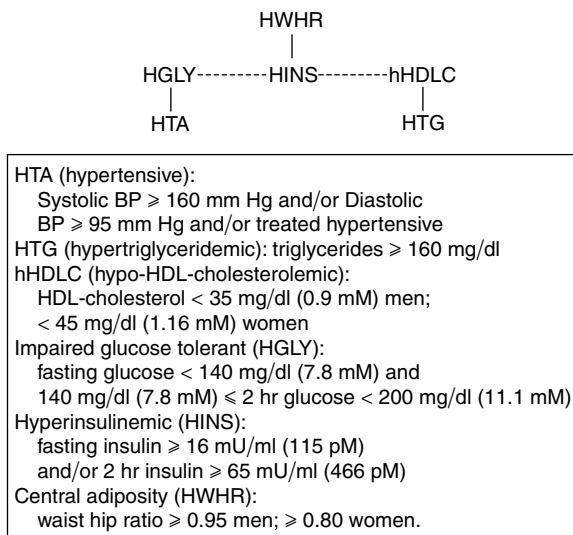


Figure 20.3 Hierarchical model showing the links between anomalies of the insulin resistance syndrome

Source: Data from the BIGPRO clinical trials

Table 20.3 Frequency of the insulin resistance syndrome abnormalities, based on treatment thresholds, by sex, in a community sample of French men and women. D.E.S.I.R. Study, 780 men, 795 women, aged 30–64 years (median 44 years)

	Men	Women
Hypertension SBP ≥ 160 mmHg or DBP ≥ 95 mmHg or treated	17%	12%
Hypertriglyceridaemia triglycerides ≥ 2.3 mM	126%	3%
Hypo-HDL cholesterolaemia HDL chol < 0.9 mM in men; < 1.1 mM in women	5%	3%
Hyperglycaemia fasting glucose ≥ 7.8 mM or treated	2.2%	0.6%

Table 20.4 Frequency of the number of insulin resistance syndrome abnormalities (definitions Table 20.3) and the median values of insulin and waist/hip ratio, by sex, in a community sample of French men and women. D.E.S.I.R. Study, 780 men, 795 women, aged 30–64 years (median 44 years)

Men			
Nb. abnormalities	Frequency	Insulin (pM)	WHR
None	71%	35	0.90
One	23%	46	0.94
Two	5%	67	0.98
Three or four	1%	100	1.00
Women			
Nb. abnormalities	Frequency	Insulin (pM)	WHR
None	84%	34	0.78
One	14%	50	0.83
Two	2%	43	0.86
Three or four	0%	81	0.85

various diseases associated with the syndrome. They are well documented elsewhere.

The insulin resistance syndrome is a multifactorial trait under the control of behavioural, physiological, metabolic as well as genetic factors. The behavioural characteristics which have been associated with the syndrome are a positive energy balance, saturated fat, lack of physical activity, stress, in particular stress related with a poor 'coping' skills, smoking and excessive alcohol consumption (3, 90). These characteristics interact with genetic factors. While the genetic heritability coefficients of the various elements of the insulin

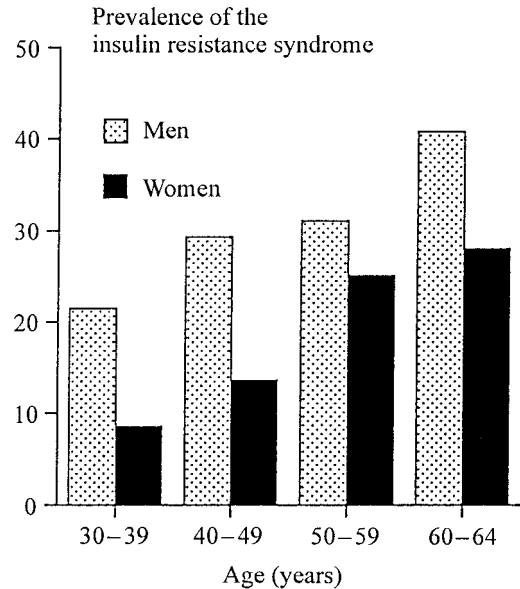


Figure 20.4 Prevalence of the insulin resistance syndrome (defined by treatment thresholds) by sex and age class. The D.E.S.I.R. Study, 780 men, 795 women, aged 30–64 years (median 44 years)

resistance syndrome are substantial (91), little progress has been made in the search for a single gene, or for polymorphic markers. For fasting insulin concentrations, the heritability was evaluated in the Kaiser Permanente Women Twins Study to be 0.47 (92). Using the 165 monozygotic twin pairs, an unmatched multivariate regression analysis (not taking into account the paired nature of the data) showed that after adjustment for behavioural factors, BMI, the waist/hip ratio and glucose intolerance were significant predictors of fasting insulin concentrations, but triglycerides, HDL-cholesterol and hypertension were not; in contrast, in a matched analysis, only BMI remained a significant predictor. Thus, the environmental or behavioural factors related with obesity were important in the determination of fasting insulin concentrations (92).

CONSEQUENCES OF AND TREATMENT FOR THE INSULIN RESISTANCE SYNDROME

The abnormalities of the insulin resistance syndrome are all risk factors for cardiovascular

disease and also for non-insulin-dependent diabetes and many have been associated with hypertension (93). While all the elements have been extensively studied, there are still no guidelines for thresholds for the elements in the case where there are slightly elevated levels of several of the elements in the syndrome. In clinical trials for the treatment of hypertension, while the mortality from cardiovascular disease has been reduced under treatment, it was less than expected (94). This may be due to the other abnormalities of the syndrome, which exist alongside hypertension as minor abnormalities, not severe enough to be recognized and treated, but nevertheless increasing the cardiovascular risk, and sometimes aggravated by hypertensive treatment (see below).

Treatment for the insulin resistance syndrome can be either by behavioural changes (diet, physical activity and perhaps management of stress) or by pharmacological treatment.

The best example of the benefits of behavioural changes comes from the Malmö study, where 181 men with impaired glucose tolerance participated in a programme which involved regular check-ups by the same physician, dietary advice and the provision of a physical activity programme (95). After 6 years of follow-up, in comparison to the control group of 79 men, the intervention group had a lower body mass index, fewer men treated for hypertension and a lower incidence of diabetes, relative risk: 0.37 (95% CI: 0.20–0.68). However, these results are from a non-randomized trial; behavioural modification is very difficult to achieve, in the long term.

There is no class of drugs which has been designed specifically to treat either insulin resistance or the insulin resistance syndrome; treatment of the individual abnormalities of the syndrome is the usual practice, but these treatments need to be carefully chosen so as not to aggravate the other elements of the syndrome. For the treatment of hypertension, thiazide-type diuretics can impair glucose tolerance and increase both LDL-cholesterol and triglycerides concentrations (96). As for the beta-blockers, they tend to lower HDL-cholesterol and increase the triglyceride concentrations. In contrast, the calcium channel blockers, angiotension-converting-enzyme inhibitors and α_1 -receptor blockers, do not have such adverse effects. Equally, for the lipid lowering drugs, the bile acid sequestrants, while having a beneficial effect on LDL-cholesterol concentrations, tend to

increase triglyceride concentrations, nicotinic acid tends to lower glucose tolerance and increase insulin resistance, the statins and probucol are neutral as concerns glucose tolerance, whereas the fibrates may increase LDL-cholesterol (97).

While blood glucose levels in diabetics have not been shown to be a prominent risk factor for cardiovascular disease (98–100), there are reasons to believe that glycaemic control could lower the risk. Improving insulin sensitivity by the treatment of hyperglycaemia at an early stage may be the key element for the treatment of the syndrome, given that chronic hyperglycaemia can generate secondary insulin resistance (101). As for the currently used treatments for hyperglycaemia, sulphonylureas increase pancreatic insulin release, but their beneficial effect on insulin sensitivity is dubious (102). Biguanides act specifically on insulin resistance. The BIGPRO trial used metformin, a commonly used anti-diabetic drug known to reduce insulin resistance (14, 15, 103). After 12 months of treatment, metformin induced a significant weight loss, a better maintenance of fasting blood glucose, total and LDL-cholesterol, a greater decrease of fasting insulin and of t-PA antigen, a marker of fibrinolytic impairment. A second family of drugs which claim to reduce insulin resistance are the thiazolidinedione derivatives (102). The results of a clinical trial in 330 diabetic patients showed that fasting plasma insulin was lower and insulin sensitivity higher after a 12-week treatment with troglitazone (104). However, as this drug was only put onto the market in Japan in early 1996, it has a very short history of use and its side effects have yet to be completely evaluated (102).

The Diabetes Prevention Program in the United States, a 6-year clinical trial of 4000 impaired glucose-tolerant subjects, will clarify the possibilities of retarding the development of diabetes. The four treatment arms in this trial will be standard care and a placebo, metformin, troglitazone, and an intensive health-diet regime. This latter treatment has three major objectives: a balanced diet, increase in physical activity and loss of weight, and the education program will consist of 16 sessions over 6 months (105).

CONCLUSIONS

There is now no reasonable doubt that the insulin resistance syndrome exists and that it is associated

with cardiovascular consequences. Additional abnormalities have been associated with this syndrome, and various diseases added since its original description by Reaven in 1988 (1). Although both physiological and epidemiological knowledge are increasing, there is still no clear explanation of its genesis. Undoubtedly, as for non-insulin-dependent diabetes, there are likely to be a multitude of causes with numerous genetic precursors.

Stern proposed that the insulin resistance syndrome could be the link which provides the 'common soil' between foetal and early life nutritional deficiencies and later Type 2 diabetes and cardiovascular disease (93,106). From the work of Barker and Hales it would appear that low birthweight, perhaps indicative of inadequate nutrition during foetal or early life, leads to a higher frequency of Type 2 diabetes and cardiovascular disease (107, 108) and, indeed, the insulin resistance syndrome (109,110). This has been observed in a number of other populations (111,112) and even in children (113–116). However, two negative studies come from cohorts of twins, where children of small birthweight were not more prone to later illnesses associated with the insulin resistance syndrome (117–118).

It is clear that more analyses of prospective epidemiologic data are required so that the mechanisms of the insulin resistance syndrome can be unravelled, criteria for its diagnosis established and appropriate treatment recommended for individuals who are insulin-resistant.

APPENDIX

Since the above text was written, there have been some developments in the epidemiology of the insulin resistance syndrome, in addition to the numerous confirmatory reports of the existence of the clustering of the syndrome abnormalities.

Firstly, an excellent review has been written by Liese (119).

A working definition of the 'Metabolic Syndrome' has been provided by the World Health Organization Consultation on the Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications (120). This was first published in a Provisional Report, and in the final published report, there was a change in the definition of hypertension (121). Their definition is as follows:

Glucose intolerance, impaired glucose tolerance or diabetes and/or insulin resistance together with two or more of the other components listed below

- Impaired glucose regulation or diabetes.
- Insulin resistance (under hyperinsulinaemic euglycaemic conditions, glucose uptake below lowest quartile for background population under investigation).
- Raised arterial pressure $\geq 140/90$ mmHg.
- Raised plasma triglycerides (≥ 1.7 mmol/l; 150 mg/dl) and/or low HDL-cholesterol (< 0.9 mmol/l, 35 mg/dl men; < 1.0 mmol/l, 39 mg/dl women).
- Central obesity (males: waist–hip ratio > 0.90 ; females waist–hip ratio > 0.85) and/or BMI > 30 kg/m².
- Microalbuminuria (urinary albumin excretion rate ≥ 20 mg/min or albumin : creatinine ratio ≥ 30 mg/g).

This definition has been criticised (122) and one of the main problems is that it requires a direct measure of insulin resistance, either by a euglycaemic hyperinsulinaemic clamp (17) or by a frequency sampled intravenous glucose tolerance test and the minimal model (18), measures which are rarely available in epidemiological studies. To date, this definition has been little used.

One of the few studies that has looked at the development of the syndrome, comes from the Atherosclerosis Risk in Communities (ARIC) Study (123). The syndrome was defined by diabetes, hypertension and dyslipidemia. Subjects who had a greater number of these anomalies after three years of follow-up had, at baseline, high insulin levels, BMI, waist–hip ratio and abdominal girth.

Finally, one of the more promising insulin sensitising drugs, Troglitazone, was withdrawn from the Diabetes Prevention Program due to liver toxicity (124). However, two newly launched members of the same thiazolidinedione family (Rosiglitazone and Pioglitazone) do not seem to be associated with the same liver toxicity. There is an ongoing surveillance of this side effect.

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Long-term Complications: Diabetes and Coronary Heart Disease

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Cardiovascular disease (CVD), which includes coronary heart disease (CHD), stroke, and peripheral arterial disease (PAD), is the major cause of morbidity and mortality in patients with insulin-dependent or non-insulin-dependent diabetes (Type 1 diabetes or Type 2 diabetes, respectively). Although diabetes is as powerful a risk factor as cholesterol, blood pressure, or cigarette smoking, the diabetes–CVD association received relatively little systematic study until the 1979 publication of Kelly West's monumental book, *Epidemiology of Diabetes Mellitus and its Vascular Complications* (1) and the development of standard (WHO[2] and NDDG[3]) criteria for the definition of diabetes in the 1980s.

The literature on the association between diabetes and CVD has increased exponentially in recent years. Nevertheless, there are still relatively few studies where the population characteristics and response rate are provided, the diagnosis of diabetes is based on standard criteria, the definition of CVD is explicitly stated, and there is an internal non-diabetic comparison group.

In addition, there are many reasons why interpretation of the epidemiologic literature on the diabetes–CVD association may be difficult. Both conditions are common and therefore may occur together by chance. Their association is known to clinicians, so that diagnosis of one condition often leads to a search for the other, which inflates the frequency of the association, and may do so differentially in different population groups or countries with different access to health care. Persons with known diabetes, who represent only half of all persons with Type 2 diabetes in the United States (4) tend to have more severe diabetes

of longer duration; therefore, studies based on subjects with clinically recognized diabetes are likely to yield falsely elevated estimates of macrovascular complication rates. In addition, patients are more apt to be tested for diabetes if they are obese or have other heart disease risk factors. Both Type 2 diabetes and CHD may remain subclinical for years; CHD is more often silent in diabetics than non-diabetics (5,6). Consequently, both within-population and cross-cultural comparisons of the Type 2 diabetes–CHD association should be interpreted cautiously unless they are population-based and unless both diabetes and heart disease have been sought in the whole study cohort—for example, by obtaining glucose tolerance tests and electrocardiograms. While Type 1 diabetes is less likely to be subclinical, most studies of Type 2 diabetes and CHD are patient-based case series derived from specialty clinics, where patients with more severe diabetes and more complications may selectively accrue.

This review has focused primarily on population-based studies with internal comparison groups. It will be seen that few studies do not have at least some of the potential biases described above.

CORONARY HEART DISEASE

Prevalence Studies

Several recent North American studies have reported the prevalence of coronary heart disease in adults who received a standard oral glucose tolerance test (OGTT), as shown in Table 21A.1 (5, 7–10). As shown, the CHD prevalence rates

Table 21A.1 Age-adjusted *prevalence* of coronary heart disease among adults by oral glucose tolerance status, North American studies

Population (Ref.)	Race	Sex	Glucose tolerance		Myocardial infarction (%)		Ischemic ECG (%)		Coronary heart disease ^d (%)
			Status	Number	History	Hx or ECG ^a	Total ^b	Silent ^c	
Rancho Bernardo, CA (population-based, 1984–87, 50–89 years) (5)	White	M	T2DM	159	—	17.1	34.7**	20.9*	43.1**
			IGT	237	—	18.4*	28.2	13.0	38.5
			Normal	591	—	13.2	22.3	12.0	32.0
		F	T2DM	157	—	13.7**	30.0**	13.7*	41.9***
			IGT	347	—	9.5	23.3	12.0	34.3*
San Luis Valley, CO (population-based, 1984–88, 25–74 years) (7)	White	M	Normal	732	—	7.2	19.6	8.8	28.5
			T2DM	79	12.3*	26.5*	16.7	7.7	36.9*
			IGT	34	11.6	18.1	19.0	7.4	37.7
		F	Normal	307	4.8	12.8	9.7	4.5	23.1
			T2DM	66	4.4	14.2*	25.5*	17.8	50.6*
			IGT	48	1.4	9.5	18.3	15.3	40.1*
	Mexican American	M	Normal	345	2.0	7.0	15.5	11.8	24.6
			T2DM	107	5.6	11.3	14.2	12.2*	29.7
			IGT	35	8.8	18.0	13.3	2.4	29.1
		F	Normal	214	6.7	16.3	12.5	5.2	29.7
			T2DM	177	2.8	12.4	18.5	13.6	44.5*
San Antonio, TX (population-based, 1979–88, 25–64 years) (8)	White	M	IGT	56	2.5	11.6	20.9	16.7	36.4
			Normal	226	0.4	8.7	14.9	10.3	32.6
		F	T2DM	37	13.3	29.9	—	—	—
			Other	790	4.0	8.2	—	—	—
	Mexican American	M	Other	41	7.2	11.7	—	—	—
			Other	995	1.2	2.5	—	—	—
		F	T2DM	154	12.6	21.6	—	—	—
			Other	1230	3.1	5.6	—	—	—
King County, WA (volunteers, 1983–85, 45–74 years) (9)	Japanese American	M	T2DM	240	4.2	10.7	—	—	—
			Other	1654	1.1	3.1	—	—	—
			T2DM	78	—	—	29.5***	16.7**	41.0***
	Japanese American	F	IGT	72	—	—	23.6	12.5	27.8
			Normal	79	—	—	6.3	3.8	8.9
			T2DM	52	—	—	—	—	36.5*
King County, WA (volunteers, 1986–88, 45–74 years) (10)	Japanese American	F	IGT	67	—	—	—	—	35.8*
			Normal	72	—	—	—	—	19.4

ECG = electrocardiogram; T2DM = Type 2 diabetes mellitus; IGT = impaired glucose tolerance; NHW = non-Hispanic white.

^a History or ECG Minn. code 1.1 (5); history or ECG Minn. code 1.1–1.2 (7); history or ECG Minn. code 1.1–1.3 (8).^b ECG Minn. code 1.1–1.3, 4.1–4.3, 5.1–5.3, 7.1 (5,7); ECG Minn. code 1.1–1.3, 5.1–5.3, 7.1 (9,10).^c Ischemic ECG without history of MI, angina, or chest pain (5,7,9).^d Possible MI, angina, or ischemic ECG (5); heart attack, angina, or ischemic ECG (7); MI, bypass, angina or ischemic ECG (9,10).* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ compared to normal glucose tolerance group.

for persons with and without abnormal carbohydrate tolerance vary by population, probably reflecting differences in age, ethnicity and body size. Within each population, diabetic Americans of European, Mexican and Japanese ancestry nearly always had significantly more clinically manifest CHD and more silent ischemia (as defined by resting electrocardiogram) than those with normal glucose tolerance. The absent diabetes–CHD association in the Mexican American men from the San Luis Valley Study may be due to chance, small sample size, or prevalence bias, i.e. increased mortality in men who have both diabetes and CHD.

The Strong Heart Study provides age-adjusted prevalence rates for 13 American Indian communities in Arizona, Oklahoma and the Dakotas (11). The prevalence of CHD defined by history and resting electrocardiogram was higher in diabetics than non-diabetics in all groups and both sexes, but there is a significant unexplained difference in the prevalence of CHD by geographic area, as shown in Table 21A.2 (11).

Results of three Finnish studies using similar methods for the diagnosis of Type 2 diabetes and CHD are shown in Table 21A.3 (12–14). In East Finland (12,13) the frequency of symptomatic CHD and ischemic ECG abnormalities was

Table 21A.2 Prevalence rates (per 100) of coronary heart disease, by sex, study center, and diabetes status, in Native Americans; The Strong Heart Study, 1989–92

	Non-diabetic				Diabetic				Prevalence ratio (PR) (diabetic: non-diabetic)			
	Women		Men		Women		Men		Women		Men	
	(no.)	(%)	(no.)	(%)	(no.)	(%)	(no.)	(%)	(no.)	(%)	(no.)	(%)
Definite CHD												
Arizona	1	0.4	1	0.5	4	0.6	5	1.5				
Oklahoma	3	0.6	19	4.7	11	3.2	20	8.7				
Dakotas	2	0.4	14	3.2	14	4.1	19	9.6				
All	6	0.5	34	3.3	29	2.2	44	5.8	4.6	1.9–11.1	1.8	1.1–2.7
<i>p</i> (center)*	0.887		0.026		0.001		<0.0001					
Possible CHD												
Arizona	44	16.1	18	9.8	134	20.9	60	18.0				
Oklahoma	89	17.4	52	12.9	86	25.3	54	23.8				
Dakotas	86	17.9	68	15.6	101	29.5	50	25.4				
All	219	17.3	138	13.4	321	24.3	164	21.4	1.4	1.2–1.6	1.6	1.3–2.0
<i>p</i> (center)*	0.815		0.140		0.010		0.090					

* *p* value for analysis of variance testing between-center differences.

Source: Adapted from Howard et al. Coronary heart disease prevalence and its relation to risk factors in American Indians. The Strong Heart Study. *Am J Epidemiol* (1995); **142**: 254–268.

remarkably similar among individuals with known diabetes or newly recognized diabetes identified by OGTT screening, while among the elderly Kuopio subjects (14) more CHD was present in persons with known than with newly diagnosed diabetes. Table 21A.3 also shows variation in the association of IGT with CHD prevalence in these cohorts.

Studies of the prevalence of diabetes or CHD in developing countries are rare. A clinical diagnosis of CHD is less commonly made, and most of the CHD prevalence data are derived from surveys of electrocardiographic abnormalities. Li and colleagues (15) have reported the low prevalence of major Q wave and ST-T wave abnormalities in 15 populations from nine countries, predominantly Asian, Melanesian, Polynesian or Micronesian populations. Data were not shown by diabetes status, but many of these populations have high rates of diabetes. Overall, blood glucose levels were independently associated with Q and ST-T wave abnormalities (combined) only in men, although women had more ST-T wave abnormalities than men (and fewer Q waves). The absent association in women is likely because ST-T wave criteria, which were developed in men, are not valid for the diagnosis of CHD in women.

Incidence Studies

None of the published North American population-based studies comparing the incidence of CHD in adults with or without diabetes used standard glucose tolerance test methods or criteria. Only four included fatal and non-fatal cases. (16–19) These studies all showed an increased risk of CHD among diabetic individuals.

Six prospective North American population or occupation-based studies of fatal CHD incidence in persons with and without diabetes are shown in Table 21A.4. These studies all used a history of physician-diagnosed diabetes (18–22); only one also included fasting hyperglycemia (23). In every study the risk of fatal ischemic heart disease was significantly greater among those with diabetes. In four of the five studies that reported sex-specific rates, the relative risk of fatal heart disease associated with diabetes was greater among women than men.

Two large prospective studies of diabetes and CHD, the Nurses' Health Study (19) and the Wisconsin study (24) separately reported CHD incidence in persons with Type 2 diabetes or Type 1 diabetes (based on age at diagnosis). The diagnosis of diabetes was based on self report in

Table 21A.3 Age-adjusted prevalence of coronary heart disease among adults by glucose tolerance status in three Finnish studies

Population (Ref.)	Sex	Glucose tolerance		Myocardial infarction (%)†		Ischemic ECG (%)	Angina pectoris (%)
		Status	No.	History of hospital-verified definite or possible MI	Definite MI by history or ECG		
Kuopio University Hospital district, East Finland: newly diagnosed T2DM patients and random sample of non-diabetic subjects, 1979–81; 45–64 years (12)	M	T2DM	70	22.5	16.5	53.3***	44.0**
		Normal	62	15.6	9.7	21.3	19.0
	F	T2DM	63	14.0	17.7*	59.1*	43.3**
		Normal	82	6.7	4.0	38.1	20.2
Kuopio University Hospital district, East Finland: previously diagnosed T2DM patients and random sample of non-diabetic subjects, 1982–84; 45–64 years (13)	M	T2DM	253	19.9***	20.3***	41.3***	44.2***
		Normal	313	4.5	8.3	21.8	19.9
	F	T2DM	257	5.6**	7.9***	39.9**+	35.7**
		Normal	336	1.7	2.1	22.2	19.8
Turku University Hospital district, West Finland: previously diagnosed T2DM patients and random sample of non-diabetic subjects, 1982–84; 45–64 years (13)	M	T2DM	328	7.4	12.5*	37.6***	12.1
		Normal	325	4.0	6.6	20.9	7.4
	F	T2DM	221	1.5.*	3.6**	45.0***	16.4***
		Normal	399	0.2	1.8	24.1	8.3
Kuopio town, East Finland: population-based, 1986–88, 65–74 years (14)	M	Previously diagnosed T2DM	82	21.2	17.3	56.4	33.3*
		Newly diagnosed T2DM	33	15.7	22.4	58.0	26.6
		IGT	84	15.4	20.2	59.7*	31.0*
		Normal	312	13.3	12.0	45.0	19.3
	F	Previously diagnosed T2DM	188	12.2**	8.9	65.9***	36.5***
		Newly diagnosed T2DM	59	2.9	10.6	56.1*	28.3
		IGT	158	7.7	6.1	44.8	15.4
		Normal	515	5.3	7.1	39.7	21.1

* $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$ compared to normal group.

† = Based on Rose cardiovascular questionnaire.

Table 21A.4 Risk of fatal coronary heart disease in diabetic vs non-diabetic white adults, United States studies

Population (Ref.)	Age (years)	Years follow-up	Sex	Number		Adjusted risk ratio	
				Diabetic	Non-diabetic	Age	Multiple
Alameda County, CA (20)	≥ 40	9	M	51	1 648	—	1.5
			F	70	1 982	3.5	3.1
Chicago, IL (21)	35–64	9	M	377	10 843	4.0	3.8
			F	170	7 860	5.9	4.7
NHANES I (22)	40–77	9	M	189	3 151	2.3	2.4
			F	218	3 823	2.8	2.6
Rancho Bernardo, CA (23)	40–79	14	M	207	893	1.8	1.9
			F	127	1 224	3.3	3.3
Nurses' Health Study (19)	30–55	8	F	1483	114 694	6.9	—
New Haven, CT (18)	≥ 65	6	M	156	994	—	1.6
			F	230	1 388	—	4.5

the Nurses' Study. In the Wisconsin study, nearly all physicians in the target area provided lists of patients with diabetes, and the diagnosis was validated by record review; 'non-diabetic' comparisons were based on statistics from the state of Wisconsin. Among the nurses, the age-adjusted relative risks for diabetic vs non-diabetic women were 12.2 for Type 1 diabetes and 6.9 for Type 2 diabetes. Similar age-adjusted comparisons in Wisconsin showed that CHD risk estimates in men with Type 1 diabetes or Type 2 diabetes were 9.1 and 2.4, respectively; in women the same risk estimates were 13.5 and 2.2. The higher relative risks associated with Type 1 diabetes than with Type 2 diabetes may reflect the longer duration of diabetes, more severe metabolic disturbances, and the relatively low CHD rates in young persons without diabetes.

Prospective studies in European population- or occupation-based cohorts comparing the risk of CHD in diabetic patients and non-diabetic subjects are shown in Table 21A.5 (25, 26). In the occupational cohorts newly diagnosed diabetes was detected using oral glucose tolerance tests and WHO or closely similar criteria. In all these studies the risk of fatal CHD was markedly increased and in the Swedish cohort (26) the incidence of major CHD events, including also non-fatal myocardial infarction, was also found to be increased.

Adjustment for traditional CHD risk factors did not diminish the impact of diabetes on the risk, with the exception of newly diagnosed diabetics in the Paris cohort.

Collins et al. (27) published one of the few prospective population-based studies of diabetes and fatal cardiovascular disease in a developing country. In Fiji, death from all causes was significantly increased ($p < 0.001$) in Indian men but not in Melanesian men who had diabetes by OGTT; no statistically significant association was seen in women. In multiply adjusted models, however, 2 hour post-challenge glucose was independently associated with cardiovascular death in Indian men and in Indian and Melanesian women.

Natural History of Coronary Heart Disease in Diabetics

Several studies of patients with myocardial infarction have shown that diabetics have a 2-fold higher hospital mortality than non-diabetics (28–34). This has been found to be mainly due to increased occurrence of left ventricular failure, cardiogenic shock, and conduction disturbances in the diabetic patients. In the Corpus Christi (Texas) Heart Project (35), diabetics had twice the risk of death within 28 days after myocardial infarction and a

Table 21A.5 Risk of fatal coronary heart disease (CHD) or major CHD events (CHD death or non-fatal myocardial infarction) in diabetic patients vs non-diabetic subjects, European population/occupation-based studies

Population (Ref.)	Age (years)	Years follow-up	Sex	Type of diabetes	Number		Adjusted risk ratio			
					Diabetic	Non-diabetic	Fatal		Major event	
							Age	Multiple	Age	Multiple
Population sample, Finland (25)	40–69	10	M	Previously diagnosed (unspecified)	273	12 299	2.7*	2.5*	—	—
			F	Previously diagnosed (unspecified)	292	12 008	3.4*	9.4*	—	—
Population sample, Gothenburg, Sweden (26)	51–59	7	M	Previously diagnosed (unspecified)	232	6 665	4.1*	3.4*	2.8*	2.3*
London civil servants**	40–64	18–20	M	Known and new T2DM	191	17 966	2.8*	2.6*	—	—
Paris policemen†	44–55	17	M	Known T2DM	125	6 055	3.5*	2.3*	—	—
				New T2DM	158		2.0	0.8	—	—

*95% confidence interval does not contain 1.0.

** Jarrett RJ, Fitzgerald AP, personal communication.

† Eschwège E, personal communication.

60% higher risk within 44 months compared to non-diabetics. In the Minnesota Heart Survey (36) diabetic patients had a 40% increased risk of death within 6 years of their myocardial infarction compared to non-diabetics. In a 6.5-year follow-up of an unselected series of survivors of myocardial infarction carried out in Gothenburg, Sweden (37), and in a similar 3-year follow-up study from Hamar, Norway (38), diabetic patients had twice the mortality and twice the rate of recurrent myocardial infarction compared to non-diabetic patients.

There are several explanations why short-term case fatality of myocardial infarction would be higher and long-term prognosis of patients surviving a myocardial infarction would be worse in diabetics than in non-diabetics. CHD is more often silent in diabetics, leading to delayed diagnosis and treatment (6, 5). Despite evidence that infarct size is similar in diabetics and non-diabetics (34), clinical studies reviewed elsewhere (39) suggest that diabetes is associated with more diffuse atherosclerosis. There may be more extensive scarring due to chronic ischemia, and this may increase the risk of developing left ventricular failure after myocardial infarction.

Sudden death is also more common in both men and women who have diabetes, compared to those who do not (40). The recently described association of a prolonged heart-rate-adjusted QT interval (a risk factor for sudden death) with glucose and insulin levels in older men without diabetes apparently also adds to their poorer prognosis (41).

Population-based studies, such as Framingham (42) and Rochester (43), have reported that diabetics have a much higher rate of congestive heart failure than non-diabetics. This may not be entirely explained by the more frequent occurrence of CHD and hypertension in diabetics, because diabetes may cause a specific cardiomyopathy independent of atherosclerosis, as recently reviewed by Bell (44). This possibility is supported by a population-based autopsy study which found that diabetics had more myocardial lesions than non-diabetics, and these lesions, but not atherosclerosis, were independent of the major CHD risk factors (45). Other epidemiologic evidence for a diabetes–cardiomyopathy association comes from a North American case-control study, which found that diabetes (present in 29% of the cases) was significantly and independently associated with

dilated cardiomyopathy (relative odds 2.6) (46). Thus the co-existence of diabetic cardiomyopathy and coronary atherosclerosis could explain some of the excess mortality of diabetic patients with myocardial infarction.

Risk Factors for Development of Coronary Heart Disease in Diabetics

Age and Duration of Diabetes

It has been difficult to distinguish between an effect of age and an effect of duration of diabetes on CHD risk. The onset of Type 2 diabetes is often insidious, which may explain why most studies have not found an effect of duration of Type 2 diabetes on CHD risk independent of age. In fact, diabetes is frequently first diagnosed at the time the patient is hospitalized with a heart attack. In one study, for example, 20% of myocardial infarction patients had diabetic levels of glycosylated hemoglobin, compatible with hyperglycemia preceding the infarction (47).

In patients with Type 1 diabetes, CHD is uncommon before the age of 30, even when diabetes began in childhood (48, 49). In one community-based study, there was an age-independent association between fatal CVD and duration of Type 1 diabetes (49), suggesting either that there is a minimum duration of diabetes required to cause CHD, or that diabetes accelerates *existing* atherosclerosis.

Sex

Diabetes is the only condition that causes women to have a risk of CHD that approaches that of men, as reviewed elsewhere by Orchard (50). Women seem to lose their usual cardioprotection against CHD when they become diabetic. In the Rancho Bernardo Study in California (23), diabetic women had CHD mortality rates similar to non-diabetic and diabetic men, while non-diabetic women had a clear longevity advantage, as shown in Figure 21A.1. The reason for this effect is unknown. Orchard (50) has suggested that non-diabetic women are normally protected from CHD by having greater tissue insulin sensitivity than men; Fontbonne (51) has proposed that women's

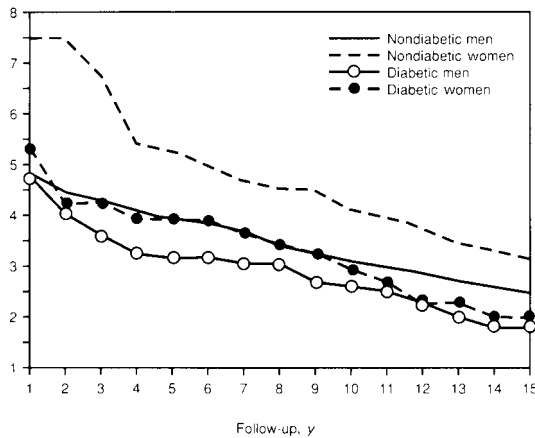


Figure 21A.1 Age-adjusted ischemic heart disease -log (-log survival) by sex and diabetes; Rancho Bernardo, CA, 1972–88. Curves were estimated by a Cox model blocked on both sex and diabetes status and adjusted for age

typical gynoid fat distribution plays a central role in explaining their greater insulin sensitivity and lower risk of heart disease.

Glycemia

There are a number of biological reasons why hyperglycemia *per se* could be expected to lead to atherosclerosis (52–54). As shown in Table 21A.6, recently completed long-term follow-up studies of three European occupational cohorts of middle-aged men, using the WHO or closely similar criteria for the definition of IGT on the basis of a single oral glucose tolerance test, demonstrated a

2-fold higher risk of CHD in men with IGT than in normoglycemic men. In two of these studies the predictive value of IGT with regard to CHD risk remained statistically significant after adjustment for traditional heart disease risk factors.

In other prospective studies, a linear association has been seen between glucose and CHD risk. For example, the 1 hour post-challenge glucose showed a linear association with CHD in Japanese men from the Honolulu Heart Study who were followed for 12 years (55). In Framingham, casual blood glucose levels were linearly associated with CVD in women, but not in men (16).

Nevertheless, a review of earlier literature shows that glucose levels below those diagnostic of diabetes have been inconsistently associated with CHD, and most studies do not show an independent graded association as is observed with serum lipids or blood pressure (56). Inconsistencies could reflect different concordance with other CHD risk factors in different populations, or the high intraindividual variability of post-challenge glucose levels and resultant misclassification, which obscures a true association (57–59). In the 19-year follow-up of the Chicago People's Gas Company Study, the mean of two 1 hour post-load glucose levels measured 1 year apart was predictive of fatal CHD, but death rates were not significantly higher in those who had hyperglycemia at only one visit (60). In the Rancho Bernardo cohort, after 9 years of follow-up, neither fasting nor 2 hour glucose levels predicted CHD in men or women, but glycosylated hemoglobin (which has less day-to-day variation) was associated with incident CHD in women (61).

Table 21A.6 Risk of fatal coronary heart disease (CHD) or major CHD events (CHD death or non-fatal myocardial infarction) in subjects with impaired glucose tolerance (IGT) vs subjects with normal glucose tolerance (NGT)

Population	Age (years)	Years follow-up	Sex	Number		Adjusted risk ratio			
				IGT	NGT	Fatal		Major event	
						Age	Multiple ^a	Age	Multiple ^a
London civil servants**	40–64	18–20	M	70	17 966	2.1*	1.7*	—	—
Paris policemen†	44–55	17	M	690	6 055	1.8*	1.3	—	—
Helsinki policemen‡	34–64	22	M	52	1 038	2.6*	2.7*	1.7*	1.8*

* 95% confidence interval does not contain 1.0.

^a Adjusted, in addition to age, for cholesterol, systolic blood pressure, body mass index, and smoking.

** Jarrett RJ, Fitzgerald AP, personal communication.

† Eschwège E, personal communication.

‡ Pyörälä K, Pyörälä M, unpublished.

Studies of a glycemia-CHD association in individuals with diabetes are harder to interpret, because it is difficult to distinguish disease severity from treatment effects. Two large prospective studies of patients with Type 1 diabetes found no association between glycemic control and CHD but the 4- and 5-year follow-up intervals may have been too short for the progression of atherosclerosis in young adults (62, 63).

Prospective population-based studies of patients with Type 2 diabetes from Finland and Sweden found a significant linear association between fasting glucose or glycosylated hemoglobin and the risk of CHD, although the association did not always persist after adjusting for other heart disease risk factors (64, 65). However Klein (66), in a population-based study of diabetic patients from Wisconsin, reported that elevated glycosylated hemoglobin was only weakly and not significantly associated with an increased risk of fatal CHD.

Clinical trials are necessary to determine whether glycemic control prevents macrovascular disease. Studies to date have had too few cardiovascular outcomes, and probably also inadequate control of glycemia. Many years ago the University Group Diabetes Program (UGDP) (67, 68), a randomized controlled trial in adults with mild diabetes or IGT, found that insulin therapy lowered glucose levels without reducing the risk of fatal or non-fatal CVD risk: at the end of 13 years 10% of participants in each of three treatment groups (standard insulin therapy, $n = 210$; variable insulin therapy, $n = 204$; and placebo, $n = 204$) had experienced a myocardial infarction. Additional details of this study have been provided in an excellent review by Genuth (68). In the Diabetes Control and Complications Trial (DCCT) (69), the largest randomized trial of strict (vs good) control in young adults with Type 1 diabetes, there was a 41% lower rate of cardiovascular disease in the tighter control group, but events were few and these differences were not statistically significant. Further, the intensively treated group may have enjoyed the cardioprotective effects of more social supports, different diets or more frequent meals.

Other studies are ongoing. In a feasibility study of 153 US veterans with Type 2 diabetes, the group who were randomly assigned to intensive insulin therapy (alone or in combination with glipizide)

showed a non-significant excess risk of cardiovascular events compared to the usual insulin group (32% vs 20.5%; $p = 0.1$). The results of a large (over 4000 patients randomized) clinical trial, The United Kingdom Prospective Diabetes Study (UKPDS), of intensive vs usual control were published in 1998 (70). In this study the group assigned to the more aggressive treatment achieved sustained glycosylated hemoglobin levels for 9 years similar to those in the DCCT and the UGDP trials (71). In UKPDS (70), there was only an 11% reduction in myocardial infarction ($p = 0.052$) compared to a 25% reduction in microvascular disease ($p = 0.009$). There is still no strong evidence that glycemic control reduces the risk of CHD in patients with diabetes—despite the documented benefit for microvascular disease prevention—although it remains possible that more physiologic levels of glycemia can reduce the risk of CHD in patients with diabetes, at present.

Insulin

Hyperinsulinemia (or insulin resistance) has been a leading candidate for the risk factor that explains the excess risk of cardiovascular disease in patients with diabetes (72, 73). This hypothesis is compatible with studies showing that insulin levels covary with other heart disease risk factors (see below). Further, hyperinsulinemia precedes the onset of diabetes (74), which is compatible with the observation that heart disease also antedates the onset of clinically manifest Type 2 diabetes (75, 76).

As reviewed elsewhere (77), prospective studies of endogenous insulin levels and cardiovascular disease or coronary heart disease in non-diabetic cohorts have yielded contradictory results. Finnish investigators found that 1 and 2 hour insulin levels, but not fasting insulin, were associated with CHD in men at 5 and 9.5 years of follow-up (78, 79). In the Paris Prospective Study, fasting but not 2 hour insulin levels predicted coronary heart disease in men at 5 years, but the reverse was true at the 15-year follow-up (80, 81). In Australia, the Busselton Study found 1 hour post-challenge insulin levels were associated with CHD incidence after 6 years in men but not women (82). By 19 years of follow-up, there was a U-shaped association between post-challenge insulin and CHD death in men and still no association in women (83).

In the Caerphilly (South Wales, United Kingdom) prospective study of middle-aged men, fasting insulin showed a significant univariate association with CHD risk, but this association was almost entirely explained by the association of insulin and CHD with plasma triglycerides and body mass index (84). In contrast, a prospective study from Quebec City, Canada, showed that high fasting plasma insulin predicted CHD risk independent of obesity and plasma lipoprotein levels (85).

Five other prospective studies of non-diabetic subjects found no association between high insulin levels and CHD risk. This was true in older men from Gothenburg, Sweden (86), in middle-aged men from the Multiple Risk Factor Intervention Trial (87), and in two studies that presented data on middle-aged men and women combined: the study of Pima Indians (88) and the San Luis Valley Study (89). The Rancho Bernardo Study of older adults (90) found no positive association between insulin levels and cardiovascular disease in women and an inverse association in men, i.e. high insulin levels were 'protective'.

Prospective studies of persons with diabetes or IGT generally show no *independent* positive association between endogenous insulin levels and the risk of CHD (88,91,92) and in the Bedford cohort, in fact, an inverse association was observed between 2 hour post-challenge insulin and CHD risk. In the Paris Prospective Study (93,94) both fasting and 2 hour insulin levels showed a positive association with the risk of CHD death in men with IGT and diabetes in univariate analysis, but after adjustment for other risk factors, particularly for triglycerides, this association was not statistically significant. In a German prospective study of patients with newly diagnosed Type 2 diabetes, a positive association was observed between fasting insulin and development of new ischemic ECG abnormalities in men, but no association was found in women (95). In a 7-year follow-up of Finnish patients with Type 2 diabetes, fasting insulin showed a statistically significant positive association with the risk of CHD death in men but not in women; after adjustment for other risk factors, including triglycerides and HDL cholesterol, the association in men was no longer significant (96).

Ecological studies do not support the insulin-CHD hypothesis either. McKeigue and Keen (97) summarized the differences between the diabetes-

CHD association in different ethnic groups, and noted that some populations such as Pima Native Americans, Nauruans, and persons of African descent have high rates of diabetes (and hyperinsulinemia) but relatively little CHD compared to Europeans or persons of European descent. In contrast, urbanized Aboriginal Australians and South Asians have higher rates of diabetes, hyperinsulinemia and CHD than Europeans or persons of European origin.

These contradictory findings could reflect age, environmental or genetic variations. Perhaps insulin is a risk factor for CVD only in the presence (or absence) of some other condition, as suggested by several post hoc analyses. Thus, hyperinsulinemia may be a CHD risk factor only in younger men (50), only in men with apo E 3/2 phenotype (rather than the more usual apo E 3/3 phenotype) (87), only in men with hypertriglyceridemia (98), only in obese men (99), or only in subjects who have both hyperinsulinemia and microalbuminuria (100). It is possible that hyperinsulinemia is a risk factor only when associated with two or more other metabolic abnormalities, as suggested by the provocative findings that insulin induces endothelin-1 release only in the presence of hypertriglyceridemia (101).

In addition, endogenous insulin levels show considerable diurnal variation and an unfavorable ratio of inter- and intraindividual variability, such that individuals are probably classified for insulin levels more poorly than for other risk factors such as cholesterol. It is also possible that it is not total insulin (as usually measured in epidemiologic studies) but rather the intact or split proinsulins (which cross-react with standard commercial assays) that are atherogenic (102-105). Concentrations of these molecules comprise only around 10% of all insulin-like molecules in non-diabetic subjects, but may represent more than 30% of these molecules in patients with Type 2 diabetes. Thus, the measurement of total immunoreactive insulin may be misleading in studies of diabetic patients and possibly also in subjects with IGT. Some evidence for the atherogeneity of proinsulin comes from a trial in which diabetic patients were treated with a biosynthetic proinsulin; this trial was terminated at 2 years when there were six myocardial infarctions in the pro-insulin-treated group and none in the control group (102). Despres and colleagues (85), however, showed an

association between high levels of fasting plasma insulin and CHD risk in non-diabetic subjects, using a radioimmunoassay that did not cross-react with proinsulin.

Exogenous insulin. If endogenous insulin is atherogenic, then one might expect that exogenous insulin would be associated with an increased risk of CHD. As reviewed by Stern (106), the role of therapeutic insulin as a CHD risk factor remains controversial: Further, any observed associations are difficult to disentangle from the severity of diabetes which prompts insulin use. Observational studies in Arizona of the Pima Indians (107) and in Germany (108) showed a significantly increased risk of CHD associated with insulin treatment, and a preliminary report from the Feasibility Trial of the VA Cooperative Study on Glycemic Control and Complications (109) found that patients with Type 2 diabetes who were randomly assigned to intensive treatment with insulin experienced significantly more cardiovascular events than those assigned to more conventional treatment ($p = 0.04$). In the University Group Diabetes Program trial (67), however, the 10 year cardiovascular death rates were nearly identical in subjects who were assigned to insulin or placebo.

The unresolved status of insulin as a heart disease risk has been summarized by Jarrett (110) who provided objections to the thesis, and by McKeigue and Davey (111) who reviewed reasons why a true insulin–CVD association could be missed.

Other Coronary Heart Disease Risk Factors

The three classical major CHD risk factors, total cholesterol, blood pressure and cigarette smoking, carry a similar increased risk in persons with and without diabetes. These risk factors appear to have an additive effect: In the 12-year follow-up of the Multiple Risk Factor Intervention Trial (112), men with known diabetes had an increased risk of fatal CVD compared to men without diabetes—in the absence of high blood pressure, hypercholesterolemia and cigarette smoking, but these risk factors more than doubled the diabetes-associated relative risk, as shown in Figure 21A.2.

On the other hand, diabetes is associated with adverse changes in CVD risk factors and these adverse effects, which are to some extent different

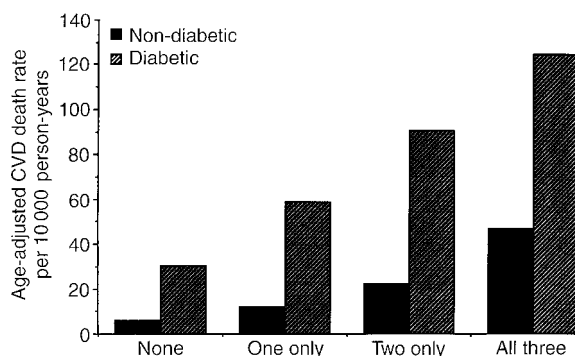


Figure 21A.2 Age-adjusted CVD death rates by presence of number of risk factors for men screened for MRFIT, with and without diabetes, at baseline

in Type 1 diabetes and Type 2 diabetes, may also contribute to the excessive CHD risk in diabetic patients. Less well studied risk factors, such as factors related to thrombogenesis and thrombolysis, may also be involved in this excess risk (113–117).

Lipids and lipoproteins. As reviewed by Laakso (118), lipids and lipoproteins appear to be normal in patients with Type 1 diabetes when adequate metabolic control is maintained. However, when glycemic control deteriorates or diabetic nephropathy ensues, total and low-density lipoprotein (LDL) cholesterol and total and very-low-density lipoprotein (VLDL) triglycerides increase and high-density lipoprotein (HDL) cholesterol decreases. In contrast, patients with Type 2 diabetes typically have elevated total and VLDL triglycerides and reduced HDL cholesterol levels. When glycemic control deteriorates in Type 2 diabetes patients, the HDL and VLDL level abnormalities become less favorable, and total and LDL cholesterol may become elevated. High triglycerides and low HDL cholesterol appear to be important risk factors for CHD in patients with Type 2 diabetes (94, 119, 120). Because lipid and lipoprotein abnormalities may be present for a long time before the diagnosis of diabetes, they may contribute to the increased occurrence of CHD in patients with IGT or newly diagnosed Type 2 diabetes.

No randomized controlled trials of the effect of treatment of dyslipidemia in diabetic patients on CHD risk have been reported. Post hoc subgroup

analyses of data from diabetic patients participating in the Helsinki Heart Study (121), a primary prevention trial using gemfibrozil, and in the Scandinavian Simvastatin Survival Study (4S) (122), a secondary prevention trial using simvastatin, however, suggest that the treatment benefit would be at least as good in diabetic patients as in non-diabetics.

Blood pressure. Many studies have shown that blood pressure is higher and hypertension more common in individuals with diabetes (both Type 1 diabetes and Type 2 diabetes) than in those without abnormal glucose tolerance (123). High blood pressure frequently precedes Type 2 diabetes (75,76), and approximately doubles the risk of CHD in persons with diabetes (112). Antihypertensive treatment reduces mortality rates in hypertensive diabetics (124), although the choice of regimens is controversial (125). As a result, it has been recommended that blood pressure treatment be initiated at lower blood pressure levels in patients with diabetes than in those without.

Metabolic syndrome. The intercorrelations between diabetes or hyperglycemia and other heart disease risk factors have been recognized for many years (126–128), leading to the thesis that CHD is a consequence of a common underlying metabolic disturbance, now variously called the metabolic syndrome, the insulin resistance syndrome, or syndrome X (129). Although the prevalence of the syndrome is unknown, in part because there is no agreement on its components, it is generally agreed that several CVD risk factors including central obesity, dyslipidemia and hypertension often occur together, particularly in Caucasians with Type 2 diabetes or hyperinsulinemia (65,130–133).

Although studies have shown that Type 2 diabetes remains a CVD risk factor after adjusting for several risk factors (120), it still remains unresolved to what extent the metabolic syndrome risk factors could explain the excess risk of CHD in Type 2 diabetes through their additive or interactive effects. Fontbonne (134) has nicely summarized the methodologic problems of multivariable risk factor analysis when the factors are both statistically correlated and metabolically linked.

Microalbuminuria. In 1984 two groups (135,136) reported an excess mortality in prospectively

studied patients with Type 2 diabetes who also had microalbuminuria. Although neither study reported cause-specific mortality, 50% and 88% of deaths, respectively, were attributed to cardiovascular disease. A study from Oxford (England) (137) separately examined CHD mortality and found a significantly increased risk of fatal CHD death in diabetic men and women who had microalbuminuria. A more recent report from Denmark (138) showed that categorically defined microalbuminuria in patients with Type 2 diabetes was associated with a significantly increased risk of fatal CVD, but, in addition, within the normo-albuminuric group an albumin excretion rate above the median was associated with a 2.7-fold increased risk of death ($p = 0.07$).

Many but not all studies of patients with Type 2 diabetes have shown an association between microalbuminuria and hyperglycemia, elevated blood pressure, and hypertriglyceridemia. A smaller number of studies have found microalbuminuria to be associated with increased levels of plasma fibrinogen, increased LDL cholesterol levels, and decreased HDL levels (139). The covariates of microalbuminuria vary in different populations, however. For example, in subjects with Type 2 diabetes from the San Antonio Heart Study, microalbuminuria was associated with higher blood pressure but not with a more atherogenic lipid/lipoprotein profile (140). In contrast, investigators in Finland found that Type 2 diabetes patients with microalbuminuria had higher LDL and VLDL cholesterol levels and lower HDL cholesterol levels compared to non-diabetics, but no differences in blood pressure (141).

A prospective Danish study has shown that microalbuminuria also predicts atherosclerotic vascular disease in patients with Type 1 diabetes; in this study the microalbuminuria-CVD association was independent of conventional heart disease risk factors and the duration and control of diabetes (142).

When microalbuminuria occurs in older adults without diabetes, it predicts an increased risk of future macrovascular disease (143,144). On the other hand, Pedrinelli et al. (145) reported that non-diabetic hypertensive men who had microalbuminuria had higher levels of von Willebrand Factor antigen (a marker for damaged vascular endothelium) than non-diabetic hypertensive men

without microalbuminuria, a finding suggesting that microalbuminuria is a marker for prevalent CHD.

SUMMARY

In Type 1 diabetes, the prevalence of clinically manifest CHD increases sharply after 30 years of age. In Type 2 diabetes, clinically manifest CHD is often already present at the time of diagnosis, and the prevalence of CHD in patients with clinically established Type 2 diabetes is about 2-fold that observed in non-diabetics.

Limited prospective data suggest that Type 1 diabetes increases the risk of CHD almost 10-fold in men and even more in women, compared to non-diabetic men and women. In Type 2 diabetes, a number of studies have reported a 2–3-fold increase in CHD risk in men and a greater increase in women. Thus, in both types of diabetes, the female protection from CHD is to a large extent abolished. After myocardial infarction, diabetics have higher short-term case-fatality rates and a less favorable long-term prognosis than non-diabetics. Data are less consistent regarding the risk or severity of CHD associated with IGT.

Although there is observational evidence to suggest that the degree of glycemia is positively related to CHD risk, this may merely reflect the severity of diabetes. Clinical trial evidence demonstrating a beneficial effect of good glycemic control on CHD risk is still pending. The relationship between plasma insulin levels and CHD risk remains a controversial issue. Diabetes is associated with unfavorable changes in cardiovascular risk factors, including hypertension, abnormalities in the levels and composition of plasma lipids and lipoproteins, and hemostasis factors. It is not yet known whether there is an independent effect of diabetes after controlling for all the diabetes-associated metabolic abnormalities.

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Long-term Complications: Diabetes, Stroke and Lower Extremity Arterial Disease

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Diabetes is a potent risk factor for stroke, as reviewed elsewhere (1,2). Most strokes occur in the elderly and are non-hemorrhagic infarcts; this is also true in diabetic patients. As is the case with coronary heart disease (CHD), diabetes is commonly not diagnosed in older adults until after the stroke.

The two largest prospective studies of stroke and diabetes were conducted in the United States and describe individuals with and without clinically recognized diabetes. The Multiple Risk Factor Intervention Trial (MRFIT) (3) determined the 12-year stroke mortality for 5163 men aged 35–57 years who reported taking medication for diabetes, and 324 815 men without a history of diabetes. The risk of fatal non-hemorrhagic stroke was increased 3.8-fold (95% CI = 2.7–5.3) among those with diabetes, independent of age, race, income, blood pressure, cigarette smoking, and other CHD risk factors. The Nurses' Health Study (4) followed 116 177 middle-aged women for 8 years, 1483 of whom had adult-onset diabetes by self report. There were 24 strokes in the women with known diabetes, compared to 235 strokes among women with no history of diabetes. In multiply adjusted analyses the independent relative risk of ischemic stroke associated with diabetes was 3.0 (95% CI = 1.6–5.7). In both of these studies the relative risk of stroke in diabetics was amplified by other risk factors, particularly high blood pressure.

In the Whitehall Study (5) of London civil servants, middle-aged men with diabetes by history had a 2-fold increased risk of stroke. A 7-year follow-up of two middle-aged cohorts from Finland found that, compared to non-diabetics, men

and women with clinically diagnosed diabetes had a 3- and 5-fold higher risk of stroke, respectively (6). A 2–3-fold increased risk of stroke in persons with diabetes has also been reported in community-based studies which screened for glycemia and included previously undiagnosed diabetics (7–9).

During an 8-year prospective population-based study carried out as part of the MONICA project in Northern Sweden (10), the impact of diabetes on the risk of incident stroke (fatal or non-fatal) was found to be 4.1-fold in men and 5.8-fold in women. The relative risks for stroke mortality were 4.4 and 5.1, respectively. Of all strokes in the population, 18% in men and 22% in women were attributed to diabetes. A large prospective study of a middle-aged cohort from eastern Finland, with an average follow-up of 16.5 years, found that 16% of stroke deaths in men, and 33% in women were attributed to diabetes (11). In this study, men who had diabetes at baseline examination had a 6-fold increased risk of death from stroke compared to non-diabetics, while the relative risk for men who developed diabetes during the follow-up (based on a registry of reimbursed drugs) was 1.7. Women who were diabetic at baseline also were at much higher risk than women who developed diabetes during the follow-up (relative risks 8.2 and 3.7, respectively), suggesting that duration of diabetes is related to stroke risk.

Only a few studies of the diabetes–stroke association have been conducted in populations other than Caucasians of northern European ancestry. Early reports found no significant excess risk of stroke in diabetic Japanese men living in Japan (12) or Hawaii (13), but an excess risk of stroke was found after a longer follow-up of the

Japanese men in the Honolulu cohort (14). African Americans have more diabetes and more strokes than white Americans. Nevertheless, follow-up of a United States national survey found that a medical history of diabetes increased the risk of stroke approximately 2.5-fold in both African Americans and Caucasians, and the increased risk associated with diabetes was nearly identical in men and women (15).

In the Minnesota Heart Survey (16) the short-term case-fatality rate for stroke was similar in diabetic and non-diabetic patients and in men and women, but the 5-year survival was significantly poorer in diabetic women. Among the stroke patients hospitalized in northern Sweden the short-term case-fatality rate for stroke was similar in diabetic and non-diabetic men, but was significantly higher in diabetic than non-diabetic women (10). In a 10-year follow-up study of stroke patients in Umea, Sweden, diabetic patients (men and women combined) were found to have significantly higher mortality and recurrent stroke rates than non-diabetic patients; in a multivariate model, gender had no significant effect on the risk estimates (17).

RISK FACTORS FOR STROKE

Data are not available on the relationship between duration of diabetes and incidence of stroke in Type 1 diabetes. In Finnish studies of Type 2 diabetes, the risk of stroke appeared to increase with the duration of diabetes, although it was not possible to entirely distinguish the effect of duration from the degree of glycemia, which also increased the risk of stroke in these diabetic patients (6,9).

Most studies agree that level of glycemia is either a risk factor for stroke or predicts a poorer outcome in patients who suffer a stroke. Several studies suggest that the prognosis after a stroke is poorer in patients who have higher glucose levels at the time of admission (18–20). In the prospective Wisconsin Epidemiological Study of Diabetic Retinopathy (21), high glycosylated hemoglobin levels were significantly associated with stroke mortality and in two prospective Finnish studies of patients with Type 2 diabetes, high fasting plasma glucose and glycosylated hemoglobin levels were significant and independent predictors of the risk of stroke (6,9). Results of the 10-year follow-up of

the Whitehall Study (5) of middle-aged London male civil servants found that men classified as glucose-intolerant by 2 hour glucose levels above the 95th percentile (who probably had diabetes) had a significantly increased risk of death from stroke independent of other risk factors. However, in the very large MRFIT study (3) the level of fasting glucose in men was an independent predictor of stroke only among cigarette smokers.

The strongest modifiable risk factor for stroke is high blood pressure, which increases the risk of stroke similarly in individuals with and without diabetes (7,8). Relatively little information has been available on dyslipidemia as a predictor of stroke in diabetics. In Finnish Type 2 diabetes patients, elevated triglycerides and low HDL cholesterol, lipid abnormalities characteristic of this type of diabetes, were predictive of stroke risk (6).

LOWER EXTREMITY ARTERIAL DISEASE

Epidemiologic studies of diabetes and lower extremity arterial disease (LEAD) have been reviewed, for example, by Palumbo and Melton (22). Early studies were largely case series based on clinic patients. Because clinicians are aware of the diabetes–LEAD association, patients with severe occlusive arterial disease are more likely to be tested for diabetes. Case studies tend to describe severe disease leading to gangrene and amputation, which is a late stage of LEAD; many more patients with diabetes have foot ulcers (a potentially pre-gangrenous lesion) or intermittent claudication. Older adults with or without undiagnosed diabetes often have bruits or loss of peripheral pulses compatible with undiagnosed LEAD. Ideally, the epidemiologic assessment of subclinical LEAD should include measurement of the ankle/brachial blood pressure index (ABI), which can be assessed using standard blood pressure cuffs and Doppler ultrasound (23); the mean of two readings should be used, as is recommended for other blood pressure studies. Additional measures of toe blood pressure have been recommended to overcome false elevations of ankle blood pressures due to arterial calcification (23). Arterial calcification detected by roentgenograms of the extremities does not necessarily imply occlusive disease, and is not considered further here.

Amputations

The most feared complication of LEAD is limb amputation. In one community-based study, adults with diabetes had an up to 70-fold increased risk of gangrene and amputation (24). A retrospective study of surgeries in Kuopio, Eastern Finland, found a 10-fold excess risk of lower extremity amputation in diabetic men and a 14-fold excess risk in diabetic women (25). In a US study of hospital discharge data from six states, the relative risk of lower extremity amputation in diabetics was approximately 15 times the rate in non-diabetics, and 45% of all amputations occurred in diabetics (26). The relative risk was most marked in younger diabetics who presumably had Type 1 diabetes, but the rates increased with age such that the absolute risk was much greater in the elderly.

A few community-based incidence studies have been reported. A study from England reported that the amputation rate in older diabetics was 8 per 1000 patient-years (24). In Finland, the 7-year amputation rate in middle-aged patients with Type 2 diabetes was 5.6% in men, and 5.3% in women (27). In Wisconsin, the 4-year amputation rate was 2.2% in known diabetics, and rates were the same in persons with onset of diabetes before or after age 30 (28).

Data about amputation rates in diabetics are almost entirely from North America or Europe. The reported wide variations in overall amputation rates around the world may reflect geographic differences in diabetes prevalence, trauma, or the availability of foot care (29).

Foot Ulcers

A foot sore or ulcer usually precedes the gangrene which leads to amputation. It is thought that the diabetic foot ulcer is a result of both impaired peripheral circulation and sensory neuropathy, but not all foot ulcers are associated with LEAD as detected by current methodology. In a study by Walters and colleagues (30), which included measures of ABI and a neurologic examination, 60% of patients with foot ulcers had a macrovascular deficit alone or with neuropathy, and 40% had neuropathy only. As a corollary, not all foot ulcers require surgery; spontaneous healing of

foot ulcers is most apt to occur in patients who have good arterial circulation as defined by high toe systolic blood pressure (31).

The prevalence of past or current foot ulcers varies in population-based studies of patients with diabetes. A history of ever having had a foot ulcer was found in approximately 5% of diabetics in a United Kingdom study (32), 10% in a Swedish study (33), and 15% in a study from southern Wisconsin (34). In an English patient registry study, which included home visits (because patients with foot disease may be housebound), the prevalence of past or present foot ulcer in diabetics was 7.4% (95% CI = 5.8–9.0) compared to 2.9% (1.6–5.5) in age and sex matched non-diabetic patients (30).

Claudication

Intermittent claudication, usually defined as exercise-induced leg pain not present at rest, is strong evidence of LEAD. The largest study using standardized criteria for diabetes and claudication, a Finnish population-based study of 5738 men and 5224 women, found the prevalence of intermittent claudication to be 3.4 times higher in diabetic men and 5.7 times higher in diabetic women than in non-diabetics of the same sex (35). Results were similar in a community-based Finnish study of patients with diabetes, where the age-adjusted prevalence of claudication was 3.8 times higher in diabetic men and 3.2 times higher in diabetic women than in non-diabetic men and women (36).

Incidence studies also show an excess risk of intermittent claudication in adults with diabetes. For example, in the Israeli Heart Study (37), the 5-year incidence of intermittent claudication was 2.2 times higher in men with diabetes compared to men without, and in the Framingham Heart Study (38), the 34-year age-adjusted incidence of intermittent claudication was 2.7 times higher in male diabetics and 3.4 times higher in female diabetics than in men and women without diabetes. In a prospective study of 619 adults with mild diabetes or IGT who were participants in the University Group Diabetes Program clinical trial (39), the 13-year cumulative incidence of intermittent claudication was 37.9% in men and 24.3% in women. These differences may reflect different age groups, criteria for diabetes, or questions used to define claudication.

Pulse Deficit

Several epidemiologic studies have shown a higher prevalence of absent peripheral leg and foot pulses in patients with diabetes than in non-diabetics (40–42). In 1980, Melton et al. (42) reported the first community-based incidence study of pulse deficits among 1073 adult residents of Rochester, Minnesota, who were found to have diabetes between 1945 and 1969. Among those without recognized LEAD at baseline, the incidence of new pulse deficits per 1000 person-years was 26.2 for men and 16.9 for women. Rates increased with age, particularly in men, and with duration of diabetes. The cumulative incidence of pulse deficits after the clinical diagnosis of diabetes was approximately 15% at 10 years and 45% at 20 years.

Ankle/Brachial Index (ABI)

Signs, symptoms and pulse deficits are absent in half of community-dwelling adults who have LEAD detected by more sensitive screening methods, such as ABI and toe systolic pressure (43). Similar results were reported from a German case series of over 600 diabetic outpatients, where 57% of those who had LEAD defined by ABI had no symptoms (44), and 14.4% of 368 female patients and 18% of 255 male patients had LEAD by ABI criteria. In a US study of patients who had Type 1 diabetes for 30 years or longer, the prevalence of LEAD defined by resting or exercise ABI was 30% in women and 11% in men (45).

Risk Factors for LEAD

Risk factors for LEAD in diabetics have been studied infrequently, with divergent results. In a diabetic population in Wisconsin, the modifiable risk factors for amputation included blood pressure, smoking and glycosylated hemoglobin (28). In a Seattle case-control study only low HDL cholesterol emerged as a modifiable factor for amputation (46). In the 7-year follow-up of Finnish patients with Type 2 diabetes, a long duration of diabetes and poor glycemic control, assessed by fasting blood glucose or glycosylated hemoglobin, were independently of each other associated with an increased risk of amputation,

and a low HDL cholesterol also showed a weak association with increased risk (27).

In the Framingham study (47) the major risk factors for intermittent claudication were the same as the risk factors for CHD: age, male sex, high plasma cholesterol, high blood pressure, and cigarette smoking; severity but not duration of diabetes was a risk factor for intermittent claudication (38). Among the University Group Diabetes Program subjects (39), all of whom had mild diabetes or IGT, only hypertriglyceridemia was a risk factor for claudication, and only in men. A German case series of diabetic patients found that LEAD defined by ABI was associated with duration of hyperglycemia and hypertension, but not with male sex or cigarette smoking (44). In a US clinic-based study of patients with Type 1 diabetes and Type 2 diabetes, hypertension and cigarette smoking were the most important risk factors for LEAD defined by ABI (48). In another US study of an incident cohort of Type 1 diabetes patients, those with an ABI < 0.80 at rest had a less favorable lipoprotein profile, higher blood pressure, and were more likely to smoke than those with a higher ABI (49).

One of two US studies of progression defined by change in ABI found that blood pressure and cigarette smoking were independently associated with the progression of LEAD (50), while the other study found that a risk score including smoking, duration of diabetes, HDL cholesterol, and blood pressure predicted progression (51).

Thus, the majority of, but not all, studies suggest that modifiable risk factors for CHD also increase the risk of LEAD among diabetics. Differences between studies could reflect patient selection and selective mortality; diabetics who have LEAD have an increased risk of an acute cardiovascular event (52).

SUMMARY

Stroke

There are relatively few epidemiologic studies of diabetes and stroke, and even fewer which include information on the type of diabetes and stroke confirmed by current diagnostic criteria. Nevertheless, the results are quite consistent, generally showing a 2-fold increased risk of stroke (all types combined) in persons with known and new

diabetes, and an even higher risk for patients with known diabetes. Although diabetes is an independent risk factor for stroke, high blood pressure is the most universal and readily treatable risk factor for stroke in diabetics.

Lower Extremity Arterial Disease

The association of diabetes with severe LEAD leading to amputation is well recognized, but the excess prevalence and incidence of LEAD defined by foot ulcer, pulse deficit or more sensitive screening methods, such as ABI, is much higher. Diabetes appears to be a LEAD risk factor independent of other risk factors; in most studies the risk factors for LEAD are the same as for CHD, with high blood pressure and cigarette smoking being particularly important.

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Long-term Complications: Diabetic Neuropathy

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INTRODUCTION

The first clinical description of peripheral diabetic neuropathy is usually attributed to John Rollo of London who described pain and paraesthesia in the legs of a diabetic patient in 1798 (1). It is now clear that diabetic neuropathy encompasses a number of distinct conditions that have potentially different aetiologies, and a simple clinical classification is generally acceptable to most diabetologists (Table 21C.1).

There have been a number of consensus statements relating to the diagnosis, staging, measurements and assessment of diabetic neuropathy (2–4). The 1988 San Antonio conference considered definition and measurement; a definition was agreed (2): ‘diabetic neuropathy is a descriptive term meaning a demonstrable disorder, either clinically evident or sub-clinical, that occurs in the setting of diabetes mellitus without other causes for peripheral neuropathy. The neuropathic disorder includes manifestations in the somatic and/or autonomic parts of the peripheral nervous system’. It was recommended, that for full classification, at

least one measure be made from each of 5 categories: symptoms, examination, quantitative sensory testing, (q.s.t.), electrodiagnostic studies (EP) and autonomic function tests.

Whereas such a strict definition is useful for clinical trials, it is clearly not feasible for day-to-day clinical practice. A follow-up meeting (3) considered the standardization of procedures and approaches used for clinical trials and epidemiological studies, and the peripheral neuropathy association similarly considered standardization of q.s.t. (4).

An international meeting was held a few years ago to consider the definition, staging and management of diabetic peripheral neuropathy (d.p.n.) for practising clinicians: neuropathy was defined as ‘the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes, after exclusion of other causes’ (5).

In this chapter most of the discussion will refer to somatic distal sensorimotor neuropathy (d.p.n.), although some reference will be made to mononeuropathies and autonomic neuropathies (d.a.n.). The aetiology and epidemiology of d.p.n. will be followed by the presentation of similar data for foot ulceration and amputation.

Table 21C.1 Clinical classification of the diabetic neuropathies

Mononeuropathies	Polyneuropathies
* Isolated	* Sensory—Acute sensory chronic sensorimotor
* Cranial	* Autonomic
* Mononeuritis multiplex	* Proximal motor (amyotrophy)
* Truncal	* Truncal

AETIOLOGY OF DIABETIC NEUROPATHIES

Mononeuropathies

These are generally considered to be due to focal ischaemia (such as cranial ocular mononeuropathies) or entrapment of a specific nerve (such as carpal tunnel syndrome or meralgia paraesthetica) (6). However, the former theory has been

questioned by Hopf et al. who, using magnetic resonance, demonstrated lesions in the ipsilateral oculomotor fasciculus in patients with third nerve palsy (7).

Polyneuropathies

Diabetic polyneuropathies (Figure 21C.1) are clearly of multifactorial aetiology and a number of metabolic and vascular defects have been implicated in their pathogenesis (5,7). Although no specific genetic factors have been implicated in the aetiology (9), more detailed study with newer techniques may yet identify certain predictive factors.

Hyperglycaemia

The DCCT study has provided definitive evidence for the importance of preceding hyperglycaemia in the pathogenesis of d.p.n. intensive insulin therapy reduced the subsequent development of clinical neuropathy by over 60% (10), and maintained nerve conduction velocities (n.c.v.), whereas significant reduction in n.e.v. was observed in the patients randomized to conventional therapy (11). Moreover, at the end of the DCCT trial, only 4% of patients had abnormal autonomic function tests

compared to 9% in the conventional therapy group (11).

Malik et al. had the opportunity to assess the effect of lifelong uncontrolled hyperglycaemia on nerve function and structure in a patient with an insulin receptor gene mutation secondary to Mendenhall's Syndrome (12). The fact that this individual had a severe neuropathy characterized by gross loss of myelinated fibres in the absence of a significant microangiopathy suggests that hyperglycaemia and its metabolic consequences alone can lead to neuropathy (12).

Polyol Pathway Activity

Considerable evidence implicates the involvement of one of the metabolic consequences of hyperglycaemia, increased activity in the polyol pathway, in the development of d.p.n. (8, 12).

Sorbitol levels are increased in peripheral nerves both in experimental diabetic animals and also in diabetic patients, and inhibition of the rate-limiting enzyme of this pathway aldose reductase, by an aldose reductase inhibitor (ARI), can prevent the development of experimental neuropathy and improve nerve function in d.p.n.. Whereas it has previously been suggested that the osmotic effect of Sorbitol accumulation resulting in nerve swelling (Figure 21.C1) and possible restriction of nerve blood flow might be the cause of nerve dysfunction, very recent evidence renders this theory unlikely. Hohman and colleagues have inhibited the next step in the polyol pathway with a sorbitol dehydrogenase inhibitor, thereby causing sorbitol accumulation in experimental animals without an increase in aldose reductase activity. This accumulation of sorbitol in non-diabetic control animals did not lead to any significant deficit in nerve conduction (14).

It now appears that disturbances in redox couples, rather than in osmolytes, is the mechanism by which increased polyol pathway activity leads to neuropathy (7, 13–15). Increased polyol pathway flux is associated with a depletion of the co-factor NADPH which is also required for glutathione reductase: consequent depletion of reduced glutathione renders the cell vulnerable to free radical damage.

Moreover, nitric oxide synthase also uses NADPH as a co-factor, so increased polyol

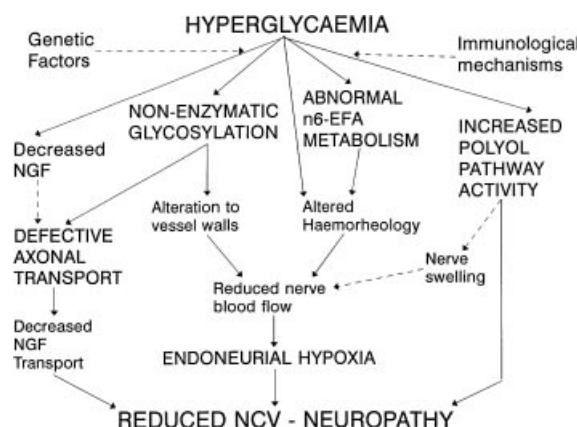


Figure 21C.1 Pathogenetic mechanisms for diabetic neuropathy

Source: Reproduced with kind permission of Elsevier, Amsterdam, from Boulton AJM. Aetiopathogenesis of diabetic neuropathy. In: SM Marshall et al (eds), *The Diabetes Annual* (7) (1993)

pathway activity compromises production of the potent vasodilator nitric oxide, leading to local ischaemia. In summary, increased polyol pathway activity in hyperglycaemic states results in relative vasoconstriction and reduced protection against oxidative tissue damage. Cameron et al. showed that ARI treatment in experimental diabetes corrects or prevents reduced nerve blood flow, thus providing support for the former theory (15).

Nerve Growth Factors (NGF)

There is increasing evidence that a number of neurotrophic factors, the best known of which is NGF, are involved in the maintenance and regulation of normal nerve function in experimental diabetes (13). As NGF has already been used in the treatment of toxic neuropathies, this raises exciting possibilities for further therapies for human diabetic neuropathy.

Non-enzymatic Glycosylation

Non-enzymatic glycosylation is a well described mechanism by which glucose can exert a detrimental effect on diabetes by the accumulation of advanced glycosylation end products (13,16). Its role in the pathogenesis of neuropathy is supported by the observation that aminoguanidine, a glycation inhibitor, partially protects against the nerve conduction deficits and nerve fibre damage in experimental diabetes (17).

Fatty Acid and Carnitine Metabolism

Disturbances in the desaturation of gamma-linoleic acid metabolism occur in diabetes and can precipitate a reduction in nerve blood flow followed by a decreased production of vasodilating eicosanoids (18). Treatment with gamma linolenic acid has been shown to improve nerve function in both experimental and human diabetes (6). Similarly, abnormal carnitine metabolism in diabetes may predispose to the development of neuropathy (8).

Nerve Ischaemia in Diabetes

Increasing evidence is accumulating to implicate neural ischaemia as a major contributory factor in the pathogenesis of diabetic neuropathy (19). This may result from a decreased availability of nitric oxide as described above (which provides a direct connection between metabolic and ischaemic theories of aetiology), or from a direct effect of diabetes leading to altered endoneurial vascular resistance. Certainly a number of drugs with dilator properties have been shown to improve nerve function in experimental diabetes (8). In addition to being efficacious in diabetic rats, preliminary evidence suggests that ACE inhibition may improve nerve conduction in human diabetes (20,21). The major contribution of microvascular abnormalities to the aetiology of d.p.n. is discussed in recent reviews (6,22).

EPIDEMIOLOGY OF DIABETIC NEUROPATHIES

Epidemiological data on the frequency and natural history of types of diabetic neuropathy are limited (1,23). As discussed by Ziegler (24), the prevalence of diabetic neuropathy is variously reported as being from 10 to 100%. This is because of a lack of a generally accepted definition as to what constitutes diabetic neuropathy, difference methods of diagnosis, variable selection criteria and a potential for referral bias.

Few data exist on the prevalence of mononeuropathies (1), which account for less than 10% of all diabetic neuropathies, although in the Rochester diabetic neuropathy study, asymptomatic (i.e. diagnosis by electrophysiology) carpal tunnel syndrome was found in 22% of diabetic patients in this population-based sample (25).

A number of more recent assessments of the prevalence of diabetic neuropathy in geographically defined populations are summarized in Table 21C.2 and will be discussed here. However, not all are population-based and few also assess the prevalence of neuropathic symptoms and signs in the background non-diabetic population.

In the first of these studies, using rigorous criteria including electrophysiology and exclusion of peripheral vascular disease, a prevalence of 11%

Table 21C.2 Epidemiological data in diabetic peripheral sensorimotor neuropathy

Authors (Ref)	Country	Pop- or Clinic-based	Total diabetic pop	Types of diabetes	Criteria for diagnosis	Prevalance (%)
Boulton et al. 1985 (26)	UK	Clinic <60 Years old	387	1, 2 (Insulin-treated)	Signs + BP	20
Knuiman et al. > 1986 (28)	Australia	Pop	1083	1, 2	Sy + signs + EP	11
Maser et al. 1989 (28)	USA	Pop	400	1	Signs	15.5
Lehtinen et al. 1989 (31)	Finland	Pop	132	2 at Diagnosis	Sy & Signs	34
Franklin et al. 1990 (32)	USA	Pop	279	2	EP alone	5.3
Walters et al. 1992 (33)	UK	Pop	1077	1 + 2	Sy & Signs	15.3
Dyck et al. 1993 (25)	USA	Pop	380	1 + 2	Sy & Signs	25.8
Veglio et al. 1993 (34)	Italy	Pop	379	1	Sy & Signs + EP	16.2
Young et al. 1993 (35)	UK	Pop	6487	1 + 2	Sy & signs + EP	47.6
Kumar et al. 1994 (36)	UK	Clinic (multi-centre: <i>n</i> = 118)	811	2	Sy L signs	28
Partanen et al. 1995 (37)	Finland	Pop	133	2	Signs	28.5
					Sy + Signs + EP	41.6
						At diagnosis = 8.3 after 10 years = 41.9

Key: Sy = Symptoms; Type 1 = insulin-dependent diabetes mellitus; Pop = Population-based study; EP = Electrophysiology; Type 2 = non insulin-dependent diabetes mellitus; Clinic = Clinic-based study.

for symptomatic neuropathy and 20% for signs alone was reported in a UK clinic population of insulin-treated patients under 60 years old (26). In a population-based study in rural Australia, Knuiman et al. (27), using a simple clinical examination alone, reported a similar prevalence. The baseline results from the longitudinal Pittsburgh diabetic complications epidemiology study showed a high prevalence of neuropathy (28) in Type 1 diabetes patients, though the prevalence in the subjects aged 18–29 was only 18% compared to the overall rate of 34%. Subsequent follow-up reports of this study have shown the poor predictive value of q.s.t. for the prediction of overt neuropathy development, and also that glycaemic control, hypertriglyceridaemia and hypertension were associated with a higher incidence of subsequent neuropathy, whereas higher levels of physical activity were associated with a lower incidence (29, 30).

Lehtinen et al. (31) assessed the prevalence of neuropathy at diagnosis of Type 2 diabetes in a population-based sample in Finland: they also

showed that 1.4% of a matched non-diabetic sample had signs compatible with peripheral neuropathy.

Although not population-based, the study by Young et al. (35) is the largest published prevalence study and included randomly selected patients from 118 UK diabetic clinics. This study confirmed an association between age and duration of diabetes with the development of neuropathy. The most recently published study, from Finland (37), attempted to assess the incidence by following a cohort of Type 2 diabetes patients for 10 years, together with a non-diabetic control group. The number of patients who had NCV abnormalities in the lower limbs increased from 8.3% (controls 2.1%) at baseline to 41.9% (controls 5.8%) after 10 years. Poor glycaemic control was predictive of the development of neuropathy in this Type 2 diabetes group of patients. In a preliminary report of a cohort study in young Type 1 diabetes patients, Young et al. (38) showed that poor glycaemic control and deteriorating neurophysiology were predictors for the development of diabetic clinical neuropathy.

NEUROPATHY ASSESSMENT FOR EPIDEMIOLOGICAL STUDIES

As stated above, variable diagnostic criteria and patient selection have resulted in widely disparate estimates of the prevalence of d.p.n. The need for a standardized nomenclature and measures of neuropathy was emphasized by Eastman (39). The 1992 consensus statement attempted to define agreed methodology for such studies (3).

Future studies should be population-based with appropriate sampling of both diabetic and representative control subjects. It is desirable to use tools that are simple, safe, characterized by small intra- and interindividual variation, but are accurate, sensitive and specific when compared to the gold standard (24). The problem in diabetic neuropathy is that such ideal measures do not exist, and that the recommendations for the multiple tests of clinical, electrophysiological and autonomic function may simply not be feasible in large-scale population-based studies in many countries.

The problems for the assessment of autonomic neuropathy are even greater as symptoms correlate poorly with signs and autonomic function tests are frequently abnormal in patients with no symptoms or signs of d.a.n. Using sensitive tests of cardiovascular autonomic function, Ziegler et al. have reported a prevalence of abnormality (defined as >3 abnormal tests out of a battery of 6) of 22% in Type 2 diabetes patients, which was significantly greater than the 17% of Type 1 diabetes patients with abnormalities (40). Few other studies of autonomic neuropathy meet the necessary criteria defined by Ziegler and the 1992 consensus (3, 24, 40).

THE DIABETIC FOOT

The loss of a limb or foot remains one of the most feared complications of diabetes and yet foot problems remain the commonest reason for diabetic patients to be hospitalized in the Western world (41). As foot ulceration and amputation are so closely interrelated in diabetes (42, 43) they will be considered together in this section of the chapter, especially as most amputations are preceded by a foot ulcer. The term 'diabetic foot' will be taken to encompass any foot lesion occurring as

a result of diabetes or its complications. The financial cost of diabetic foot disease is staggering: recent data from Sweden suggest that the cost of a single foot ulcer episode was US \$7850 if amputation was avoided, rising to US \$52 920 if amputation was necessary (44). An estimated US\$ 500 million was spent on amputation in the USA in 1988 (45). In addition to the obvious social, economic and personal consequences of foot ulceration and amputation, the reason for the increased interest in this area in recent years is because the majority of foot ulcers, and consequently amputations, are preventable (46). A thorough understanding of the risk factors for foot lesions is therefore essential if a reduction in the late sequelae of neuropathy and peripheral vascular disease (p.v.d.) is going to be achieved (41).

RISK FACTORS FOR THE DIABETIC FOOT

The breakdown of the foot has traditionally been considered to be a consequence of peripheral vascular disease, neuropathy and infection. However, there is no direct evidence that infection is a primary cause, rather it occurs after initial ulceration and makes progression to a serious lesion more probable. In addition to d.p.n. and p.v.d. other more recently recognized risk factors such as high pressures and plantar callus will be considered here.

Peripheral Vascular Disease

A 50% excess of absent foot pulses in both sexes was reported in diabetic subjects from the Framingham Study (47) and other reports from the USA and Finland have confirmed that p.v.d. is a major contributory factor in the pathogenesis of foot ulceration and major amputation (46, 48). It is rarely a single cause in the pathogenesis of ulceration: it is usually the combination of minor trauma, neuropathy and p.v.d. that leads to the neuroischaemic ulcer. Other vascular diseases, such as systolic hypertension and a history of stroke, have recently been confirmed as independent risk factors for amputation in a case-control study from California (49). McNeeley et al. have also confirmed that p.v.d. (as measured by

decreased transcutaneous oxygen tension) is an independent risk factor for diabetic foot lesions (50).

Peripheral Neuropathy

Both peripheral somatic and autonomic neuropathy have been confirmed as independent risk factors for foot ulceration (51). Patients can progress to the degree of insensitivity necessary for trophic ulceration without ever having experienced neuropathic symptoms (an important point in terms of the identification of the 'high-risk' foot), whereas others develop the 'painless-painful foot' with positive symptoms, but insensitivity on examination rendering the foot at high risk of ulceration (51). Young et al. have confirmed for the first time, in a prospective study, the direct causative link between d.p.n. and ulceration (52) whereas Reiber et al. have demonstrated causal pathways for incident lower-extremity ulcers (46). Sympathetic autonomic neuropathy leads to decreased sweating and dry skin that is prone to crack and fissure, and increased blood flow, resulting in the warm, insensitive foot at high risk of ulceration. Severe deficits in somatic and autonomic function are contributory factors (together with minor trauma and possibly reduced bone density) to the development of neuropathic arthropathy (Charcot foot) (53).

Foot Pressure Abnormalities

The combination of high plantar pressures and d.p.n. have been shown to result in a 28% risk of ulceration during a 2½-year prospective study (54). High-risk pressures have also been demonstrated in the remaining foot of unilateral amputees and may contribute to the high risk of second amputations in such patients (55).

Callus

A combination of dry skin from autonomic dysfunction and increased vertical shear stresses is believed to lead to callus formation. Removal of callus reduces high foot pressures (56) and the presence of callus under weight-bearing areas has

recently been shown to be strongly predictive of subsequent ulceration (57).

Other Risk Factors

Patients with other microvascular complications, particularly nephropathy at all stages, have an increased risk of foot ulceration (58). Perhaps the most at-risk group of both ulceration and amputation, however, are those with a past history of any diabetic foot lesions (51).

EPIDEMIOLOGY OF DIABETIC FOOT PROBLEMS

There is a paucity of reliable population-based data as to the prevalence and incidence of diabetic foot problems. One of the major problems is the lack of universally accepted definitions for some of the key risk factors for neuropathy as discussed above (59). Despite these problems a number of reports have produced useful data that are summarized in Table 21C.3. In their Oxford community study, Neil et al. (60) found that 7% of a small cohort of diabetic patients had ulceration, 4% were amputees and 23% had risk factors for ulceration. In the largest population-based study from the UK, Carrington reported on a sample of 5260 individuals in the North West of England. Depressingly, 4.9% of patients had a past history of, or a current, foot ulcer and 1.25% were already amputees (below or above knee). Using a modified neuropathy disability score (NDS as a measure of neuropathy (neuropathy = moderate or severe NDS) and reduced or absent foot pulses as a measure of p.v.d. (35), 41.6% of the diabetic population had one or more risk factors for foot ulceration (62). The fact that more than 50% of patients over 60 years of age in this study and that of Kumar et al. (36) had risk factors for foot lesions presents important implications for screening and preventive foot care education of the diabetic population. With respect to incidence of amputation in the UK, a study from Scotland suggested a rate of 10 amputations per 1000 diabetic persons per year (63); it is certainly recognized in the USA that amputations are at least 15 times more common amongst diabetic patients (45).

Table 21C.3 Epidemiological data on diabetic foot problems

Authors (Ref)	Country	Pop- or clinic- based	Total diabetic population (<i>n</i>)	Prevalence		Incidence		Risk factor or ulcers (%)
				Foot ulcers (%)	Amputation (%)	Foot ulcers (%)	Amputation (%)	
Neil et al. 1989 (60)	UK	Population (age 7/60 years)	259	7	4			23
McLeod et al. 1991 (61)	UK	Clinic	6 500	2.6	2.1			
Kumar et al. 1995 (36)	UK	Population (Type 2 diabetes only)	811	1.4				41.6
Carrington 1995 (62)	UK	Population	5 260	4.9	1.25			64
Borssen et al. 1990 (64)	Sweden	Population (age 15–50)	395	0.75				
Siitonen 1993 (48)	Finland	Population	477				0.5	
Bouter et al. 1993 (65)	Holland	Population	300 000			0.8 *	0.4	
Pendsey 1994 (66)	India	Clinic	11 300	3.6				
Moss et al. 1992 (67)	USA	Population	2990		3.6	10.1 **	2.1 **	

* Only include annual incidence of foot ulcers in patients hospitalized for this problem.

** Incidence figures over 4 years.

Two studies from Scandinavia report data on the prevalence and incidence of ulcers and amputation, suggesting that these problems are both less common than in published series from elsewhere (48,64). Higher rates have been observed in Holland, India and the USA (65–67).

PREVENTION OF ULCERATION AND AMPUTATION IN DIABETIC PATIENTS

There is now strong evidence that education of both patients and health care professionals results in a lower incidence of both ulceration and amputations (41). The two compelling reasons for patient education are: (1) that a number of studies have confirmed a depressingly low level of knowledge of foot problems amongst diabetic patients; and (2) that targeted education at high-risk groups can have a major impact. Malone et al. (68), for example, reported that a 1 hour education session of high-risk patients conducted by a podiatrist resulted in a 3-fold reduction in major amputations over a 2-year follow-up period when compared to a matched control group. With

respect to education of health care professionals, Fletcher reported that 1 in 5 of diabetic foot ulcers resulted from some form of professional mismanagement and that up to 50% of heel ulcers might result from poor preventive measures (69).

The needs and requirements for reducing ulceration and amputation rates worldwide are therefore straightforward:

1. Establish a programme of regular screening to identify high-risk patients. The concept of the annual review whereby all patients have a thorough examination at least annually is well established in some countries (71). National patients' organizations have published guidelines as to what care to expect (71,72). Screening programmes should be simple but effective and do not require expensive equipment (41).
2. Plan an effective educational programme that is tailored to the needs and educational levels of the target 'high-risk' population. Causal pathways to ulceration and amputation are well researched (46); education should prevent the combining of a number of component

causes that provide a sufficient cause that leads to ulceration or amputation.

CONCLUSIONS

The rewards of establishing an effective foot care screening and education programme are potentially great, and include a realization of the St Vincent's target (73) of a 50% reduction in diabetic amputations.

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Long-term Complications: Diabetic Nephropathy

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DEFINITIONS AND NATURAL HISTORY OF DIABETIC NEPHROPATHY

Diabetic nephropathy is defined as persistent proteinuria (more than 500 mg of protein or 300 mg of albumin/24 hours) in patients without urinary tract infection or other diseases causing the proteinuria. This definition is based on clinical findings but patients with clinical diabetic nephropathy will also have classical histopathological changes (1) as first described by Kimmelsteel and Wilson (2). In patients with insulin-dependent diabetes (Type 1 diabetes) development of clinical nephropathy is a relatively late event, but in patients with non-insulin-dependent diabetes (Type 2 diabetes) proteinuria may be present at diagnosis (3).

Clinical diabetic nephropathy is a relatively late stage in the progression of diabetic renal disease progressing from normoalbuminuria over microalbuminuria to clinical diabetic nephropathy and end-stage renal failure. The *normal urinary albumin excretion rate* in non-diabetic individuals as well as in patients with newly diagnosed Type 1 diabetes is well below 30 mg/24 hours. In non-diabetic individuals the median albumin excretion is 2.3 µgram/min, highest in males (2.6 vs 2.2 µgram/min) but independent of age in the age-interval 30–70 years (4). Thus there is a very wide range from these normal values to the level defining nephropathy. The term *microalbuminuria* or incipient nephropathy was first used in relation to three independent prospective studies of the prognostic value of albuminuria, showing that increased urinary albumin excretion rate (UAER) predicts subsequent development of diabetic nephropathy (5–8). Microalbuminuria was subsequently defined

as UAER between 30 and 300 mg/24 h (20–200 µg/min) in two out of three consecutive urine samples (9). From this stage the patient may progress further to *clinical diabetic nephropathy*, defined as an albumin excretion exceeding 300 mg/24 h or total protein excretion exceeding 0.5 g/24 h. At this stage the patient will also experience a gradual loss of renal function and subsequently develop *end-stage renal failure* (ESRF) needing treatment by dialysis or renal transplantation to avoid death from uraemia. Before the introduction of treatment at each of these stages, the median duration of normoalbuminuria in patients' progression to nephropathy would be approximately 7–10 years. With a mean progression rate of 20% per year in the microalbuminuric stage this would correspond to a mean duration of 6–9 years (10), and without treatment the median survival of patients with nephropathy would be 7–8 years (11). As discussed later, all these figures have changed considerably over the last 20 years, primarily due to the introduction of antihypertensive treatment of patients with diabetic nephropathy.

INCIDENCE AND PREVALENCE OF DIABETIC NEPHROPATHY

As seen in Figure 21D.1 the incidence of diabetic nephropathy in Type 1 diabetes patients is low during the first 10–15 years of diabetes duration (11, 12). Thereafter, it increases to a maximum after 18 years of duration, and then it declines. This pattern is found in all populations of Type 1 diabetes patients where the natural history has been studied (11–14). In Type 2 diabetes patients diabetes onset may precede the clinical diagnosis

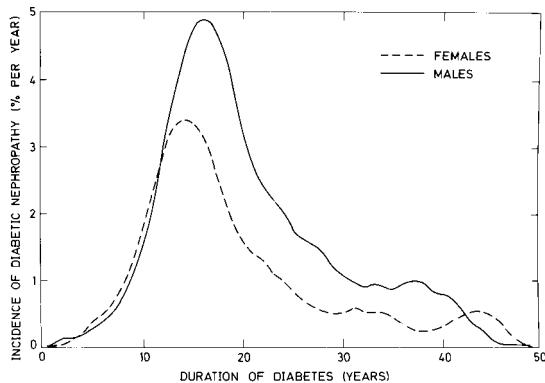


Figure 21D.1 Incidence of diabetic nephropathy in patients with insulin-dependent diabetes mellitus (--- Females, — Males)

Source: Reproduced from Borch-Johnsen K, Andersen PK, Deckert T. The effect of proteinuria on relative mortality in Type 1 (insulin-dependent) diabetes mellitus. *Diabetologia* (1985); **28**: 590–596 by permission from the Springer-Verlag

by many years (15, 16), which may explain the high prevalence of nephropathy at diabetes onset (Table 21D.1). Only very few populations have undergone regular screening programmes for Type 2 diabetes, allowing a precise identification of diabetes onset. Pima Indians in Arizona, USA, are a high-risk population for Type 2 diabetes where not only regular screening with oral glucose tolerance tests, but also regular screening for proteinuria is performed. In this population, where the prevalence of Type 2 diabetes by age 50 years is 50% (17) the incidence of diabetic nephropathy is also almost identical to what is found in Type 1 diabetes patients (18).

In Type 1 diabetes patients microalbuminuria is also rare before 5 years of diabetes duration, but thereafter the prevalence of microalbuminuria increases (19,20). In patients developing diabetic

nephropathy the mean increase rate of microalbuminuria is 20%/year but with large interindividual variation (10). As shown in Table 21D.1 the prevalence of microalbuminuria is also high in newly diagnosed Type 2 diabetes patients (21,22). Again the most likely explanation is the diagnostic delay of diabetes in Type 2 diabetes patients.

DIABETIC NEPHROPATHY— A DISAPPEARING DISEASE?

Over the last 50 years the natural history of diabetic nephropathy has changed dramatically. In patients developing Type 1 diabetes before 1950 the risk of developing diabetic nephropathy was nearly 50% (11). The risk was higher in males than in females, and highest in patients developing Type 1 diabetes during childhood. Since the 1950s the incidence of diabetic nephropathy has decreased considerably, and this decreasing risk has been confirmed in several different countries (12–14). It seems, however, as if the typical incidence pattern with the highest incidence after 15–18 years of duration followed by a marked decline is unchanged. If this is correct, then the decreasing incidence would be due to a decreasing lifetime risk of developing nephropathy, and not only to a postponement of the disease. Recent Swedish data could indicate that diabetic nephropathy is about to disappear in Sweden (14), but data from a Danish cohort from the same period have not been able to confirm this observation. Thus, there is no doubt that the incidence of diabetic nephropathy is decreasing in many countries, while the most likely explanation for the very low incidence of nephropathy in the Swedish cohort would be that the median HbA1c level was nearly normal and far below what has been found in most other studies.

Table 21D.1 Stages of diabetic nephropathy in Type 2 diabetes and Type 1 diabetes

Stage	U-albumin (UAER) (µg/min)	Blood pressure	Prevalence in Type 2 diabetes (%)	Prevalence in Type 1 diabetes (%)
Normo-albuminuria	0–20	Normal		
Micro-albuminuria	21–200	Normal or elevated	13–27	9–20
Clinical diabetic nephropathy	> 200	elevated	5–48	8–22
End-stage renal failure	> 200	Hypertension	—	2–5

MORTALITY, DIABETIC NEPHROPATHY AND MICROALBUMINURIA

Patients with persistent proteinuria have a very poor prognosis compared to patients without nephropathy. Untreated, patients with nephropathy will develop end-stage renal failure and die after 7–8 years (11). As seen in Figure 21D.2 the very high excess mortality rate in Type 1 diabetes patients is due to patients developing nephropathy, while patients not developing nephropathy have a much lower excess mortality (23). Type 1 diabetes patients with microalbuminuria also have a substantial excess mortality rate compared to normo-albuminuric patients (24), but the impact of microalbuminuria on mortality is not as pronounced as in Type 2 diabetes patients. In Type 2 diabetes patients proteinuria is also a poor prognostic sign with mortality rates in patients with proteinuria being several times higher than in normo-albuminuric patients. The prognostic impact of microalbuminuria in Type 2 diabetes patients was first described by Mogensen (25) and Jarrett (26) in 1986. They both found that microalbuminuria was associated with increased mortality, primarily from cardiovascular disease. More recently, this was confirmed by Gall et al. (27) in a large, clinic-based population of Type 2 diabetes patients. Thus, development of diabetic nephropathy (or microalbuminuria) is the stron-

gest marker of poor prognosis in Type 1 diabetes as well as in Type 2 diabetes patients.

NEPHROPATHY, MICROALBUMINURIA AND CAUSE OF DEATH

In Type 1 diabetes patients with clinical diabetic nephropathy, end-stage renal failure/uraemia is the dominating cause of death, responsible for nearly 60% of all deaths (11,13,28). However, cardiovascular disease (CVD) is almost as frequent, which would be rather surprising in a group dying between the ages of 30 and 55 years. Thus, the majority of the excess mortality from cardiovascular disease seen in Type 1 diabetes patients is due to development of diabetic nephropathy (29).

In Type 2 diabetes patients the association between proteinuria and CVD is even stronger, with most of the patients dying from CVD before ever developing end-stage renal failure (30). This is also true for Type 2 diabetes patients with microalbuminuria, where the excess mortality is predominantly due to development of cardiovascular disease with accelerated atherosclerotic manifestations, acute myocardial infarctions and stroke (31).

DIABETIC NEPHROPATHY—AETIOLOGY AND RISK FACTORS

The aetiology of diabetic nephropathy is only partly understood, and several hypotheses need further confirmation. Several risk factors are involved, however, some of which are modifiable while others are genetic or otherwise unmodifiable.

Metabolic regulation is a very important risk factor for development of diabetic nephropathy. Epidemiological studies in Type 1 diabetes patients as well as in Type 2 diabetes patients have consistently demonstrated that poor metabolic control is associated with an increased risk of developing nephropathy (13,32,33). Even stronger evidence for the impact of metabolic control comes from the controlled clinical trials using different intensified treatment regimens for obtaining good metabolic control. In Type 1 diabetes patients (34–37) as well as in Type 2 diabetes patients (38) strict metabolic control leads to a significant reduction in the risk of

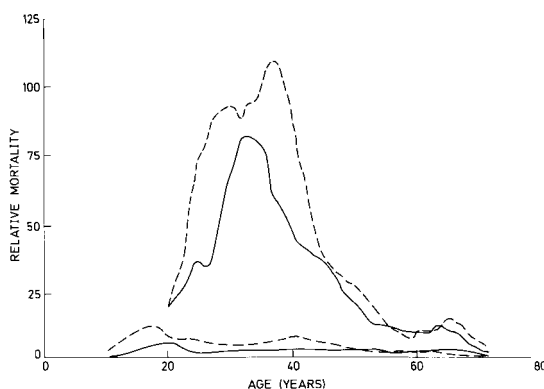


Figure 21D.2 Relative mortality in Type 1 diabetes patients with (upper lines) and without (lower lines) diabetic nephropathy (- - Females, — Males)

Source: Reproduced from Borch-Johnsen K, Andersen PK, Deckert T. The effect of proteinuria on relative mortality in Type 1 (insulin-dependent) diabetes mellitus. *Diabetologia* (1985); 28: 590–596 by permission from the Springer Verlag

developing microalbuminuria and the risk of progressing from microalbuminuria to persistent proteinuria. A large number of smaller trials have been performed, and in 1993 Wang et al. (39) calculated the risk reduction in Type 1 diabetes patients associated with strict metabolic control using a meta-analysis (Table 21D.2). The overall risk reduction was in the order of 50%, and thus very close to the risk reduction found in the DCCT trial including 1441 Type 1 diabetes patients (37). On the basis of the results of the DCCT study there appears to be a direct (linear or even log-linear) relationship between blood glucose and the risk of microvascular complications. The clinical and practical implication of this is that any improvement in metabolic regulation—at individual level as well as on a population level—would be followed by a reduction in the risk of developing diabetic nephropathy.

The impact of strict metabolic control on prognosis is most pronounced in normoalbuminuric patients and patients with microalbuminuria. Very few trials have included patients with overt diabetic nephropathy. Viberti et al. (40) studied 12 patients with proteinuria and declining glomerular filtration rate. The patients were randomized to continuous subcutaneous insulin infusion (insulin pumps) or conventional treatment, and they were followed-up for 12–24 months. No significant difference in the decline rate of GFR was found between the groups, but because of the limited size of the study and the relatively short follow-up the study should be interpreted with caution.

Increasing blood pressure and hypertension are associated with progression of diabetic renal disease (41–44). Epidemiological studies show that the prevalence of hypertension is higher in patients with nephropathy than in normoalbuminuric patients in Type 1 diabetes as well as in Type 2 diabetes patients. In patients with microalbumi-

nuria relatively few have hypertension according to the WHO criteria (45–47), but there is significant difference in blood pressure levels between patients with microalbuminuria and normoalbuminuric patients. Thus, blood pressure has been shown to be a strong prognostic marker once microalbuminuria and nephropathy have developed. It is, however, still unclear whether blood pressure at diabetes onset predicts later development of diabetic renal disease. Epidemiological studies, comparing long-term surviving Type 1 diabetes patients with patients developing nephropathy, indicate that there is no difference in blood pressure at diabetes onset between patients developing nephropathy and those not developing nephropathy (48). Other studies indicate that the increase in blood pressure goes together with the increase in UAER. Thus the importance of blood pressure for the aetiology of nephropathy remains unclear. What is known is that long-term surviving Type 1 diabetes patients (more than 40 years) without complications are characterized by having blood pressure levels identical to those they had at diabetes onset, suggesting that increasing blood pressure/ hypertension may well be an important element in the pathogenetic mechanism leading to progression in diabetic renal disease. As discussed later, genetic factors associated to hypertension and familial predisposition to hypertension may be associated with development of diabetic nephropathy.

Numerous other risk factors have been suggested for diabetic nephropathy. Cigarette smoking is one risk factor that has been suggested by several groups (49–52). The potential mechanisms for cigarette smoking as a risk could either be through the vaso-constriction and regional hypoxia induced by smoking or alternatively through the increase in blood pressure induced by smoking. Three previous studies have been cross-sectional (49–51), while the last (52) is a follow-up of a cohort, first examined by 9 years of diabetes duration. Because of these methodological problems it is impossible to draw firm conclusions regarding causality. Recent studies seem to indicate that continued cigarette smoking promotes progression of already existing microalbuminuria/nephropathy (53). However, because of the high risk of cardiovascular disease in these patients, and with smoking being the most important risk factor for development of cardiovascular disease, there is every good reason to

Table 21D.2 Relative risk of microvascular complications in patients treated with intensified insulin therapy compared to conventional treatment, based on a meta-analysis (39) and the DCCT study (37)

	Nephropathy	Retinopathy
Meta-analysis by Wang et al. (39)	0.34 (0.20–0.58)	0.49 (0.28–0.85)
DCCT study (37)	0.44	0.55

intensify smoking cessation programmes in any clinic or unit treating diabetic patients.

Other risk factors may well be relevant in specific regions where environmental factors cause non-diabetic renal disease in a large proportion of the population. It would therefore be relevant to perform epidemiological studies of diabetic nephropathy in such regions. Finally, the epidemiology of diabetic nephropathy as well as risk factors for its development have predominantly been studied in White, European, Caucasian, Type 1 diabetes populations, and population-based studies in Type 1 diabetes patients in the rest of the world and in Type 2 diabetes patients should definitely be encouraged.

GENETIC AND OTHER NON-MODIFIABLE RISK FACTORS

Clustering of disease within families is a good indicator of inherited factors playing a role in its aetiology or pathogenesis. Familial clustering cannot distinguish between genetic inheritance and shared environment, but even so simple family studies provide a good basis for further research and also for the search for candidate genes. Seaquist et al. (54) were the first to show familial clustering of diabetic nephropathy, and this observation has subsequently been confirmed by other groups (55,56). The fact that only 50% of the patients developed diabetic nephropathy before 1950, when strict metabolic control was almost unobtainable, would also suggest that there is interindividual variation in the susceptibility for developing diabetic nephropathy (57). It is therefore likely that genetic factors play an important role in determining the susceptibility of the individual patient. The *HLA system*, strongly associated with the risk of developing Type 1 diabetes (58), has been extensively studied, but the evidence so far does not suggest that factors in the HLA region play a major role (59). In 1994 Marre et al. (60) found that *insertion/deletion polymorphism in the angiotensin converting enzyme gene* was associated to development of diabetic nephropathy, but subsequently other groups have been unable to confirm this observation (61). Increased sodium-lithium countertransport activity, which is associated with essential hypertension (62), has also been found in patients with diabetic nephropathy (63,64). There

are conflicting data as to whether this increase is induced by diabetes and enhanced by diabetic nephropathy or whether it is a genuine risk factor for development of nephropathy, and family studies seem to indicate that the increased Na/Li-countertransport activity in patients with nephropathy is not an inherited trait (65). *Familial predisposition to hypertension* (transmitted through unknown genetic factors) has also been suggested by some (66) but disputed by others. It should be recognized here, that studies of transmission of phenotype as blood pressure will be confounded by secular changes in the phenotype studied. For blood pressure this is highly relevant. The prevalence of essential hypertension has decreased considerably over the last 30 years (67), and furthermore the treatment of hypertension is much more effective now than it was 30 years ago. Therefore better studies are needed to settle this discussion, and without the relevant genetic markers it is going to be very difficult to solve the problem.

In 1989 Deckert et al. formulated the 'Steno Hypothesis' (68), suggesting that impairment of heparan-sulphate metabolism is a key event in the development of diabetic nephropathy, and that this impaired metabolism is the link between diabetic nephropathy and associated generalized cardiovascular disease. This hypothesis has led to intensive search for genetic factors related to the synthesis of heparan and to the sulphatation of heparan. As described by Kofoed-Enevoldsen (69) in his review in 1995, the evidence is still inconclusive, but there is some support for the hypothesis from genetic studies in animal models as well as in diabetic patients.

In conclusion, genetic susceptibility is clearly important, but with our limited understanding of the exact pathogenesis of diabetic nephropathy it is difficult to identify the relevant genetic markers. Identification of these markers may, however, give important clues to the pathogenetic mechanisms and lead to preventive and therapeutic actions.

NEPHROPATHY, RETINOPATHY AND MACROVASCULAR DISEASE—WHAT IS THE LINK?

Patients with diabetic nephropathy are at very high risk of developing other late diabetic complications. This is true for retinopathy, neuropathy and

cardiovascular disease. The *renal-retinal syndrome* has been known for years, and refers to the fact that nephropathy and retinopathy are often present at the same time. In Type 1 diabetes patients the age- and duration-adjusted risk of developing sight-threatening proliferative retinopathy is 4–6-fold higher in patients with nephropathy than in patients without nephropathy (70). This is also true in older onset insulin-treated patients (diagnosed after 30 years of age) and in Type 2 diabetes patients (71). Poor metabolic control and hypertension are important risk factors shared by retinopathy and nephropathy (70–73) which may in part explain why the two complications go together. Common, underlying pathogenetic mechanisms as suggested in the Steno Hypothesis (68) may, however, also explain this phenomenon.

As discussed already, there is a link between *nephropathy and macrovascular disease*, as demonstrated through the increased risk of dying from CVD in patients with established nephropathy or microalbuminuria. In Danish Type 1 diabetes patients the risk of dying from cardiovascular disease is 10-fold higher in patients with nephropathy than in patients without nephropathy, adjusted for age and diabetes duration. We recently confirmed this observation in Finland (74), which not only has the highest incidence of Type 1 diabetes in the world (75), but also is among the leading countries with respect to coronary heart disease and stroke (76). In a

population-based study of more than 5000 Type 1 diabetes patients followed-up for 20 years we found that the risk of CHD, stroke and CVD is 10-fold higher in patients with nephropathy than in patients without nephropathy (74). Mortality studies may be seen as less valid, as they rely on the recorded cause of death. They are therefore sensitive to diagnostic misclassification. We therefore performed a cohort study in Type 1 diabetes patients, looking at myocardial infarction, classifying ECGs on the basis of Minnesota coding (77). Again we found a 10-fold increased risk in patients with nephropathy. These observations have been confirmed in Type 1 diabetes patients (24) as well as in Type 2 diabetes patients (27). Another consistent finding in all these studies is that the risk of CVD is the same in males and females. In the non-diabetic population the risk of developing CVD is much higher in males than in females, particularly below the age of 70 years. If a woman develops diabetes she will lose this relative protection from CVD for reasons not yet fully understood. The pathogenesis of the increased risk for developing cardiovascular disease in patients with diabetic nephropathy is only partly understood. Patients with diabetic nephropathy are characterized by generalized changes in their risk-factor profile, favouring the development and progression of atherosclerosis (78, 79). Table 21D.3 summarizes some of the well-known risk factors for cardiovascular disease that are affected in patients

Table 21D.3 Changes in cardiovascular risk factors and in mortality/morbidity associated with increased albumin excretion in diabetic patients and non-diabetic individuals with increased UAER

	Type 1 diabetes patients		Type 2 diabetes patients		Non-diabetic individuals
UAER (µg/min)	20–200	> 200	20–200	> 200	> 8 (or 15)
Blood pressure	↑	↑ ↑	↑	↑ ↑	↑
Cholesterol	↑	↑	↑	↑	—
HDL-chol.	—	↓	—	↓	↓
LDL-chol.	—	↑	—	↑	—
Triglyceride	—	↑	—	↑	—
Fibrinogen	↑	↑	—	↑	—
von-Willebrand	↑	↑	↑	↑	—
TER-albumin	↑	↑	↑	↑	↑
Selectivity index	↓	↓	—	—	↓
Mortality	↑	↑	↑	↑	↑
Cardiovascular disease	↑	↑	↑	↑	↑

This table is based on the following references:
Type 1 diabetes and Type 2 diabetes: 16, 20, 22, 24, 43, 44, 78, 79.
Non-diabetic individuals: 4, 88–98.

with diabetic nephropathy. Many of these atherogenic risk factors are changed in the same direction in patients with microalbuminuria in Type 1 diabetes patients as well as in Type 2 diabetes patients. Recently we have been able to demonstrate similar changes in non-diabetic individuals with elevated UAER ($> 10 \mu\text{g}/\text{min}$). As seen from Table 21D.3 the changes are rather extensive with respect to the number of parameters affected, but within each risk factor the difference in the distribution between patients with and without nephropathy is modest. Our interpretation therefore, is that this aggregation of risk factors cannot by themselves explain the huge differences in the risk of developing CVD. Again, we therefore suggest a common, underlying pathogenetic mechanism for micro- and macrovascular complications as stated in the Steno Hypothesis (68).

DIABETIC NEPHROPATHY—FUTURE PERSPECTIVES

As already discussed, progression of microalbuminuria to clinical diabetic nephropathy can—at least in part—be prevented by strict metabolic control. Furthermore, antihypertensive therapy in general decreases or normalizes the urinary albumin excretion rate. Most intervention trials with antihypertensive therapy in patients with microalbuminuria have been short-term studies (6–24 months) (80–82) leaving unanswered the question whether it would prevent development of diabetic nephropathy. One long-term study has shown that the risk of developing overt diabetic nephropathy is significantly lower in patients treated with an ACE inhibitor (Captopril) than with placebo (83), and this observation was confirmed in a larger study with 92 patients followed-up over 2 years (84). Thus ACE-inhibitor treatment is effective in preventing progression to diabetic nephropathy. Whether this is also the case for other antihypertensive agents remain unanswered.

In patients with diabetic nephropathy the most important treatment is antihypertensive treatment. The beneficial effect was first shown by Mogensen (41) and Parving (42). In a follow-up of patients with diabetic nephropathy diagnosed before the ‘antihypertensive era’ (1957–73) and in the early ‘antihypertensive era’ (diagnosed 1979–83) Mathiesen et al. found that the 8-year survival

increased from 48 to 87% (85). This study showed that after using antihypertensive treatment as a routine in the clinic, but not as part of a controlled clinical trial, the prognosis considerably improved. In these three studies (41,42,85) different antihypertensive regimens were used, and a beneficial effect of lowering of blood pressure was seen independent of type of treatment. In the study by Lewis et al. (86) the aim was to obtain the same blood pressure level in the two groups, using Captopril or placebo in combination with other (non-ACE-inhibitor) antihypertensive agents. In this study there was an additional effect of ACE inhibitors compared with the control group, but whether the antihypertensive effect in itself was effective could not be analysed due to the design of the study. Thus, it is likely that control of blood pressure significantly reduces the annual rate of decline in GFR, and thereby considerably postpones the development of end-stage renal failure.

In conclusion, screening for microalbuminuria and proteinuria in combination with antihypertensive therapy is the key element in the prevention of end-stage renal failure in diabetic patients. The generally accepted recommendation for treatment target is a blood pressure $\leq 140/90$ (87).

PROSPECTS FOR FUTURE INTERNATIONAL COLLABORATIVE RESEARCH

As already mentioned, the research within the field of diabetic nephropathy has been done on White, European Caucasian populations. This is true for epidemiological studies as well as for intervention studies and basic physiological and genetic studies. Thus, very little is known about the effect of ethnicity on the risk of developing nephropathy and the progression of the disease once it has developed. From epidemiological studies of cardiovascular disease it is, however, well known that the prevalence of important risk factors for progression of nephropathy as hypertension shows great variation between ethnic groups. Thus, collaborative, population-based studies using standardized protocols should be encouraged, similar to the worldwide standardized incidence registers for Type 1 diabetes.

Continuous search for genetic factors associated with development of nephropathy is another area

which calls for international collaboration. Such studies will only be successful if sufficient numbers of informative families can be co-opted, and very few countries will have sufficient numbers of informative families to perform these studies on their own.

Finally, future large-scale controlled clinical trials should take into consideration that potential treatment effects may depend on factors such as ethnicity, socio-economic status and general living conditions related to where the person is living. Therefore international collaboration in this field is also needed to ensure generalizability of the results of future trials.

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Long-term Complications: Diabetic Retinopathy

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The study of the epidemiology of diabetic retinopathy has been greatly improved by the development and adoption of a standardized grading scheme. Many studies of the prevalence, incidence, and risk factors for diabetic retinopathy have been conducted and a Medline® search generates hundreds of references. However, it is difficult to compare the results from some of the earlier studies because the methodology employed varied significantly.

CLASSIFICATION

The manifestations of diabetic retinopathy have been the subject of extensive study over the past three decades and examples of retinal changes associated with diabetes are shown in Figures 21E.1a through to 21E.1e. The modified Airlie House classification of diabetic retinopathy used in the Diabetic Retinopathy Study (DRS) (1) was extended for use in the Early Treatment Diabetic Retinopathy Study (ETDRS) (2). This classification was based on the findings in seven standard 30° retinal photographic fields, with reference to standard photographs of characteristic abnormalities. This classification was further modified to develop a retinopathy scale (3), which divides diabetic retinopathy into 13 levels ranging from absence of retinopathy to severe vitreous haemorrhage. This classification has become the gold standard for subsequent epidemiological study, including the Diabetes Control and Complications Trial (DCCT) (4).

Simplified classifications of diabetic retinopathy are used by clinicians to grade disease severity, usually on the basis of findings from ophthalmologic

scopic examination. The simplified classification shown in Table 21E.1 is now widely accepted (5). Previous terminology is included in brackets.

The microaneurysm is the hallmark of retinal microvascular change in non-proliferative diabetic retinopathy. Mild non-proliferative changes will usually be present for many years before vision is affected. The grading of retinopathy has significant implications regarding risks of visual loss, timing of follow-up, and necessity for treatment. In the ETDRS, the cumulative rate of progression from *mild* non-proliferative retinopathy (mild NPDR) to high-risk proliferative diabetic retinopathy (PDR) was 0.8% at 1 year and 15.5% at 5 years. In contrast, the rate of progression from *severe* NPDR to high-risk PDR was 14.6% at 1 year and 56% at 5 years. Therefore, eyes with mild NPDR may be safely followed at yearly intervals, whereas eyes with severe NPDR must be followed at least 4 monthly.

The commonest cause of visual loss in non-proliferative diabetic retinopathy is macular oedema. This is characterized by the gradual accumulation of fluid and lipid in the macular region of the retina as a result of chronic retinal capillary leakage. Macular oedema typically causes gradual, moderate visual loss which can progress to legal blindness (vision less than 6/60 in both eyes).

In addition to classifying levels of retinopathy, the ETDRS used the term 'clinically significant macular oedema' (CSME) to describe thickening of the retina (often associated with lipid exudates) involving the centre or near the centre of the macula. Retinal thickening is detected ophthalmoscopically using binocular stereoscopic viewing but may also be detected on stereoscopic photographs. The finding of CSME has significant

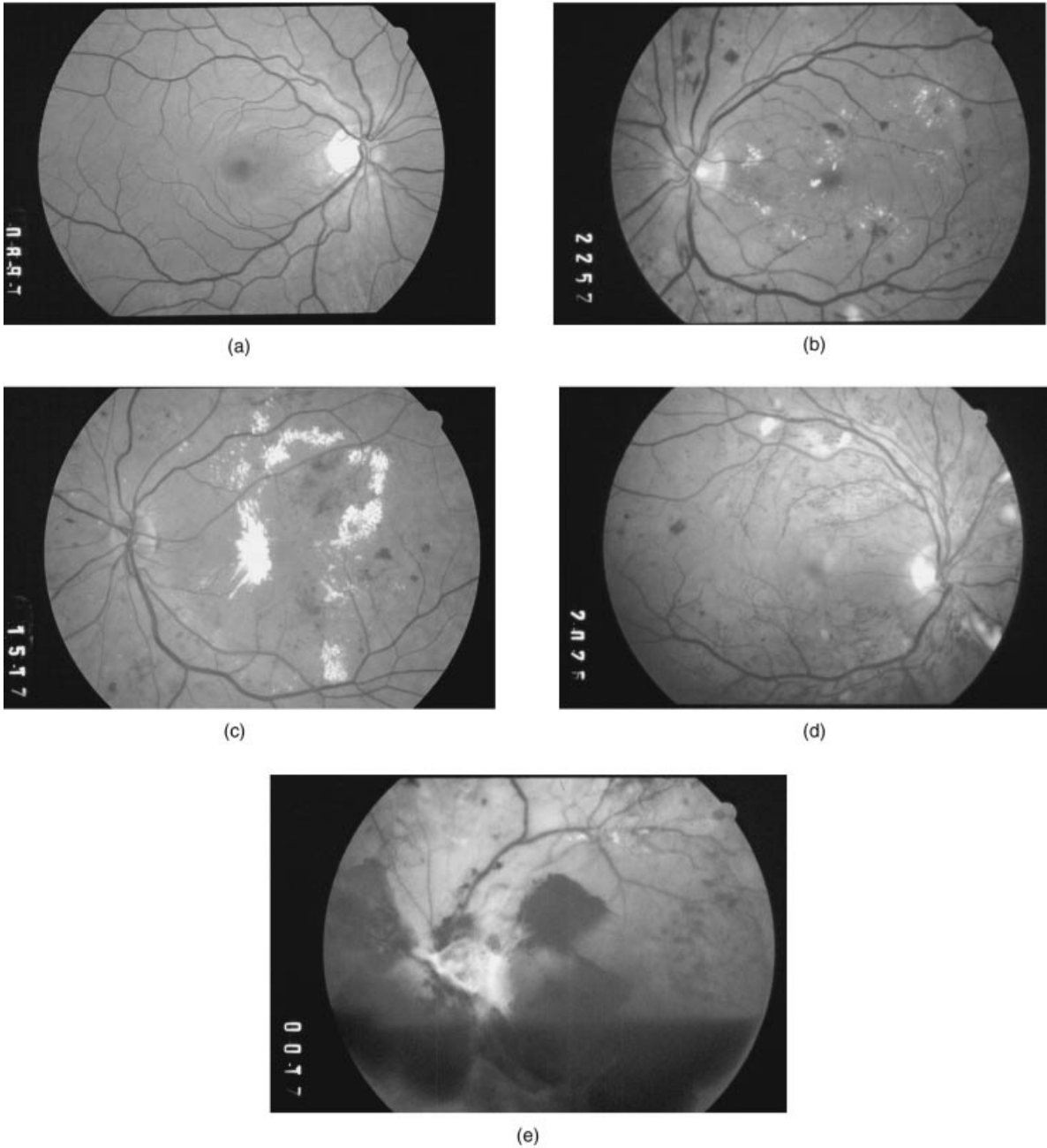


Figure 21E.1 Natural progression of diabetic retinopathy

- a. Normal retina (right eye)
- b. Moderate non-proliferative retinopathy with microaneurysms, haemorrhage and lipid exudate (left eye)
- c. Moderate non-proliferative retinopathy with visual loss due to macular oedema (left eye)
- d. Severe non-proliferative retinopathy with widespread IRMA and cotton wool spots (right eye)
- e. Advanced proliferative retinopathy with visual loss due to vitreous haemorrhage (left eye)

Table 21E.1 Classification of diabetic retinopathy (1)

Diabetic retinopathy stage	Clinical features
Minimal NPDR (background)	Mas only
Mild NPDR (background)	Mas and occasional retinal haemorrhage
Moderate NPDR (transitional)	Mas, more severe retinal haemorrhage, cotton wool spots and hard exudates
Severe NPDR (preproliferative)	At least one of the following: Severe Mas and severe haemorrhage in all quadrants Venous beading in at least two quadrants
PDR	NVE, NVD < $\frac{1}{3}$ disc area
High-risk PDR	NVD > $\frac{1}{3}$ disc area, NVE > $\frac{1}{2}$ disc area with vitreous or preretinal haemorrhage
Advanced PDR	High-risk PDR with traction retinal detachment involving the macula or dense vitreous haemorrhage

NPDR = non-proliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy; Ma = microaneurysm; NVE = neovascularization elsewhere; NVD = neovascularization on or within one disc diameter of the optic disc; IRMA = intraretinal microvascular abnormalities.

implications for treatment which will be discussed in a later section.

Proliferative diabetic retinopathy is characterized by the formation of neovascularization (new blood vessels growing forward from the surface of the retina) in response to widespread retinal ischaemia. These new vessels are fragile and prone to bleeding (vitreous or preretinal haemorrhage), causing sudden visual loss which may be severe and prolonged. Continued fibrovascular proliferation into the vitreous may result in traction, retinal detachment and permanent blindness.

PREVALENCE AND INCIDENCE

Prevalence

One of the major limitations of prevalence studies is the inability to establish temporality. Selective survival can be a source of disparity when comparing quantified risk factors between prevalence and incidence studies. (6)

Prevalence rates of diabetic retinopathy are available from many studies and are summarised in Table 21E.2 (7–53). The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) is the only study devoted solely to describing the prevalence, incidence, and risk factors associated with diabetic retinopathy (20,21). Patients were recruited through their physicians between 1 July 1979 and 30 June 1980. The cohort comprised 1210 Type 1 diabetes patients diagnosed before the age

of 30 and 1370 patients diagnosed after the age of 30. Results from WESDR comprise a major number of papers on the epidemiology of diabetic retinopathy and will be referred to throughout this chapter.

Although rates of diabetic retinopathy vary by time and geographic location, nearly everyone with diabetes will develop diabetic retinopathy within 20 years of diagnosis. The prevalence of any diabetic retinopathy in people with diabetes duration less than 5 years varied from 0 in Detroit (10) and 2% in Portuguese (40) to 18% in Italians (31), 22% in Nauruans (16–18), 23% in Africans (28), 32% in non-Hispanic whites in the US (35) and Spanish (43), and 35% in Taiwanese (42). At the time of diabetes diagnosis, prevalence of any diabetic retinopathy varied from less than 1% in Rancho Bernardo, California (38), to 10% in Beaver Dam, Wisconsin (39), 14% in non-Hispanic whites in the US and 16% in Mexican Americans (30), and 14% in female Samoans and 17% in male Samoans (51). These differences in retinopathy rates at diabetes identification clearly reflect access and use of health services.

Incidence

In comparison with prevalence studies, there are far fewer studies of the incidence of diabetic retinopathy (54–69) (Table 21E.3). Also, different grading systems have been used, making it difficult to compare the results across study populations.

Table 21E.2 Prevalence of diabetic retinopathy in various populations

Author (ref), year	Setting	Number	DM type	DM duration (y)	Retinopathy stage	Prevalence (%)
Osuntokun (7), 1969	Nigeria	758	Type 2 diabetes + Type 1 diabetes	<5 >5 >10 >15 >20	Any	3.6 7.0 11.7 23.1 50.0
Kahn (8), 1975	Joslin Clinic	914	Type 2 diabetes + Type 1 diabetes	<10 10–14 15+	Any	7 26 63
Jarrett (9), 1979	WHO multinational	Varied by site	Type 2 diabetes + Type 1 diabetes	0–6 7–13 14–20	Any	Range 2.2–30.0 Range 17.8–75.0 Range 32.4–77.8
Frank (10), 1980	Detroit	122		0–4 5–9 10+	Any	0 27 71
Mitchell (11, 12), 1980, 1990	Clinic in Newcastle, Australia	1210	Type 2 diabetes + Type 1 diabetes	Varied	Any Proliferative Maculopathy	49 7 10
		5519			Any Proliferative Maculopathy	35 5 10
Segal (13), 1983	Israel	445	Type 2 diabetes Type 1 diabetes	Varied	Any	28 64
Heriot (14), 1983	Cook Islands	986	Type 2 diabetes	Varied	Any	8.2
Yanko (15), 1983	Israel	178	Type 2 diabetes + Type 1 diabetes	11–13 14–16 >16	Any	23 43 60
King (16), 1983 Heriot (17), 1983 Zimmet (18), 1984	Nauru	1583	Type 2 diabetes	0 1–4 5–9 10+	Any	6 22 37 57
Kollarits (19), 1984	Rural Ohio	624	Type 2 diabetes + Type 1 diabetes	≤10 11–20 21–40	Background Proliferative Background Proliferative Background Proliferative	8.4 1.9 20.1 7.1 27.3 18.2
Klein (20–23), 1984, 1987	Wisconsin WESDR	2366	Type 2 diabetes	Varied	Any Proliferative IRMA Macular oedema	39.1 2.9 2.6 3.7
			Dx < 30y		Any Proliferative IRMA	71 23 16.5
			Type 1 diabetes Dx > 30y		Macular oedema Any Proliferative IRMA Macular oedema	11.1 70.2 14.1 8.8 15.2
Jerneld (24), 1986	Sweden	399	Type 1 diabetes	0–10 11–20 21–30 31+	Any Proliferative Any Proliferative Any Proliferative	19 2 58 10 88 34 100 65
Fujimoto (25), 1987	Japanese American men	78	Type 2 diabetes + Type 1 diabetes	Varied	Any Proliferative	11.5 2.6
Kingsley (26), 1988 Orchard (27), 1990 Rolfe (28), 1988	Pittsburgh children's hospital Central Africa	696 600	Type 1 diabetes Type 2 diabetes + Type 1 diabetes	Varied 0–6 7–13 14+	Severe Any Severe Any Severe	57 (♂), 64 (♀) 22.8 2.0 49.3 5.0 73.7 15.8

Table 21E.2 (continued)

Author (ref), year	Setting	Number	DM type	DM duration (y)	Retinopathy stage	Prevalence (%)
McLeod (29), 1988	Rural England	191 eyes	Type 1 diabetes	0–9	Any	17.9
					Severe	0
				10–19	Any	47.2
					Severe	5.7
				20–29	Any	75.5
					Severe	14.3
				30+	Any	72.7
					Severe	31.8
Haffner (30), 1988	Mexican Americans (MA)	313	Type 2 diabetes	New Dx	Any	15.7 (MA), 14.3 (NH)
	Non-Hispanic Whites (NH)				Severe	3.9 (MA), 0 (NH)
				<10	Any	38.8 (MA), 29.4 (NH)
					Severe	16.3 (MA), 8.8 (NH)
				≥10	Any	84.7 (MA), 46.7 (NH)
					Severe	66.1 (MA), 26.7 (NH)
Garancini (31), 1989	Italy	838	Type 2 diabetes + Type 1 diabetes	≤5	Background	18.2 (ID), 17.4 (NID)
					Proliferative	13.6 (ID), 3.1 (NID)
				6–10	Background	43.3 (ID), 27.9 (NID)
					Proliferative	0 (ID), 7.1 (NID)
				11–20	Background	63.0 (ID), 41.5 (NID)
					Proliferative	7.4 (ID), 6.5 (NID)
				>20	Background	50.0 (ID), 35.0 (NID)
					Proliferative	35.7 (ID), 21.7 (NID)
Moriarty (32), 1989	Jamaica	158	Mature onset	0–4	Maculopathy	27
				5–20		42
				21+		81
Lester (33), 1991	Ethiopia	1699	Type 2 diabetes + Type 1 diabetes	20+	Any	45.5
					Proliferative	33.1
Verhoeven (34), 1991	The Netherlands	137	Type 2 diabetes	Varied	Background	31
					Proliferative	4
Hamman (35), 1991	Hispanics (H), Non-Hispanic Whites (NH)	187H 92NH	Type 2 diabetes	<5	ANY	18 (H), 32 (NH)
	San Louis Valley, US			5–14.9		48 (H), 53 (NH)
				15+		61 (H), 85 (NH)
Gall (36), 1991	Denmark	549	Type 2 diabetes	Varied	Any	35
					Proliferative	4
Samanta (37), 1991	Leicester, UK, migrant Asians	456	Type 2 diabetes + Type 1 diabetes	Varied	Background	4.6 (♂), 5.8 (♀)
	Caucasians	451			Proliferative	4.9 (♂), 3.5 (♀)
					Background	11.7 (♂), 15.1 (♀)
					Proliferative	13.9 (♂), 5.4 (♀)
Klein (38), 1991	Rancho Bernardo California	155	Type 2 diabetes	New Dx	level ≥15	0.7
Klein (39), 1992	Beaver Dam Wisconsin	445	Type 2 diabetes + Type 1 diabetes	New DX	Any	10.2
					Proliferative	0
					Mascular oedema	2.0
				Previous Dx		
			Type 1 diabetes		Any	69.6
					Proliferative	6.3
					Macular oedema	10.3
			Type 2 diabetes		Any	29.9
					Proliferative	0.4
					Macular oedema	0.7
Pinto-Figueiredo (40), 1992	Portugal	1302	Type 1 diabetes Dx < 30y	0–4	Any	2
					Proliferative	0
				5–9	Any	36
					Proliferative	0
				10–14	Any	78
					Proliferative	7
				15–19	Any	87
					Proliferative	23
				20–24	Any	86
					Proliferative	33
Joner (41), 1992	Norway	371		Varied	Any	32.8
					Proliferative	0
Chen (42), 1992	Taiwan	527	Type 2 diabetes	New Dx	Any	23
					Proliferative	0.5
				<4	Any	35.3
					Proliferative	3.2
				5–9	Any	49.3
					Proliferative	4.0
				<10	Any	55.1
					Proliferative	2.9

Table 21E.2 (*continued*)

Author (ref), year	Setting	Number	DM type	DM duration (y)	Retinopathy stage	Prevalence (%)
Fernandez-Vigo (43), 1993	Spain	1179	Type 2 diabetes + Type 1 diabetes	<5	Any	31.5
					Proliferative	4.0
				6–10	Any	46.2
					Proliferative	5.6
				11–15	Any	59.2
Farrell (44), 1993	Cherokee Indians	606	Type 2 diabetes + Type 1 diabetes		Proliferative	6.8
				>15	Any	67.2
					Proliferative	9.3
				Varied	Any	24.6
					Proliferative	8.7
Freeman (45), 1993	American Indians	1147	Type 2 diabetes + Type 1 diabetes	Varied	Proliferative or Macular oedema	1.7
Sparrow (46), 1993	England	101	Type 2 diabetes	Varied	Background	48
Falck (47), 1993	Finnish children	194	Type 1 diabetes	<5	Proliferative	2
				5–10	Any	1.9
				>10		20.6
Fairchild (48), 1994	Australian adolescents	255	Type 1 diabetes	2.2–8.4		26.3
Kuzuwa (49), 1994	Japan	2115	Type 2 diabetes + Type 1 diabetes	0–4	Any	42
					Any	13.8 (NID), 16.7 (ID)
					Proliferative	2.9 (NID), 3.3 (ID)
				5–9	Any	33.0 (NID), 27.3 (ID)
					Proliferative	6.1 (NID), 3.0 (ID)
				10–14	Any	43.7 (NID), 79.1 (ID)
					Proliferative	10.9 (NID), 29.2 (ID)
Stolk (50), 1995	Rotterdam	6191	Entire population	15–19	Any	56.6 (NID), 80.8 (ID)
					Proliferative	15.0 (NID), 26.9 (ID)
				Varied	Any	4.8
				New Dx	Any	17.2 (♂), 14.3 (♀)
					Proliferative	0 (♂), 0 (♀)
Collins (51), 1995	Western Samoa		Type 2 diabetes	Previous Dx	Any	45.7 (♂), 41.5 (♀)
					Proliferative	5.7 (♂), 3.8 (♀)

As seen with the prevalence data, the incidence of retinopathy is related to the duration of diabetes. Consistent temporal trends are not obvious because of the variation in methodology and reporting of results.

RISK FACTORS

Extensive research has been conducted to define risk factors associated with the prevalence and incidence of diabetic retinopathy. Information from this body of research has led to the development of medical and public health interventions targeted towards primary, secondary and tertiary prevention of diabetic retinopathy. However, it is difficult to summarize the results of the studies because of the different methodologies employed. Some of the larger studies have presented their findings in numerous papers and have not presented a definitive integrated risk factor paper. This makes it difficult to assess the

independence and relative importance of the different risk factors.

It has been noted that selective survival can influence comparisons in retinopathy risk factors between incidence and prevalence studies (6). Therefore, it will be clearly noted whether various factors were found to be associated with an increased prevalence or incidence of diabetic retinopathy.

Duration of Diabetes

Duration of diabetes has been shown in nearly every study to be the strongest predictor for both the incidence and prevalence of diabetic retinopathy. As can clearly be seen in Tables 21E.3 and 21E.4, the association between diabetic retinopathy prevalence and incidence and diabetes duration appears linear, although there may be a leveling off of risk after 30 years duration, possibly due to a survivorship effect.

Table 21E.3 Incidence of diabetic retinopathy in various populations

Author(ref), year	Setting	Number	Follow-up (y)	DM type	DM Duration (y)	Retinopathy stage	Incidence
Nielsen (52), 1984	Denmark	215	1	Type 1 diabetes	<10	Background Proliferative	2.7 0
					10–19	Background Proliferative	4.7 8.1
					≥20	Background Proliferative	3.7 1.9
Nielsen (53), 1984	Denmark	273	1	Type 2 diabetes	<5	Background Proliferative	2.6 0
					6–10	Background Proliferative	4.3 2.9
					>	Background Proliferative	4.5 1.1
Sjølie (54), 1985	Denmark	577	8	Type 1 diabetes	10 15 20 25 30	Background Proliferative	1♀, 6♂ 10♀, 10♂ 16♀, 20♂ 19♀, 33♂ 21♀, 38♂
Mitchell (55), 1985	Australia	1210	Person-years	Type 2 diabetes + Type 1 diabetes	Varied	None–any None–vision threatening Mild–worse Mild–vision threatening Moderate–vision threatening	8 0.4 8 4 13
Dwyer (56), 1985	Rochester Minnesota	1135	Person-years	Type 2 diabetes Type 1 diabetes	Varied	Any Proliferative Any Proliferative	15.6 7.0 45.8 1.1
Teuscher (57), 1988	Switzerland	358	8	Type 2 diabetes Type 1 diabetes	Varied	None-proliferative None-proliferative	3 9
Klein (58), 1989	Wisconsin WESDR	1370	4	Dx < 30y Dx > 30y Type 2 diabetes	Varied	None-proliferative None-proliferative	8 34.4
				Type 1 diabetes		Any Progression Progression to proliferative Any Progression Progression to proliferative Proliferative	24.9 2.3 47.4 34 7.4 0 2
Nelson (59), 1989	Pima Indians	953	1000 person-years	Type 2 diabetes + Type 1 diabetes	0–5 5–10 10–15 15–20 ≥20	Proliferative	5 26 12
Klein (60), 1989	Wisconsin WESDR	1262	4	Type 2 diabetes Dx < 30y Dx > 30y	Varied	Mascular oedema	2.9 8.2 8.4
Sasaki (63), 1990	Japan	976	1000 person years	Type 2 diabetes	Varied	Any	39.8
Cohen (64), 1991	New Zealand	188	1000 person years	Dx > 30y	Varied	All Proliferative	60 7
Lee (65), 1992	Oklahoma Indians	370	Mean 12.7	Type 2 diabetes	<4 4–7 8–11 ≥12	Non–proliferative	12.4 15.0 13.0 34.8
Rith-Najarian (64), 1993	Minnesota Chippewa Indians	346	1000 person-years	Type 2 diabetes	Varied	Proliferative	12
Agardh (65), 1993	Sweden	325	4	Dx > 30y	Varied	Severe	5.7
			Type 2 diabetes Type 1 diabetes				16.1
Klein (68), 1994	Wisconsin WESDR	1298	10	Type 2 diabetes Type 1 diabetes Dx < 30y Dx > 30y	Varied	Any Progression to proliferative Any Progression to proliferative Any Progression to proliferative Macular oedema	67 10 89 30 79 24 13.9
							20.1 25.4
Chen (68), 1995	Taiwan	471	4	Type 2 diabetes	New Dx <4 ≥4	Any Progression to proliferative Any Progression to proliferative Any Progression to proliferative	4.8 0 15 3.6 31.1 8.2
Vitale (71), 1995	Baltimore	189	Mean 6.1	Type 1 diabetes	Varied	Clinically significant macular oedema	21.7

Glycated Haemoglobin/Blood Glucose Control

Blood glucose control has consistently been shown, along with duration of diabetes, to be one of the strongest predictors of the incidence, prevalence, and progression of diabetic retinopathy (70–78).

The Diabetes Control and Complications Trial (DCCT) was a multicentre randomized control trial to determine whether intensive diabetes treatment to achieve blood glucose levels as close to non-diabetic as possible would reduce the risk of development and/or progression of diabetic retinopathy and the other long-term complications of diabetes in Type 1 diabetes patients (4). Two patient groups were randomized: (1) a cohort of 726 patients free of retinopathy at baseline; and (2) 715 patients with mild or non-proliferative diabetic retinopathy. After an initial early worsening at the first 6 and 12 months visits, there was an increasing beneficial effect in the treatment groups as compared with the control groups. The trial was stopped early when it became unethical to randomize patients to the control groups that received standard insulin treatment.

The DCCT results were convincing for the effect of tight control in Type 1 diabetes patients and they support the recommendation that most Type 1 diabetes patients should also receive intensive treatment to maintain blood glucose levels as close to non-diabetic as possible. However, the extent to which the results are applicable to Type 2 diabetes patients is not known. The association of blood glucose control with diabetic retinopathy in Type 2 diabetes has been demonstrated in cross-sectional and prospective studies, but a clinical trial similar to the DCCT would be necessary to evaluate the costs and benefits of tight control in Type 2 diabetes.

Type of Diabetes

Incidence and prevalence rates of diabetic retinopathy are generally higher in Type 1 diabetes patients, even considering duration of diabetes (Tables 21E.2 and 21E.3). WESDR investigators have demonstrated a higher incidence (60, 79) and prevalence (20–23) of retinopathy in Type 1 diabetes patients, regardless of their age at diagnosis. No full multivariate analyses have been

published that examine difference in retinopathy rates between Type 1 diabetes and Type 2 diabetes patients while controlling for known confounders such as duration and blood glucose control.

Gender

In the vast majority of studies, gender was found not to be associated with the incidence (80, 81) or prevalence (21, 46–48, 82–90) of diabetic retinopathy.

WESDR investigators found that the severity of retinopathy prevalence was significantly higher in males diagnosed under 30 years of age with duration of at least 10 years (standardized coefficient = -1.96) (20). However, they did not find any significant difference in the 4-year (58) or 10-year (66) incidence or progression of diabetic retinopathy by gender.

Blood Pressure

Because diabetic retinopathy is a vascular disorder, it is biologically plausible that disturbances of the vascular system such as hypertension could be causally related to the pathogenesis of diabetic retinopathy. There have been a large number of publications that included analyses regarding blood pressure and diabetic retinopathy (16, 20, 21, 31, 46–48, 51, 59, 80–85, 88, 90–97). The results have been inconsistent, even among the studies that reported a significant association. Blood pressure is a potentially important risk factor because it is amenable to change through behavioural or medical intervention.

Blood pressure was not significantly related to retinopathy prevalence in Nauruans with Type 2 diabetes (16, 17, 98), Minnesotans with Type 2 diabetes (83), Italians (31), the Pittsburgh Epidemiology of Diabetes Complications Study cohort (95), clinic patients with Type 1 diabetes (81), Finnish children (47), Japanese patients (88), adolescents with Type 1 diabetes (48), and Western Samoans with Type 2 diabetes (51). Additionally, blood pressure was not related to the incidence or progression of retinopathy in the WESDR (94).

In the Pima Indians, systolic blood pressure was significantly related to the incidence of exudates (9% increase in exudate incidence for 20 mm

increase in blood pressure), but was not significantly related to the incidence of retinal haemorrhages (91). The incidence of proliferative retinopathy was more than twice as common in people with systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg (61). In a study of Oklahoma Indians, systolic blood pressure was found in multivariate analyses to be positively associated with retinopathy prevalence, although the effect was quite small ($\beta = 0.009$) (82). In multivariate analyses, systolic blood pressure was also significantly related to retinopathy incidence (RR = 1.32 for systolic blood pressure ≥ 160 mmHg compared with pressure < 130 mmHg) (80).

WESDR investigators found that systolic blood pressure was positively associated with the severity of diabetic retinopathy prevalence in younger onset people with diabetes (21). However, it was diastolic blood pressure that was positively associated with the severity of diabetic retinopathy in older age onset people with diabetes (20). In older onset people with diabetes, systolic blood pressure was positively associated with the presence of macular oedema (22).

Systolic blood pressure was found to be positively associated with the prevalence of diabetic retinopathy in Western Australians ($\beta = 0.013$ for supine pressure) (84), in Japanese Type 2 diabetes patients ($\beta = 0.259$) (92), Type 2 diabetes Hispanics and non-Hispanic whites (OR = 1.29 for each 10 mmHg rise) (93), Italian Type 2 diabetes patients ($\beta = 0.29$) (96), rural English Type 2 diabetes patients ($\beta = 0.023$) (46), black Maryland Type 2 diabetes residents (OR = 2.92 for systolic blood pressure > 150 mmHg compared with blood pressure ≤ 120) (97), and rural Swedish Type 2 diabetes residents (90). In a separate study of Type 2 Swedish patients, systolic blood pressure was positively associated with the prevalence of retinopathy (85), while elevated diastolic blood pressure was found to predict the progression of retinopathy (99). However, multivariate analyses were not presented for the prevalence data and for the incidence data it is not clear what variables were included in the multivariate analyses to control for confounding.

The disparity in conclusions from these many studies could be due to a number of factors. Obviously, differences in measurement can affect classification of both the blood pressure and the

retinopathy status. Failure to adequately control for confounders in an analysis can seriously affect interpretation of the data. Finally, other factors such as genetics and environment could be acting as effect modifiers or confounders in the association between blood pressure and diabetic retinopathy. It is an area that requires further study.

Blood Cholesterol

The role of blood cholesterol in the aetiology of diabetic retinopathy has also been investigated because of the biological plausibility of an association between these two diseases and the possibility of modification through diet and/or medication. The majority of studies found no significant associations between total blood cholesterol level and retinopathy incidence (80, 81) or prevalence (42, 48, 52, 82, 84, 91, 100). In several studies, triglyceride levels were also not related to retinopathy incidence (80) or prevalence. (82, 90)

In the Pittsburgh Epidemiology of Diabetes Complications Study, the odds of proliferative retinopathy were not significantly associated with LDL cholesterol, but were associated with triglycerides in Type 1 diabetes patients aged 30+ (OR = 1.44, range 1.01–2.07 excluding nephropathy, n.s. including nephropathy) (87). There does not appear to be any convincing evidence for a strong association between blood cholesterol and the prevalence of diabetic retinopathy.

Smoking

A number of cross-sectional study designs have been employed to investigate the potential association between cigarette smoking and retinopathy prevalence (42, 46, 59, 82, 83, 91, 93, 95, 101, 102). Because smoking is a modifiable behaviour, cigarette smoking as a risk factor for diabetic retinopathy could have enormous public health importance. In 1977, researchers reported that the number of smokers with proliferative retinopathy rose with increasing diabetes duration, but did not report the results of multivariate analyses (101). All other cross-sectional studies found no significant association between cigarette smoking and retinopathy prevalence after controlling for confounders (42, 46, 59, 82, 83, 90, 93, 95, 102).

After controlling for potential confounders, cigarette smoking was found not to be a risk factor for the incidence of retinopathy in the Pima Indians (59), in a clinic-based study of Type 1 diabetes patients (81), or in the WESDR (103, 104).

Alcohol Consumption

Alcohol consumption is also important to consider as a risk factor for diabetic retinopathy because of the public health potential for behaviour modification. In cross-sectional analyses, alcohol use was not associated with retinopathy prevalence in the Pittsburgh Epidemiology of Diabetes Complications Study (95) or the WESDR (105).

Conflicting results have been reported from the only two prospective investigations of alcohol and retinopathy. An English study of 296 diabetic men free of retinopathy at baseline examination found that heavy drinkers (>10 pints beer per day) were three times as likely to develop exudates or proliferative retinopathy (59). WESDR investigators found no association between alcohol consumption (classified as none, light, moderate, heavy) and the incidence or progression of retinopathy (106). The discrepancy in results could have arisen from differences in classification or cut-off levels of the exposure variable, with less statistical power to detect a significant association in the WESDR due to relatively low exposure levels compared with the British cohort.

In summary, there does not appear to be any convincing evidence that moderate alcohol consumption is a risk factor for diabetic retinopathy.

Socio-economic Factors

Low socio-economic status has been shown to be associated with morbidity and mortality from a number of chronic diseases, ostensibly because of the relationship with poor nutrition, poorer medical care and control and high-risk behaviours. Several studies have assessed the effect of various socio-economic factors on diabetic retinopathy (42, 107, 108). A study of Type 2 diabetes participants in the San Antonio Heart Study revealed no association between socio-economic status and retinopathy prevalence in Mexican Americans and non-Hispanic Whites (107). Similarly, re-

searchers in China did not find an association between socio-economic factors and retinopathy prevalence (42).

WESDR researchers investigated the association of socio-economic factors and the incidence of proliferative retinopathy and vision loss (108). They found that younger onset women with less education were nearly four times as likely to develop proliferative retinopathy, but found no associations with vision loss or in older onset women or men.

In summary, the relation between socio-economic factors and diabetic retinopathy is not clear and the existing evidence would not lead to the development of any targeted public health campaigns to decrease the incidence or prevalence of diabetic retinopathy.

Miscellaneous Medications

WESDR researchers found no association between aspirin use and retinopathy prevalence (111) or digoxin and retinopathy progression (109) or digoxin and retinopathy progression (110).

One of the objectives of the Early Treatment Diabetic Retinopathy Study was to assess whether use of aspirin for cardiovascular disease or other indications affected the course of diabetic retinopathy. (111, 112) Nearly 400 patients with mild to severe non-proliferative or early proliferative diabetic retinopathy were randomly assigned to receive either 650 mg per day aspirin or placebo. The data revealed that aspirin treatment was neither beneficial nor harmful in the progression of retinopathy.

Physical Activity

Physical activity is prescribed to people with diabetes as a means for controlling blood glucose levels. Therefore, it is plausible that physical activity could be indirectly related to decreasing the risk of diabetic retinopathy through glycaemic control. This potential association has been investigated in several studies (42, 95, 113).

Physical activity, categorized as light, moderate, or heavy, was not associated with retinopathy prevalence in Type 2 diabetes subjects in a population-based study conducted in Taiwan (42).

Researchers with the Pittsburgh Epidemiology of Diabetes Complications Study found that, although physical activity in young adult life was associated in univariate analyses with lower risk of diabetic retinopathy after 25 years of Type 1 diabetes, this was not significant in a multivariate analysis (95). WESDR researchers found some associations between physical activity and retinopathy prevalence in women but did not find a significant association between physical activity, by various categories, and incidence or progression of retinopathy (113).

In summary, although moderate physical activity can assist in blood glucose control and weight maintenance, the evidence does not support a role for the prescription of physical activity to prevent diabetic retinopathy.

Hormonal Influences

The potentially causal role for various hormones and conditions affecting serum hormone levels in relation to diabetic retinopathy has been explored in a number of studies (48, 114–120). Diabetic retinopathy rarely occurs before puberty. Recently, Australian researchers reported that pubertal stage was not associated with the prevalence of diabetic retinopathy after controlling for confounders (48). Three previous studies, including the WESDR (115), documented an increasing prevalence of retinopathy by pubertal stage after accounting for duration of diabetes. (114, 116). In WESDR, Type 1 diabetes patients with a diabetes duration of 5–10 years, the retinopathy prevalence was six times higher in postpubescent patients than in prepubescent patients and the effect was even greater with diabetes duration greater than 10 years (115). Although these results are compelling, in all three studies investigators failed to control for blood glucose control in the analyses. Current recommendations for screening of diabetic retinopathy state that children do not have to be screened until after puberty as no vision loss has been documented prior to that time in previous studies.

The WESDR investigators have evaluated the impact of sex hormones (117), insulin growth factor I (118) and oral contraceptives (119) on diabetic retinopathy. In males with Type 1 diabetes, sex hormones were not found to predict the incidence of severe retinopathy (117). Low

serum sex hormone binding globulin was associated with increased progression to proliferative retinopathy, although this relationship did not remain significant in multivariate logistic models. After controlling for confounders, insulin-like growth factor I was not associated with retinopathy prevalence in Type 1 diabetes patients diagnosed before the age of 30 (118). Use of oral contraceptives in women of childbearing age was not associated with the severity of diabetic retinopathy (119).

In conclusion, the role of hormonal status and the development and progression of diabetic retinopathy is not clear and requires further investigation.

Pregnancy

Although an early study failed to show any worsening of diabetic retinopathy during pregnancy (121), several studies have demonstrated a definite increase in the development and progression of diabetic retinopathy during pregnancy. (122–124) Recent data have shown a significant increase in retinal blood flow during pregnancy associated with progression of diabetic retinopathy (125).

The relationship between pregnancy and retinopathy was explored in the EURODIAB Type 1 diabetes Complications Study, a study of 3250 Type 1 diabetes patients between the ages of 15 and 60 years from 31 centres in Europe (120). In multivariate analyses controlling for age, duration, centre and glycated haemoglobin, parous women had 0.50 the odds of having proliferative retinopathy compared with nulliparous women.

Proteinuria/Albuminuria

Retinopathy and nephropathy are the most common microvascular complications of diabetes and have common risk factors. Although a few studies found no independent association of proteinuria, a clinical marker of nephropathy, and retinopathy (42, 80, 83), an independent association of proteinuria and/or albuminuria has been documented in a number of studies.

In multivariate analyses, WESDR investigators found increased odds of proliferative retinopathy

prevalence in younger onset Type 1 diabetes (OR = 3.17) and increased odds of any retinopathy in older onset Type 1 diabetes (OR = 1.97) and Type 2 diabetes (OR = 1.88) (126). They also found that gross proteinuria significantly predicted proliferative retinopathy in younger onset diabetics with no or mild retinopathy at baseline (OR = 2.76), but did not detect any other significant associations (127). A 2.5-fold increase in the incidence of diabetic retinopathy was seen in Type 2 diabetes Pima Indians with proteinuria after controlling for confounders (59).

Persistent proteinuria increased the odds of retinopathy prevalence in elderly Japanese (88) and the presence of diabetic nephropathy was associated with 4.31 times the risk of proliferative retinopathy in Type 1 diabetes patients aged 18–29 years and 3.47 times in Type 1 diabetes patients aged 30+ in the Pittsburgh Epidemiology of Diabetes Complications Study (87). Albuminuria was significantly related to the prevalence of diabetic retinopathy in western Australians ($\beta = 0.49$) (84) and Swedish patients diagnosed at age 30+, although multivariate analyses were not presented (85,99).

The data independently relating proteinuria and albuminuria with the prevalence and incidence of diabetic retinopathy are quite substantial. They support the recommendations for multidisciplinary medical teams to treat all complications of diabetes, as the complications occur concomitantly.

Body Mass Index

Obesity has clearly been shown to predict Type 2 diabetes. Body mass index and fatness have been investigated as potential risk factors for diabetic retinopathy because of the effect on blood glucose control. With the prevalence of obesity on the rise in Western countries, even a small relative risk of retinopathy associated with obesity could have a large impact on the population attributable risk.

Body mass index was found not to be independently associated with the prevalence of diabetic retinopathy in Nauruans (16, 17, 98), the WESDR participants with diabetes diagnosis before the age of 30 (20), Chinese Type 2 diabetes patients (42), Japanese patients (88), and rural Swedish Type 2 subjects (90). Body mass index was also not independently associated with the incidence of

retinopathy in the Pima Indians (59) and Oklahoma Indians (80).

The prevalence of diabetic retinopathy was positively related to body mass index in Minnesotans (hazard ratio = 2.01) (83) and Western Australians ($\beta_a = 0.008$) (84) and inversely related to body mass index in Western Samoans (OR = 0.91) (51). Inverse associations were also detected in relation to retinopathy incidence in Type 2 diabetes WESDR subjects diagnosed at age 30 or greater (standardized coefficient = -2.13) (21) and Oklahoma Indians ($\beta = -0.0126$) (82).

The relation between body fatness and diabetic retinopathy is not clear. Further research is needed to understand the independent effect of body mass index on the development of diabetes complications, including retinopathy, in different subgroups of the population and to develop appropriate guidelines for intervention.

Genetics

Diabetic retinopathy was investigated in 31 twin pairs concordant for Type 1 diabetes, 27 pairs discordant for Type 1 diabetes, and 37 pairs concordant for Type 2 diabetes (128). Twin pairs were excluded if diabetes duration was less than 9 years. Retinopathy prevalence was graded after pupil dilatation as nil, background or severe; 35 of the 37 Type 2 diabetes pairs and 21 of the 31 Type 1 diabetes pairs had the same retinopathy score. There was no significant difference in Type 1 diabetes pairs by concordance. The investigators concluded that genetics may be related to retinopathy in Type 2 diabetes, but not Type 1 diabetes.

GAD Antibodies

Glutamic acid decarboxylase (GAD) is an enzyme that is present in the majority of Type 1 diabetes patients before diagnosis and that persists in some Type 1 diabetes patients for a long time after diagnosis. There has been only one report of an investigation of an association between GAD antibodies and diabetic retinopathy (129). In a sample of 146 German Type 1 diabetes patients, after stratifying for diabetes duration, GAD antibodies were not related to the prevalence of any diabetic complication, including retinopathy.

Summary

Overall, duration of diabetes and glycaemic control have consistently been shown to be the strongest predictors of the incidence and prevalence of diabetic retinopathy. These important risk factors are the basis for guidelines aimed at decreasing the prevalence and incidence of diabetic retinopathy and visual impairment due to diabetic retinopathy in the future (see the final two sections below). Knowledge of the association of retinopathy with risk factors thought to be associated with other diabetes complications as well as other chronic diseases (such as body mass index) is important for the development of public health strategies to improve community health through primary prevention of diabetes and its complications as well as comorbidities. Future investigations need to account for established or hypothesized risk factors in both the study design and the analysis of data.

RELATIONSHIP OF DIABETIC RETINOPATHY TO VISUAL OUTCOME AND MORTALITY

Diabetic retinopathy is the most common cause of blindness in working-age adults. The most recent long-term follow-up data of visual loss in a population with diabetes come from the WESDR (130). The 10-year incidence of blindness (vision less than 20/200) was 1.8, 4.0 and 4.8% in the younger onset, older onset taking insulin, and older onset not taking insulin, respectively. The 10-year rates of visual impairment (vision less than 20/40, driving vision) for these three groups were 9.4, 37.2 and 23.9%, respectively. Macular oedema and severe retinopathy were associated with increased visual loss during this time period. The rates of blindness decreased from the first part of the study at a rate that could not entirely be explained by treatment or mortality, suggesting that perhaps the natural history of the disease is changing (131).

Not only is diabetic retinopathy associated with vision impairment and blindness, but the presence of retinopathy also predicts mortality in Type 2 diabetes. An 11-year follow-up of a community-based population in England revealed a 1.35 relative risk of mortality from all causes in non-

insulin treated people with any retinopathy at baseline (132). After controlling for age and duration of diabetes, the existence of proliferative diabetic retinopathy at baseline has been shown to significantly increase the risk of mortality in a diabetic population in Wisconsin (133) and in Mexican Americans (134). Further research is needed to determine whether diabetic retinopathy, particularly advanced forms of the disease, is a marker for severity of diabetes and general health, and therefore indirectly linked to increased mortality or whether diabetic retinopathy is truly an independent causal risk factor for mortality.

TREATMENT OF DIABETIC RETINOPATHY

The visual prognosis for *untreated* PDR is often dismal. Natural history studies conducted in the 1960s (135) before the advent of laser treatment demonstrated that 50% of patients who develop PDR will be legally blind (vision less than 6/60 in both eyes) within 5 years. Eyes with high-risk PDR that were randomized to observation in the original Diabetic Retinopathy Study (DRS) protocol had a 25–35% chance of developing severe visual loss (vision <5/200) after only 2 years of follow-up (136).

The impact of timely laser treatment in patients with PDR is dramatic. Scatter photocoagulation reduced the risk of blindness by 60% in DRS-treated eyes and became the standard of care for all eyes with high-risk PDR (136). Subsequent studies have further demonstrated the effectiveness of prompt and thorough treatment. Only 4% of eyes with PDR treated with panretinal photocoagulation in the ETDRS had reached severe visual loss by 5 years (137), and only 1% of patients had this degree of visual loss in both eyes (138). The comparison between the DRS control group and the ETDRS treated group is shown graphically in Figure 21E.2 (138). This graph dramatically illustrates the impact of early treatment. All eyes in this comparison had PDR and vision >5/200 at baseline, although it is noted that those in the ETDRS may have been less severe on average than those in the DRS.

The ETDRS also demonstrated that focal laser treatment for eyes with clinically significant macular oedema (areas of retinal thickening around the macula) reduced the risk of moderate

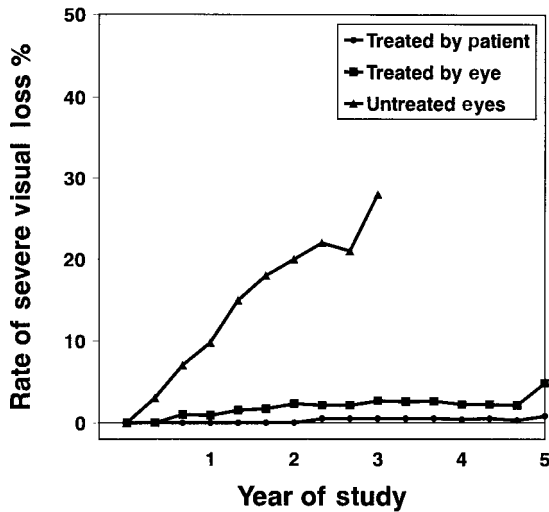


Figure 21E.2 Efficacy of treatment of proliferative diabetic retinopathy. Rates of severe visual loss in untreated eyes with proliferative diabetic retinopathy from the Diabetic Retinopathy Study compared to untreated eyes and patients with proliferative diabetic retinopathy from the Early Treatment of Diabetic Retinopathy Study

Source: Redrawn from Ferris FL, 3rd, How effective are treatments for diabetic retinopathy? *J Am Med Assoc* (1993); **269**: 1290–1291

visual loss by 50% or more. However, all studies emphasize that to be most effective, laser treatment must be applied *before* significant visual loss occurs.

PREVENTION OF BLINDNESS FROM DIABETIC RETINOPATHY

The key to reducing the incidence of diabetic blindness is regular eye examinations. Regular eye examination will lead to the early detection of asymptomatic vision-threatening retinopathy, so that laser treatment may be applied before significant visual loss occurs. It is also apparent from the DCCT that improved control in Type 1 diabetes will delay the onset and slow the progression of retinopathy (4) which has major implications for the management of these patients.

The following schedule of retinal examinations is recommended:

Diabetes onset <30 years of age: Initial examination 5 years after diagnosis

Diabetes onset >30 years of age: Initial examination at diagnosis.

Thereafter examine at least two yearly or more often if:

1. Visual symptoms
2. Pregnancy
3. Other risk factors develop (e.g. hypertension, nephropathy)

Regular examination according to this schedule will effectively detect retinopathy, providing that the method of examination is of adequate sensitivity. Direct ophthalmoscopy through dilated pupils has a sensitivity of approximately 60%. Regular repeat examination will compensate for this relatively low sensitivity so that this is an efficient and highly cost-effective screening method. Javitt has demonstrated that there is diminishing additional cost benefit for screening tests with sensitivity greater than 60% (Figure 21E.3) (139).

Indirect ophthalmoscopy performed by ophthalmologists has a sensitivity of approximately 85% (140), although this may approach 100% with newer slit lamp biomicroscopic techniques. Annual examination of all diabetics by an ophthalmologist is currently recommended in the United States (5), although many other countries do not have sufficient manpower to enable this.

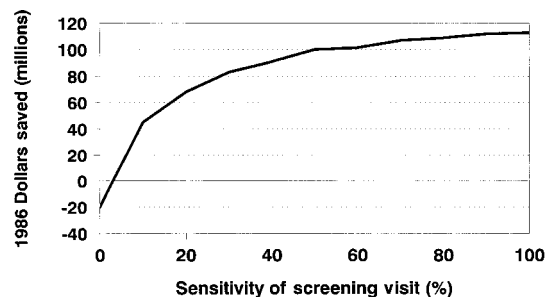


Figure 21E.3 Predicted savings of screening procedures related to sensitivity of screening procedures. Effect of differing screening sensitivity on annual economic returns (estimates of annual USA federal budgetary savings in 1986 US\$) assuming a 60% implementation of screening and treatment of Type 1 diabetes. For screening sensitivities greater than 60%, there is a diminishing additional benefit because it is likely that cases of retinopathy that are missed on one visit will be detected on the next visit

Source: Redrawn from Javitt et al. Detecting and treating retinopathy in patients with Type 1 diabetes. Savings associated with improved implementation of current guidelines. *American Academy of Ophthalmology. Ophthalmology* (1991); **98**: 1565–1573

Alternative detection methods such as retinal photography are being examined and are promising. (141, 142) Non-mydiatric retinal cameras may be operated by personnel with minimal training and the photographs forwarded to a reading centre. This technique has an overall sensitivity of approximately 85% (140), its main limitation being the proportion of unreadable photographs, particularly in older patients due to small pupils and media opacity such as cataract (143), although these patients probably should be referred on for ophthalmic assessment.

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Diabetes Mortality

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The late Kelly West, in the 1978 introduction of his classic textbook *Epidemiology of Diabetes and its Vascular Lesions* said of diabetes mellitus that ‘... it has become one of the most important of human problems. It is a significant cause of disease and death in all countries and all major races. In the past quarter century diabetes has killed more people than all wars combined’. In the mortality chapter he states ‘well collected data on mortality have considerable potential for promoting a better understanding of the nature of diabetes and the factors that increase or decrease prevalence, morbidity, and survival’ (1).

Much information has been gathered since that time. But the usefulness of diabetes mortality studies in descriptive and analytical epidemiology is severely limited by the considerable problems of ascertainment from death certificate data. National mortality statistics on diabetes deaths do not provide any currently useful measure of the distribution and magnitude of the condition. Prior to the sixth revision of the International Classification of Diseases (ICD-6) in 1949, diabetes was given a high priority in ranking as a major cause of death, even when other lethal conditions such as cardiovascular disease were present. Himsworth exploited this situation by conducting international comparisons of death rates from diabetes from 1900 to 1930. (2) He used mortality rates as a direct reflection of incidence rates, and he demonstrated a dramatic decline in diabetes deaths during World War 1 in those countries where profound restriction of food supplies occurred. He was able to demonstrate a strong positive association between death rates from diabetes and estimated national fat consumption. But following the ICD-6 revision, death certificates had to contain information on the chain of events leading to death, including the immediate cause of death,

and the priority previously given to diabetes as a cause of death was arbitrarily downgraded. As a result between 1948 and 1949 there was a sharp apparent drop in the figures for mortality of diabetes.

Many other problems occur with the use of mortality data based on death certificates. Marked under-reporting of diabetes has been documented repetitively (3–6). Thus a large proportion of actual deaths from diabetes are not identified. There is a huge potential for inaccuracies based on medical practitioners’ misinterpretation of causes of death, and the contribution of diabetes to the death, and lack of a precise diagnosis. There is much ambiguity about causes of death attributed to ‘acute complications’, ‘coma’, and ‘diabetes’ itself. Misclassification occurs where sudden death occurs, and the actual cause may be heart attack, arrhythmia, hypoglycaemia, stroke or self-inflicted overdose. From a clinician’s perspective, deaths due to hypoglycaemia are substantially underestimated. Many studies fail to distinguish Type 1 and Type 2 diabetes.

Well-designed prospective cohort studies will yield much more useful epidemiological data, especially for identifying the magnitude of the burden of diabetes deaths as well as focusing on underlying causal mechanisms. Cohort studies allow accurate diagnosis of the type of diabetes at baseline, and careful age- and sex-specific comparisons with the natural population can be made. Any inaccuracies due to the entry of new diabetics during the observation period probably do not bias results to any extent unless there is a very high prevalence of diabetes in the population under study. Cohort studies use defined groups of persons with diabetes. Clinic populations are valid for children and young adults with Type 1 diabetes, where there is centralization of care and

the patients studied represent almost all available cases. Such studies allow more precise interpretation of causes of death, and have given very useful perspectives over time (for example the Joslin Clinic studies (7), the Pittsburgh studies (8), and the Wisconsin Epidemiologic Study of Diabetic Retinopathy) (9). Bias may exist in clinic-based studies but less than in other cohorts such as applicants for life insurance. Population-based studies are of course preferable but very large numbers are required to achieve sufficient persons with diabetes. In the study of non-insulin-dependent diabetes, population-based studies are valuable especially because of the ability to compare baseline measures of risk factors in diabetic and non-diabetic persons.

THE MORTALITY OF TYPE 1 DIABETES (INSULIN-DEPENDENT DIABETES MELLITUS OR IDDM)

For a detailed review the reader is referred to Portuese and Orchard (10). In the earlier part of the century there were marked changes in total mortality rates of young persons with diabetes. Prior to 1914, the annual mortality rate for children with diabetes under 10 years of age was 824 per 1000, and for diabetic children aged 11–20 years it was 600 per 1000. In the era of the Allen diet, but prior to the introduction of insulin therapy, death rates fell to 386 per 1000 and 390 per 1000 respectively in these age groups (11). By 1966–1981, total mortality for persons with diabetes under 20 years age was in the range 1.5–3.0 per 1000 (8). Mortality rates have probably levelled since 1980 (10).

The Joslin Clinic mortality experience from the 1960s is quite representative of other US studies. When age of diagnosis is 10–20 years there is a mean reduction of life expectancy of 15 years (7). The survival in childhood onset diabetes is 88% after 20 years, and 83% after 25 years (10), and this is quite consistent in the Joslin Clinic (7), Pittsburgh (8), and Erie County (10) data.

The cause of death in Type 1 diabetes has shown marked changes by epoch and this reflects advances in treatment. Ketoacidotic coma predominated both before the introduction of insulin in 1922 and in the decade that followed. Subsequently a pattern has emerged of deaths due to

renal disease in the intermediate term, and due to cardiovascular disease in the longer survivors. In the Pittsburgh Epidemiology of Diabetes Complications Study, those with childhood onset of diabetes and 10–19 year duration had death rates due to renal disease of 51%, and cardiovascular disease 18%. After 30 years duration, the death rates due to renal disease were 20% and cardiovascular disease 68% (10, 12).

Similar findings are reported from the Steno Clinic population in Denmark (10, 13). Individuals with insulin-dependent diabetes diagnosed under the age of 30 years were followed from 1943 to 1984. Under 35 years duration, renal failure deaths were 54% as compared to cardiovascular disease deaths 27%; but beyond 40 years of duration the rates were 5% for renal failure and 67% for cardiovascular disease. Cardiovascular disease is the major cause of death for long-duration Type 1 diabetes.

TIMED-RELATED VARIABLES AND ALBUMINURIA

Age at onset and duration of diabetes are critical in the interpretation of mortality data. Borch-Johnsen and colleagues describe a 'bell shaped' relationship between diabetes duration and relative mortality in those with persistent proteinuria, such that risk increases until 30 years duration after which there is a dramatic reduction in risk (13). Figure 22.1 shows estimated mortality of male Type 1 diabetes patients aged 10 years and 20 years at diagnosis in comparison with mortality of standard lives from Danish life insurance company data. After 15 years of diabetes, mortality rates increase dramatically, and remain constantly increased for about 25–35 years, thereafter becoming closer to the general population (14). The interpretation is that the high relative mortality of Type 1 diabetes patients is confined to a sub-population with specific risk characterized by persistent proteinuria and poor prognosis.

In pursuing this hypothesis that proteinuria in Type 1 diabetes is a marker for generalized vascular disease and may account for premature cardiovascular disease deaths as well as renal disease deaths, Borch-Johnsen reviewed the relative mortality from cardiovascular disease in 2644 patients, one quarter of whom had persistent

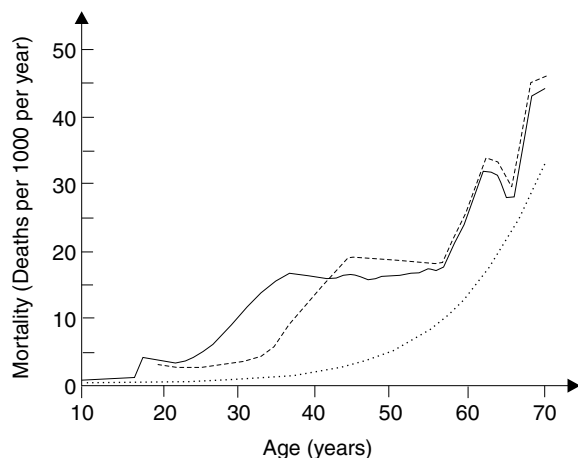


Figure 22.1 Mortality of Type 1 diabetes patients diagnosed in 1965, age at diagnosis — 10 years; 20 years; and of — standard lives from Danish life insurance

Source: Attributed to Ramlau-Hansen 1985; reproduced from Borch-Johnsen K, The prognosis of insulin-dependent diabetes mellitus. An epidemiological approach. *Danish Medical Bulletin* (1989), 36: 336–348

proteinuria and the remainder did not. The relative mortality from cardiovascular disease was much greater in those with proteinuria and peaked at 25–30 years duration, in comparison with those without proteinuria who showed a moderate consistent increase in relative mortality unrelated to diabetes duration (14), as shown in Figure 2.

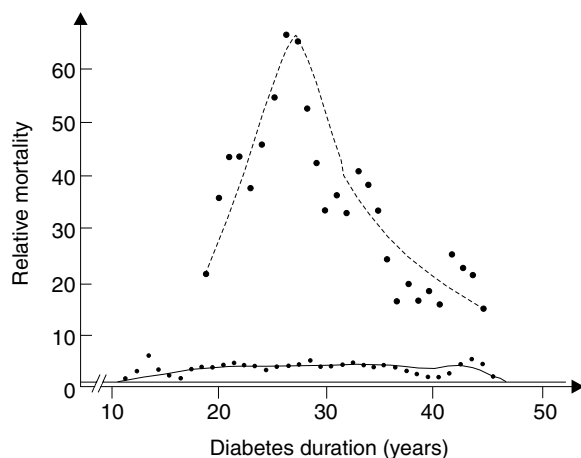


Figure 22.2 Relative mortality of cardiovascular disease in Type 1 diabetes patients with (.....) without (—) persistent proteinuria

Source: Reproduced from Borch-Johnsen K, The prognosis of insulin-dependent diabetes mellitus. An epidemiological approach. *Danish Medical Bulletin* (1989), 36: 336–348

The median life expectancy after the onset of frank albuminuria in this group was 7 years.

OTHER RISK FACTORS

Hypertension in the Joslin Clinic data was shown to be a risk factor in case-control analysis for those diabetics dying of renal or cardiac disease, and their findings suggested a threshold level of blood pressure of 140/90 mmHg (15). Hypertension was associated with mortality in the Wisconsin Epidemiologic Study of Diabetic Retinopathy (16). Heavy smoking predicted all cause mortality in female Type 1 diabetes but not males in the Pittsburgh cohort (17), but there was no relationship with smoking to mortality in the Joslin Clinic data.

Lipoprotein risk factors are an unstudied area. There are insufficient data to make any confident assessment about relationship of cholesterol, triglyceride, or HDL levels to subsequent mortality in Type 1 diabetes. However, an early report from the prospective Epidemiology of Diabetes Complications Study of 658 insulin-dependent diabetic individuals, mean age 28 years, mean duration 20 years, showed a significant association between LDL-cholesterol levels and cardiovascular disease mortality (18).

Glycaemic control (metabolic regulation) was the strongest predictor of long-term survival in a Steno Memorial Hospital cohort (19). Use of diuretics showed a marked increase in mortality in two studies (10).

INTERNATIONAL COMPARISONS

The Diabetes Epidemiology Research International (DERI) study was designed to make cross-country comparisons of mortality rates in four countries. Quite large population cohorts of subjects with the diagnosis of Type 1 diabetes before the age of 18 years in 1965 through 1980 were followed from Allegheny County, USA, Finland, Israel and Japan. A total of 8151 young persons with diabetes were registered in the baseline period and mortality status was retrieved in 1990 from 94 to 100% of cases. This is the first study that accurately quantifies the role of diabetes

in contributing to excess mortality in young people (19).

The DERI group adopted a standardized approach to the collection of mortality data and the classification of causes of death (20). This required multiple sources of data acquisition from hospital records, physicians, medico-legal avenues, personal informants, and autopsy data. There was a particular focus on circumstantial evidence for renal disease, cardiovascular disease, admissions for diabetes control, and any evidence for potential self-destructive behaviour. There were standardized rules for identifying: (1) the most likely cause of death; (2) the ranking order of contributory causes of death; and (3) the specific role of diabetes (whether direct cause, or contributing significantly to the death, or contributing marginally to the death).

With the standardized procedure applied, a major redistribution in causes of death occurred, as is shown in Table 22.1. Acute complications of diabetes (hyperglycaemia, hypoglycaemia, ketoacidosis, unspecified coma) were seriously underestimated from the death certificate data, and the rates for this category were increased 4-fold by reclassification. Diabetic kidney disease was also quite under-represented in the death certificate data.

Cross-country differences in the risk of young persons with Type 1 diabetes dying were identified (21). The Japanese cohort exhibited markedly higher age-adjusted mortality rates than the other three countries, but all countries showed a disturbing increase in the risk of premature death. Kidney disease and acute diabetic complications accounted for three-quarters of all the Japanese deaths, compared with about one-third of deaths in the other countries. Accidents and suicide

accounted for 36% of deaths in Finland compared with 18% of deaths in Israel and the United States and 2% of deaths in Japan.

In a definitive analysis of differential survival using life table analyses plus Cox regression analysis, the mortality experience for Type 1 diabetes individuals in Japan and the United States was much worse than in Finland and Israel, as shown in Figure 22.3. The age-adjusted mortality rates per 100 000 person years were 760 (Japan), 408 (Allegheny County, USA), 250 (Finland) and 158 (Israel). It is hypothesized that these marked differences in mortality trends reflect differences in health care systems of the individual countries studied. In Japan Type 1 diabetes is an extremely rare condition and clinical services lacked the critical mass of cases to allow experienced management. Unexplained is the remarkable excess of deaths in Allegheny County, which is said to have one of the better integrated systems for regional care in the USA. In Finland and Israel, diabetes treatment (and availability of insulin) is virtually free through national insurance and subsidy schemes. But in the USA persons with diabetes have to pay for care. Thus, despite a good standard of care, less frequent access to the health care system in the USA could account for the differential mortality. This is the subject of further study.

Table 22.1 Diabetes Epidemiology Research International (DERI) Study (19): causes of death in 124 young Type 1 diabetes by death certificate coding and after mortality reclassification

	Death certificate (%)	Mortality reclassification (%)	Factor
Acute complications	6.5	27.4	×4.2
Diabetic kidney disease	8.1	17.7	×2.2
Accident/suicide	21.0	25.0	×1.2
Other	64.5	29.8	×0.5

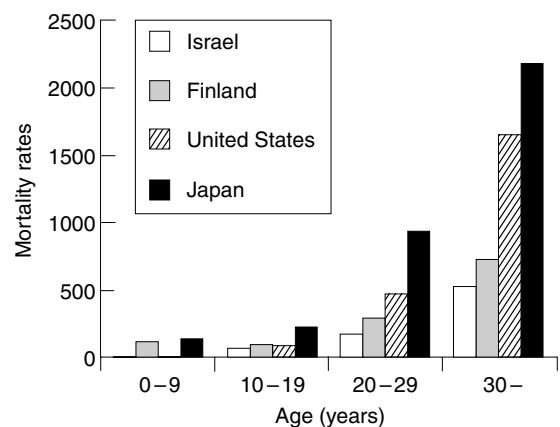


Figure 22.3 Age specific mortality rates per 100 000 person-years among individuals with insulin-dependent diabetes mellitus from four national cohorts 1965–79 (Allegheny County taken to be representative of the United States), from the Diabetes Epidemiology Research International Study 1965–1979.

Previous reports from the Steno Memorial Hospital in Denmark (22, 23) showed convincingly that frequent contact with a specialized diabetes centre in the early stages of the disease, geographic proximity, supervision, and an emphasis on metabolic control were all factors associated with reduced mortality and complications. A similar conclusion derives from the Pittsburgh study where frequency of contact was associated with reduction in mortality (16).

MORTALITY OF TYPE 2 DIABETES (NON-INSULIN-DEPENDENT DIABETES OR NIDDM)

A definitive review of this topic by Geiss, Herman and Smith is recommended reading (24). There are sufficient cohort studies of Type 2 diabetes, both population-based and also from hospital clinic and work-site groups, to make the following generalizations. Studies (predominantly from the US but also from Finland, Sweden, UK, Germany, Australia and Japan) confirm the consistent excessive mortality of this form of diabetes (24). In general, for middle-aged patients with Type 2 diabetes there is a 2-fold increase in total mortality. Females show a moderate increase in relative risk compared with males in some studies. Where time-related variables are considered, duration is an important determinant of mortality and thus younger age-of-onset groups (<45 years of age) have increased risk of premature death. In some studies the older age groups (>75 years) have a negligible increase in mortality rate above the general population. The nature of the data is too varied to make any comparisons between population groups. From death certificate data, it appears that age-adjusted death rates in African Americans (25, 26) and Hispanic Americans (27) are similar to the rates in whites. An increased mortality in North American Indians with Type 2 diabetes is apparent, their age-adjusted rate being at least 2.7 times the rate for the general US population, but when adjusted for under-reporting of heritage, the rate may be 4.3 times the rate for whites (28).

Death rates for persons with Type 2 diabetes in the United States show remarkable consistency in three studies with an average annual death rate of 5.5% based on the 1986 National Mortality

Follow-back Survey (4), the National Health and Nutrition Examination Survey (NHANES 1) (29–31) and the National Health Epidemiologic Follow-up Survey (NHEFS) (32).

There is general agreement as to the distribution of causes of death in Type 2 diabetes. An amalgamation of four US cohort studies provides representative data—the deaths are due to:

- ischaemic heart disease 40%
- other heart disease 15%
- diabetes 13%
- malignant neoplasms 13%
- cerebrovascular disease 10%
- pneumonia/influenza 4%
- all other 5%

These data indicate that two-thirds of diabetics die of heart disease and stroke, and that the risk of cardiovascular disease mortality is 2–4 times higher in persons with diabetes than in persons without. The excess risk of cardiovascular disease persists despite adjustment for age and for known risk factors. 'This suggests that something about diabetes itself, or some unmeasured factors unique to persons with diabetes other than these risk factors, increases the risk of death' (24). Furthermore 'the amount of increased risk of mortality in persons with diabetes compared with persons without diabetes is greater in the younger age and younger age-at-onset groups than in the older age and older age-at-onset groups' (24).

In a 9-year national cohort of the NHANES 1 survey, the standardized mortality ratios in subjects aged 40–77 was 2.78 for men and 2.56 for women (29). Heart disease in diabetic persons appeared earlier, and affected females almost as often as males. There are substantial clinical data indicating marked increased risk of reinfarction and of death following myocardial infarction in diabetic as compared to non-diabetic patients.

It is often reported that there is an increased rate of coronary heart disease or cardiovascular disease in diabetic females as compared to diabetic males, and that the usual male to female gradient of risk is abolished by diabetes. This phenomenon is seen in some but not all studies (24). In general it can be said that variation in data collection and study design account for some of the differences. Those population studies that show female preponderance of cardiovascular disease or coronary heart

disease deaths are not fully representative and usually have comparatively small numbers studied.

**MODIFIABLE CARDIOVASCULAR RISK
FACTORS IN TYPE 1 DIABETES AND TYPE 2
DIABETES**

Although the relevance of conventional risk factors in diabetic vascular disease had earlier been questioned and the exact nature of the ‘diabetic factor’ was and still is unknown, further evidence has emerged. The continuing problem is the great variation in data collection and study design and diagnostic criteria. Information from the WHO multinational study of vascular disease in diabetics has proved to be quite variable, even when single country cohorts were analysed. A rather patchy pattern of positive associations with conventional risk factors was identified (32). A more useful comparison of cardiovascular mortality in patients with newly diagnosed Type 2 diabetes versus non-diabetic controls was achieved in a prospective study in Finland (33). In 133 diabetic subjects and 144 non-diabetic control subjects, cardiovascular mortality rates were substantially higher in the diabetic men versus controls (15.0% versus 5.2%) and diabetic women versus controls (16.6% versus 2.2%). In this small sample cardiovascular mortality was unrelated to treatment modality, whether diet, oral drugs or insulin at 5 years from diagnosis. In multiple logistic regression analysis, age, LDL-triglycerides, smoking, blood glucose and an ischaemic ECG pattern at baseline had independent associations with cardiovascular disease mortality in the diabetic patients. The importance of atherogenic lipid fractions was suggested.

DYSLIPIDAEMIA

The Multiple Risk Factor Intervention Trial (MRFIT) (34) made use of a very large cohort of 361 662 US men aged 35–57 years who were screened as potential participants for preventive intervention. The subjects were voluntary self-referrals from employee groups or communities but were comparable to US middle-aged males. Of there, 5625 men reported taking drug therapy (tablets or insulin) for diabetes, and although

excluded from the trial proper, they were studied in parallel with the other screenees. The diabetic men, as compared to controls, were older (49 versus 46 years), had higher systolic blood pressure levels (136 versus 130 mmHg), and a greater proportion of black subjects (14% versus 6%). Follow-up averaged 12 years, and crude coronary heart disease and cardiovascular disease death rates were five times higher in the diabetic men.

After adjustment for age and other risk factors, the overall risk ratios for diabetic men for cardiovascular disease and coronary heart disease deaths were 3.0 and 3.2 respectively.

It was clear from MRFIT that for men with diabetes, the conventional risk factors serum cholesterol, systolic blood pressure, and cigarette smoking were highly significant predictors of cardiovascular disease mortality. For example, in each class of serum cholesterol, men with diabetes had a far greater mortality rate than those without (Table 22.2). But it is of interest to note that where the risk factor level is lowest, risk ratio for diabetic versus non-diabetic persons is greater, another expression of the ‘diabetic factor’. This is also seen when the other risk factors and combinations of risk factors are examined (Table 22.3). Overall the risk ratios for diabetic versus non-diabetic men are much higher, but where conventional risk factors are less marked, the gradient of risk for being diabetic increases.

Thus diabetes proved to be a very strong independent risk factor for cardiovascular disease mortality over and above conventional risk factors, and interestingly the risk ratios were highest among diabetic men with the best risk

Table 22.2 Multiple Risk Factor Intervention Trial (34) (MRFIT): age-adjusted cardiovascular disease death rates by classes of serum cholesterol for men with and without diabetes at initial screening

Serum cholesterol (mmol/l)	Cardiovascular deaths per 1000 men per 10 years		
	Men without diabetes	Type 2 diabetes	Risk ratio (diabetic/non-diabetic)
< 5.2	31.1	138.4	×4.4
5.2–6.3	44.7	165.7	×3.7
>6.4	110.7	361.8	×3.3

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Table 22.3 Multiple Risk Factor Intervention Trial (34): age-adjusted cardiovascular disease mortality in men with and without diabetes at initial screening. Those with no risk factors, and combinations of risk factors, are shown. Definitions of risk—systolic blood pressure >120 mmHg; serum cholesterol >5.2 mmol/l; any cigarette smoking

Number of risk factors	Cardiovascular disease deaths per 1000 men per 10 years		
	Men without diabetes	Type 2 diabetes	Risk ratio (diabetic/non-diabetic)
None	6.0	30.7	×5.1
Any one	12.2	58.8	×4.8
Any two	22.4	90.9	×4.1
All three	47.4	125.2	×2.6

Reproduced from (34) by permission.

factor profile. This phenomenon is attributed to 'diabetes *per se*' and may relate to glycation, endothelial damage, or subtle atherogenic lipid fractions.

With the current focus on the specific dyslipidaemia of 'the metabolic syndrome' (the syndrome of insulin resistance) high triglyceride levels and low HDL-cholesterol levels without any marked elevation of total cholesterol levels are recognized as a marker for cardiovascular disease risk. The concept has emerged of hidden atherogenic lipoprotein such as small dense LDL. There is convincing evidence from studies of predominantly non-diabetic populations that the pattern of an adverse cholesterol to HDL ratio and low levels of HDL-cholesterol and high triglycerides strongly predict cardiovascular disease deaths in diabetic subgroups, as evident in the Prospective Cardiovascular Munster (Procam) Study (35), the Helsinki Heart Study (36), and a retrospective analysis of the Framingham Heart Study (37).

Incidental observations on diabetic subjects taking part in intervention trials support the hypothesis that dyslipidaemia is an important determinant of cardiovascular death in diabetic subjects. In the Helsinki Heart Study (38) 135 men with Type 2 diabetes from a cohort of 4081 men in a primary prevention trial used the lipid modifying agent gemfibrozil, for middle-aged men with high-non-HDL-cholesterol (>5.2 mmol/l). Compared with non-diabetic subjects, Type 2 diabetes men had lower HDL-cholesterol and higher triglyceride concentrations, greater body mass index, and more

were hypertensive. The incidence of myocardial infarction and cardiac death was significantly higher among diabetic than non-diabetic participants (7.4% versus 3.3%). Coronary heart disease incidence in the gemfibrozil-treated diabetic men was 3.4% compared to 10.5% in the placebo group ($p = 0.19$). Although the comparatively low numbers precluded any possibility of a statistically significant outcome, the dramatic reduction in deaths in the diabetic males (Figure 22.4) was very suggestive.

The Scandinavian Simvastatin Survival Study ('4S') was designed to evaluate the effects of cholesterol reduction with simvastatin on mortality in patients with pre-existing coronary artery disease. A total of 4444 patients with serum cholesterol levels 5.5–8.0 mmol/l were randomly assigned to double blind treatment with simvastatin or placebo. Subgroup analysis of those with and without diabetes showed marked reduction in risk of all cause mortality and of major coronary events by the cholesterol-modifying agent (Table 22.4) (39).

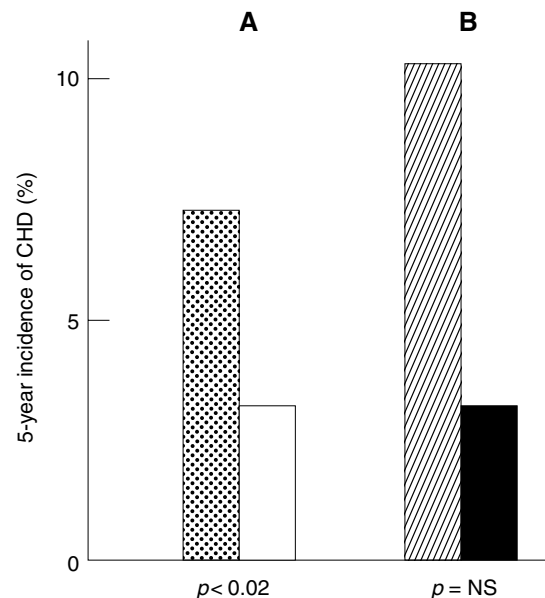


Figure 22.4 Helsinki Heart Study: five year incidence of myocardial infarction and death from coronary heart disease (CHD)

A: Type 2 diabetes patients ($N = 135$ stippled bar)

Other subjects ($N = 3946$ open bar)

B: Type 2 diabetes patients on placebo ($N = 76$ hatched bar)

Type 2 diabetes patients on gemfibrozil ($N = 59$ solid bar)

Table 22.4 Scandinavian Simvastatin Survival Study (39) of subjects with prior myocardial infarction: major coronary events in the subgroup with diabetes (97 on placebo, 105 on Simvastatin) compared with non-diabetics (2126 on placebo, 2116 on Simvastatin) and the relative risk over 5.4 years follow-up

Scandinavian Simvastatin Survival Study			
End Point Category	Percentage with Endpoints		Relative risk (95% confidence limits and <i>p</i> values)
	On placebo (%)	On Simvastatin (%)	
Total Mortality			
Diabetes	25	14	0.57 (0.03–1.08; <i>p</i> = 0.087)
No diabetes	11	8	0.71 (0.58–0.87; <i>p</i> = 0.001)
Major coronary events			
Diabetes	45	20	0.45 (0.27–0.74; <i>p</i> = 0.002)
No diabetes	27	19	0.67 (0.61–0.77; <i>p</i> = < 0.0001)

Reproduced from (39) by permission.

Thus there is suggestive evidence for a major role of lipids in causing the excess cardiovascular disease mortality in Type 2 diabetes, and clearly a compelling need to conduct appropriate intervention trials in diabetic subjects. Haffner and colleagues (40) recommend an aggressive approach to the treatment of dyslipidaemia in Type 2 diabetes. They show that Type 2 diabetic patients in Finland *without* prior myocardial infarction have as high a risk of coronary heart disease mortality as non-diabetic patients *with* a history of myocardial infarction.

HYPERTENSION (AND ENDOTHELIAL FUNCTION)

In the UKPDS, ‘tight control’ of elevated blood pressure levels in Type 2 diabetes, compared with less tight control, reduced deaths related to diabetes by 32% (*p* = 0.019). All cause mortality was reduced by 18% but this was not significant (*p* = 0.17). The mean blood pressure level at entry was 160/94 mmHg (41).

In contrast, the HOPE study evaluated the use of the antihypertensive agent ramipril, (an angiotensin converting enzyme inhibitor) in patients at high risk of cardiovascular disease, but without a specific focus on lowering blood pressure levels. In the subgroup with Type 2 diabetes, mean blood pressure levels at entry were 142/80 mmHg and were not lowered significantly by therapy. But treatment resulted in marked reduction in cardiovascular deaths of 37% (*p* = 0.001) and a reduction in total mortality of 24% (*p* = 0.004). The

authors suggest that the benefit may be mediated through a direct protective effect on the arterial wall, and by improving endothelial function (42).

MICRO-ALBUMINURIA AS A RISK FACTOR FOR MORTALITY

Studies of micro-albuminuria in uncomplicated Type 1 diabetes through to mortality are just not available, although the inference is quite firm that micro-albuminuria leads to an increased risk of macro-albuminuria and hypertension, and there is little doubt that macro-albuminuria is a major risk factor for death especially nephropathy, but also coronary heart disease, in Type 1 diabetes.

There has been debate as to whether anti-hypertensive agents protect against progression of nephropathy merely by their blood pressure lowering properties, or whether angiotensin converting enzyme inhibitors (ACE inhibitors) have specific benefit by an action in lowering increased glomerular capillary pressure to normal (43).

Table 22.5 The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. Outcome events in patients in Captopril and placebo groups (41)

Event	Captopril (<i>n</i> = 207)	Placebo (<i>n</i> = 202)
Death	8 (4%)	14 (6%)
Dialysis or transplantation	20 (10%)	31 (15%)
Death, dialysis or transplantation	23 (11%)	42 (21%)

Reproduced from (41) by permission.

In a carefully designed study with definitive outcome, therapy with ACE inhibitors (in this instance Captopril), significantly reduced mortality rate and the combined end point of mortality or renal transplantation or dialysis (44). This benefit was shown to be independent of blood lowering effect *per se*. ACE inhibitor therapy was associated with a 50% reduction in risk from the combined endpoints (Table 22.5). This outcome was meaningful and independent of the small disparities in baseline blood pressure levels in the two groups ($p = 0.006$).

GLYCAEMIC CONTROL

The issue as to whether small departures from normoglycaemia contribute to the 'diabetic factor' that magnifies and accelerates atherosclerotic disease has not yet been resolved. Subjects in the Bedford Study with borderline diabetes (impaired glucose tolerance) had almost the same 10-year mortality from coronary heart disease as frank diabetics (45). A 'threshold phenomenon' for the 2 hour plasma glucose levels and subsequent coronary heart disease mortality was demonstrated in the Whitehall Study (plasma glucose level >5.3 mmol/l) and the Paris Prospective Study (plasma glucose level >7.8 mmol/l) (46, 47). The University Group Diabetes Program had specifically addressed this issue in a clinical intervention trial (48). No benefit from close glycaemic control as achieved with variable dose insulin injections was seen, but an unexpectedly high mortality occurred in the tolbutamide treated group. This has been the subject of continuing controversy and disagreement (49). Recent retrospective analysis of 22 studies involving 95 783 persons has shown that non-diabetic elevation of blood glucose levels on univariate analysis is associated with increased cardiovascular morbidity/mortality of modest degree. Compared with a glucose level of 4.2 mmol/l, a fasting plasma glucose of 6.1 mmol/l and a 2 hour level of 7.8 mmol/l have relative risks of 1.33 (1.06–1.67) and 1.58 (1.19–2.10) respectively (50). There is as yet no evidence that moderate hyperglycaemia if modified influences mortality outcomes. Indeed, the United Kingdom Prospective Diabetes Study (51) reports that attempted intensive blood glucose control of established Type 2 diabetes, while reducing substantially the incidence

of microvascular complications, especially retinopathy, had a small and non-significant impact on all cause mortality (6% lower, $p = 0.44$) and on diabetes-related deaths (10% lower, $p = 0.34$). Importantly, neither sulphonylurea drugs nor insulin therapy led to any adverse cardiovascular outcomes (51).

CONCLUSION

In the next decade, mortality studies will provide continuing insights into factors associated with the unacceptably high death rates of diabetic subjects. Careful description of baseline cohorts of persons with diabetes, and the subsequent accurate assessment of true causes of death from multiple source ascertainment are required. The precise nature of 'the diabetic factor' that contributes to cardiovascular and renal disease in both Type 1 diabetes and Type 2 diabetes needs urgent elucidation. The changing patterns of mortality that are emerging over time demand an explanation (52). It is to be hoped that current clinical intervention trials in diabetic subjects, long overdue, will not only establish the value of risk factor modification but also will give new and valuable insights into the mechanisms of lethal diabetic vascular complications.

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Part V

Implications

Economic Costs

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INTRODUCTION

A common question posed throughout the world today regards the costs associated with diabetes. Cost and other forms of economic data are now important contributors to the decisions made by health departments, health care providers, and health insurers regarding diabetes. Decision-makers need reliable economic information to equitably determine which health services should be funded (e.g. diabetic care vs the control of communicable disease). They need information for decisions on payment for insulin, syringes, oral hypoglycemic agents, and blood glucose testing supplies, and for decisions on the number of facilities for patients with diabetes and the number of medical personnel trained to treat them. Decision-makers also need information on the relative value for money of health care treatments and programmes to determine the merit of new treatments in diabetes: such as intensive insulin treatment and screening for microalbuminuria.

How did we get to this point? Several factors have contributed to the current situation. First, health care is a dynamic process. Medical advances and new therapies require us to adapt and change our approaches to health care. Many new advances, though, are expensive technologies, surgeries, or drugs. Second, health care provision has, in many circumstances, been a political—process. In many areas, an oversupply of physicians and a redundancy in facilities (hospitals) exists. Third, the life expectancy of the world's population is increasing. With aging populations comes an increased need for the long-term treatments that surround chronic diseases.

These characteristics have all played a role in the current reality that faces many health systems.

1. The costs of health care are rising at a significant rate. Over the last 30 years, expenditures for medical care have risen extensively throughout the world (1,2,3). Indeed, health care expenditures have risen much faster than the cost increases reported in other sectors of the economy.
2. There are limited resources available for health care and, often, an inability to obtain more.
3. Health care coverage is often not available to all individuals in a population, and many governments are unable to provide it.
4. There is a large variation in health care use by geographical area and health care setting. This variation exists with no apparent difference in a patient's health.

As a result, fundamental changes are taking place in health care systems throughout the world. There is now an expanding focus being placed on the economic aspects of health care. The underlying issue throughout most of the discussions on health care reform and the appropriateness of health care is that of costs. Are we spending health care resources wisely? How much does it cost to provide treatment? What benefits are obtained with that treatment? Which treatments provide benefits and at what cost? With limited resources, health care decision-makers must make choices about the direction to pursue in health care and the intensity with which to pursue it.

HEALTH ECONOMICS

Health economics is a discipline involved with the study of health care costs, limited resources, and the subsequent choices made regarding health care and health. Health economic studies provide

information which can help to guide decisions regarding health care funding, planning, provision, and evaluation. Common economic issues that are examined include:

- The costs related to disease or illness, such as the money that we spend to treat patients. These costs involve the expenditures for medical care and the treatment of a disease and its complications (hospital care, physician services, nurse educator services, long-term care, drugs, facilities, and overheads, etc.).
- The indirect costs associated with disease, such as the impact of disability or premature mortality. These costs relate to lost productivity, an inability to continue working, or from an interference in usual activities.
- The costs of disease that directly affect the patient. Persons with severe illnesses face several economic decisions. These include the out-of-pocket payments for health care and the sacrifices in time (opportunity costs) made in searching for medical care, employment and insurance.
- The costs of using resources devoted to a specific disease or treatment inappropriately, or the costs of pursuing inappropriate priorities.
- The influence of excesses or shortages in the number (supply) of health care providers, the availability (supply) of medical technologies and drugs, and the demand for health care.

There are several reasons why it is important to understand these issues as they apply to diabetes care. First and foremost is that governments increasingly have little money to spend on the health of the public. In this environment, it is important that appropriate levels of resources are directed to diabetes, and that the money available for diabetes is used to its greatest benefit.

IDENTIFYING THE COSTS OF DIABETES

What are the costs of diabetes? As outlined above, there are a number of different approaches that one can take to examine the costs associated with diabetes. The types of economic costs related to diabetes mellitus include the medical costs of treating persons with diabetes, the indirect costs

related to early disability or early death, the costs that individuals with diabetes face personally when they forgo spending money in one area to help pay for treating diabetes (opportunity costs), the costs of using resources available inappropriately, and the costs of having too few diabetes services (not everyone gets care) or too many diabetes services.

Direct Medical Costs

Studies of the medical costs of treating diabetes are the most common form of diabetes economic analysis in the literature. Direct medical costs of disease include the expenditure for medical care and treatment of the illness (hospital care, physician services, related laboratory tests, nursing home care, drugs and the cost of daily diabetes management (insulin, syringes, oral hypoglycemic agents, blood testing supplies) among other items. The monetary costs of medical treatment are often easily measured by surveys and studies of medical or billing records.

Indirect Morbidity and Mortality Costs

Indirect economic costs include the consequences of morbidity, disability and premature mortality resulting from diabetes. These non-medical costs of disease are not easily measured or calculated, but are commonly associated with detrimental changes in activity among persons with diabetes. For instance, the degree to which an individual must stop or decrease the amount of time spent in usual activities. One example is with work. Persons with the complications of diabetes often have to stop working. There is a cost incurred here related to the lost productivity of that individual. These types of costs are also found for persons who die prematurely or for persons with higher rates of absenteeism from work than the general population.

Estimates of the monetary costs of these effects are usually based on the human capital approach whereby costs from the illness are valued in terms of lost earnings and production of the patient. This allows for the estimates to be applied as monetary units. However, there is some controversy over the most appropriate method to value losses from premature disability and mortality (4–6). Other

methods exist, such as the willingness-to-pay approach, that value lost opportunities from an estimate that patients provide of the monetary figure that they would be willing to pay to avoid illness, disability, or premature death. The human capital approach has been the only methodology used in the cost of diabetes studies.

DIRECT AND INDIRECT COST ESTIMATES

Estimates of both direct and indirect costs have been calculated under the framework of cost of illness studies. Dorothy Rice pioneered this estimation approach in the 1960s (7) and further refinements have occurred since. Specific details of these methods are discussed more thoroughly elsewhere (7–11).

Table 23.1 outlines the cost of illness estimates reported in the literature for diabetes. Most of the reports are specific to the United States experience, but a number of reports have emerged recently from other countries. Is the economic burden of diabetes significant? The estimates outlined clearly show that the medical costs of diabetes have risen

substantially over the last 25 years. Recent reports suggest that the medical costs of diabetes may be even higher than previously thought. In all of the reports, the largest component of direct medical costs is generally the cost of hospital care related to diabetes (27).

The earliest reports on the cost of diabetes were based on work originating from the Statistical Bureau of the Metropolitan Life Insurance Company (SBMLIC) conducted by Paul Entmacher. The SBMLIC estimated the costs of diabetes mellitus over a period of years, and in their reports, the total economic impact of diabetes rose from US \$2.6 billion in 1969 to a projected \$13.8 billion in 1984 (12). Several reasons have been cited for this increase in costs. They include the inflation of medical care prices, the increased prevalence of diabetes, the increased use of medical services by persons with diabetes and the development of new and expensive treatment technologies for diabetes.

In the mid 1980s, cost studies began to examine situations where diabetes was a secondary or tertiary factor listed in health care records. This was due to some concern that estimates based only

Table 23.1 Estimates of the economic cost of diabetes mellitus (cost figures shown are \$US bn unless otherwise specified)

Study	Year	Country	Total costs	Direct costs	Indirect costs
Metropolitan Life (12)	1969	USA	2.6	1.0	1.6
Metropolitan Life (12)	1973	USA	4.0	1.7	2.3
Metropolitan Life (12)	1975	USA	5.3	2.5	2.8
Metropolitan Life (12)	1977	USA	6.8	3.4	3.4
National Medical Care Expenditure Survey (12)	1977	USA	—	6.9	—
Policy Analysis (13)	1977	USA	10.8	3.7	7.1
Jonsson (14)	1978	Sweden	Kr 1317m	Kr 568m	Kr 749m
Platt, Sudovar (15)	1979	USA	15.7	5.6	10.1
Miller (16)	1979	USA	12.4	7.4	5.0
Laing (17)	1979–80	UK	£144m	£83.7m	£60.6m
Metropolitan Life (12)	1980	USA	9.7	4.8	4.9
Smeeding, Booton (17)	1980	USA	18.9	5.7	10.0
Carter Center (18)	1980	USA	—	7.9	—
Metropolitan Life (12)	1984	USA	13.8	7.4	6.3
Gerard (19)	1984	England & Wales	£259–603m	£239m	£20–364m
Huse (Type 2 diabetes) (20)	1986	USA	19.8	11.6	8.2
Laing, Williams (21)	1986–87	England & Wales	—	£484m	—
Fox, Jacobs (22)	1987	USA	20.4	9.6	10.8
Fox (23)	1992	USA	91.8	45.2	46.6
Rubin (24)	1992	USA	—	105.2	—
Gray (Type 1 diabetes) (25)	1992	England & Wales	—	£96m	£113m
Stern (Type 1 diabetes) (26)	1993	Israel	—	Shk 104 000 per patient	—

upon primary diagnosis data would underestimate the true impact of diabetes. Fox and Jacobs (22) and Huse (20) estimated the cost of diabetes in this fashion. They used primary diagnosis data in their report, but also included costs where diabetes was not a primary reason for health care use, disability or death. Not surprisingly, this approach provided higher estimates for the cost of diabetes: approximately \$20 billion in 1986–7.

The latest studies have considered even more health care resources in their estimates, including items such as the costs related to emergency room visits, home health care, and the use of dieticians. Fox-Ray (23) estimated that the cost of diabetes was a staggering \$91.8 billion in 1992. Rubin (24) estimated that the health care costs of persons with diabetes were \$105.2 billion in 1992. Both findings suggest that the cost of diabetes may be substantially higher than previously thought.

The estimates outlined in Table 23.1 have been applied to address many different arguments. These include arguments for changes in reimbursement or health care practices, and the need for adopting new technologies. With incidence-based estimates, it is also possible to have some indication of the savings that might be achieved if the development of diabetes were prevented.

Most often, though, cost estimates have been used to highlight the importance of diabetes to health care systems and health care insurers. Diabetes organizations commonly use these data as evidence of the need to devote more resources to diabetes care. Examples of this approach can be found on the World Wide Web. The Juvenile Diabetes Federation in their document, 'The Economics of Medical Research' (28), use the cost estimate by Rubin (24), to advance the argument that investing in diabetes research is worthwhile.

Is this argument true? Not necessarily. While cost of illness studies can estimate the monetary burden of diabetes, they cannot tell you if you have been spending the money wisely, or if investments in research or clinical practices are worthwhile. These issues are best addressed with another type of economic analysis; a cost-benefit, cost-effectiveness, or cost-utility study.

There are limits to the interpretation of all cost estimates. Comparisons between studies are difficult to make because methods and assumptions applied in the studies differ. For example, the 1992 estimate by Fox-Ray is nearly four times larger

than another estimate generated by the same author in 1987. Both studies used different methodologies; the latter including new cost categories and a much higher estimate of the costs of a hospital stay.

The framework of the analysis may differ as well. Rubin examined all health care costs among persons with diabetes. This approach may include costs that have little or no connection to diabetes. As most of the expenditures were among persons over age 65 years, it is probable that a great deal of the costs cited had very little to do with diabetes. Thus, the study may over-represent the impact of diabetes.

Other cost studies have examined specific topics in diabetes care, rather than the overall cost of diabetes. Examples of these assessments include reports on the cost of diabetes complications, or the cost of diabetes management. Table 23.2 outlines these studies.

Opportunity Costs

It is not only the health care sector which bears the costs of disease. Individuals with diabetes also face opportunity costs. These are costs that are encountered when a person makes a decision to do one task rather than another. For example, the costs of medicines and equipment sometimes are borne by individuals and their families. Patients may also pay higher life and motor insurance premiums. Persons with diabetes must spend time and money on these items that could otherwise have been spent on something else. They face decisions regarding their lives that other individuals do not. Thus, when we think about the impact of diabetes from the viewpoint of the patient, the costs of diabetes can be quite different, yet still substantial.

Specific mechanisms in which diabetes may influence the lives of those with the disease include a diminished access to health care, fewer job opportunities, and, for some, a lower quality of life. There are other areas as well. Persons with diabetes, though, often face decisions over the affordability of diabetes care, and whether it is available or not. They face discrimination in the types of jobs that they can do, and restrictions on or increased payments for health, life, and automobile insurance.

Table 23.2 Topic-specific cost studies in diabetes care

Study, year	Diabetes care issue	Findings
Gagliardino, 1993 (29)	Cost of control relative to the cost of treating complications	Prevention of complications would pay for itself.
van Houtum, 1995 (30)	Cost of lower extremity amputation in diabetes	The average cost per hospital admission for amputation related to diabetes was £10 531
Apelqvist, 1994 (31)	Cost of treating diabetic foot ulcers	Costs in patients with ulcers that heal primarily are lower than costs in patients with amputations
Apelqvist, 1994 (32)	Cost of treatment for foot ulcers	The average weekly cost for topical treatment ranged from £40–385
Olsson, 1994 (33)	The impact of excess morbidity in persons with diabetes	The excess cost of lost productivity was \$7000 per person per year. Excess costs for inpatient care were \$800 per person
Stern, 1994 (26)	Cost of treating Type 1 diabetes and cost of treating complications	About 70% of the total direct costs of treating complications of Type 1 diabetes relate to treating complications
Gray, 1995 (25)	Cost of treating Type 1 diabetes and the cost of treating complications	About one-half of the total costs of Type 1 diabetes relate to treating complications
Lenisa, 1995 (34)	Treatment for diabetic end-stage renal disease	Kidney transplants increase renal disease survival and reduce overall treatment costs relative to hemodialysis

ESTIMATES OF COSTS FACED BY PATIENTS WITH DIABETES

Few reports have examined the economic impact of diabetes in the daily lives of individuals living with the disease. In the United States, however, there is evidence that individuals living with chronic diseases face an increased health care cost burden. Health care in the United States is the most expensive in the world. Access to this expensive system is dictated by the presence of health insurance; both public-based and private. Health insurance coverage varies widely and marked inequities exist in access to health care. About 14% of the general population under age 65 has no health insurance coverage (35). The figure for the diabetes population averages close to 10–12% (36,37). Persons without work or in low-paying jobs are the individuals most likely to be without coverage (38). About 15% of families with Type 1 diabetes children have difficulty in obtaining coverage because of pre-existing illness clauses in the insurance policies (39).

As most persons with diabetes use health services more frequently than the general population (40), the out-of-pocket payments for diabetes care can be

extensive. In the United States, where some payment from the patient is often required for services received, out-of-pocket costs to the patient are roughly two times higher for a person with diabetes than for someone without diabetes under age 65 (41). A similar pattern exists among families with Type 1 diabetes children (Table 23.3). Nearly one-third of the families with a child with diabetes surveyed in one study spent more than \$1000 of their own money on health care compared to 16% in the families having no diabetic children (39). The burden of out-of-pocket medical expenses appears to be more profound among the lowest income Type 1 diabetes families (Figure 23.1).

Table 23.3 Out-of-pocket health care expenses in families with and without diabetic children

Spent per year (\$)	Type 1 diabetes families (%)	Control families (%)
0–499	32	65
500–999	33	19
1000–1499	17	6
1500–1999	5	4
More than \$2000	13	6

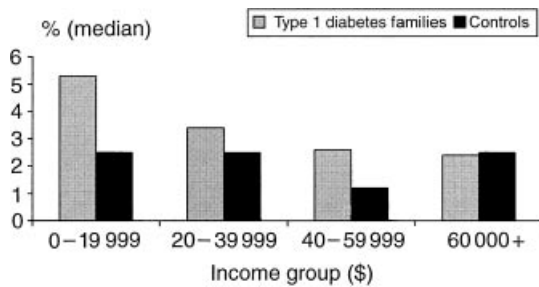


Figure 23.1 Percentage of income spent on health care by income group (health insurance premiums included)

THE COSTS OF USING RESOURCES UNWISELY

Economic Evaluation

A recent and rising practice in diabetes economics has been the use of evaluative studies to examine the economic efficiency of diabetes treatments and programs. Evaluative studies attempt to consider the costs of a treatment or intervention relative to the health outcomes produced. In an era of rising health care costs, these evaluations provide important information that can further decisions about the proper allocation of limited resources. Most often, the costs and outcomes of a new treatment are compared to the costs and outcomes of an existing form of treatment to determine if an efficient and effective use of resources might be gained from adopting the new approach (42).

Evaluative designs include cost-benefit, cost-effectiveness, and cost-utility analyses. All three designs evaluate the costs and benefits of one intervention or treatment relative to another intervention to determine if resources might be used more efficiently with a change in clinical practice (42–44). Cost-benefit, cost-effectiveness, and cost-utility studies are generally similar in how they estimate costs in an evaluation. Nearly all costs are expressed in monetary terms. The three forms of analysis, though, differ in how they assess the outcomes of a program or treatment (Table 23.4). Cost-benefit studies place a monetary value on the health outcomes of a program. Cost-effectiveness studies usually summarize health outcomes in physical units (such as the number of lives saved). Cost-utility studies generally

Table 23.4 Analyses used in economic evaluation

Cost-Benefit Analysis:

- examines the costs and benefits of an objective in monetary terms
- compares this to an alternative program.
- examines if the objective is worthwhile to pursue relative to other programs

Cost-Effectiveness Analysis:

- examines the monetary cost of an intervention relative to its health outcome
- compares this to an alternative (usually an existing standard treatment).
- assumes the overall objective is worthwhile, so it examines which intervention better meets the objective

Cost-Utility Analysis:

- examines the financial cost of a treatment relative to the quality of health produced
- compares this to an alternative or a QALY league table
- assumes the overall objective is worthwhile, so it examines which intervention better meets the objective

summarize health outcomes in terms of quality of life gained as well as quantity of life gained. More details on these analyses are available elsewhere (42–44).

Differences in the assessment of health outcomes between these three studies can also affect the manner in which these instruments are used in policy decisions. Cost-benefit analyses often seek to determine if an objective (like reducing the impact of diabetes complications) is worthwhile from an economic perspective (4, 45). Since cost-benefit studies value outcomes in monetary terms, the results can be compared directly with other programs (both inside and outside of the health sector). It is then, possible to examine whether such a program is worth pursuing and to what degree resources might be committed to it.

In contrast, cost-effectiveness and cost-utility analyses already assume that the objective is worth pursuing. The decision here is determining whether one type of intervention or another is better able to meet the intent of the objective. For example, one may find that the objective of reducing blindness from diabetic retinopathy is economically efficient. The task of cost effectiveness and cost-utility analyses, then, is to evaluate which intervention on retinopathy is the most efficient. In general, cost-effectiveness and cost-utility studies are favored over cost-benefit studies in the health-care sector (43). Nearly all of the reports relevant to diabetes have been cost-effectiveness studies.

Undertaking a cost-effectiveness study can be complex as data are needed from a variety of areas. The appropriate data and endpoints to consider in an evaluation will vary according to the intervention taking place. Most evaluations, however, consider the costs of starting and operating an intervention, the additional direct and indirect costs involved to improve health outcomes, the savings in direct and indirect costs when disorders are prevented or delayed, and the costs associated with any side-effects of the intervention. Other basic principles include stating the perspective in which the evaluation is being conducted, discounting costs that occur in future years, testing the results to consider the impact of uncertainty, and providing a summary measure of the efficiency of an intervention, such as a ratio of costs to effects. These principles are outlined in more detail elsewhere (46), and one recent publication suggests standards that all cost-effectiveness analyses should follow (47).

Estimates from Evaluation Studies

Economic studies of various diabetes interventions have been gaining in popularity in recent years. Evaluation studies differ substantially from cost of diabetes studies. They usually consider the costs of a diabetes program or treatment relative to the benefits obtained. In this design, comparisons are often made with an existing standard in an attempt to prioritize the direction of future resources and treatments. One current example is the evaluation of screening programs for determining the appropriate detection method and treatment setting for identifying diabetic retinopathy in the population.

The first studies in the literature dealing with the economic benefits of new treatments primarily examined diabetes education programs. Kaplan and Davis (48) critically discuss a large portion of this literature in their benchmark publication. They point out that many of the early studies neglected significant issues, such as accounting for the costs of starting and operating the education program. Most focused instead on the benefits of the program, and thus, the results give an unbalanced perspective. The majority of studies also did not include control groups for comparative purposes in their evaluations. Kaplan and Davis also point out the danger of evaluating

programs simply on the basis of a reduction of medical costs since health care costs can be influenced by a variety of factors, including simple changes in how services are paid for.

Many of the reports examined by Kaplan and Davis were completed in the 1970s and early 1980s. Since that time, there has been an explosion in the number of reports that address economic issues in diabetes from an evaluation perspective. Table 23.5 outlines the majority of these studies. The evaluations conducted center around screening or treatment programs for diabetes complications (e.g. retinopathy, renal disease, foot ulcers) or adverse outcomes of diabetic pregnancies.

Overall the findings suggest that screening for and treating diabetes retinopathy is extremely cost-effective. Javitt (55) found that it saved \$62–109 million for an annual incidence cohort of patients with Type 1 diabetes (when compared to not screening). A further report found that additional savings of \$9500 may occur with each new Type 1 diabetes person enrolled in a screening program (over the number already being screened)(57).

While it appears that some type of screening for diabetic retinopathy is better than no screening at all, there is debate over its level of efficiency in different settings and among different populations. Dasbach (56), for example, found that the costs of screening and subsequent treatment were recovered for persons using insulin (both young and old), but not for persons diagnosed with diabetes at a later age and not on insulin. Lairson (61), Griffith (68), and Joannu (83) reported that screening with retinal photographs can be an efficient alternative to a standard ophthalmologist's examination in settings where ophthalmologists are scarce. The underlying message of these reports is that appropriate screening strategies (and appropriate interventions in general) will vary. The most efficient means for screening can depend upon the population being screened, the training level of the screeners, the availability of equipment, and the goals of the program relative to the resources available to carry it out.

A similar message exists with regards to screening and treatment for microalbuminuria. The general findings of three reports suggest that screening for microalbuminuria and treatment with angiotensin converting enzyme inhibitors (64,79) or anti-hypertensives (66) would be beneficial and cost-efficient. The strength of the data that underlie

Table 23.5 Evaluative studies of diabetes-related issues in the literature

Study	Issue examined	Results
Deckert, 1978 (50)	Cost-benefit analysis of outpatient care in a diabetes clinic	Outpatient care in a Danish diabetes clinic involved little cost (\$10 000) and saved \$100 000 over 40 years
England, 1981 (50)	Cost-effectiveness of a vaccine to prevent Type 1 diabetes	Vaccinating all children at age 3 is preferable to vaccinating only those at high risk. A 50% effective vaccine would save \$30 million yearly in direct costs
Weiner, 1986 (51)	Screening strategies for gestational diabetes	The number of oral glucose tolerance tests required and the cost of identifying gestational diabetes is reduced with 2 hour screening test compared to a 1 hour test
Kaplan, 1987 (52)	Cost-utility of diet and exercise intervention in Type 2 diabetes patients	The cost-utility of the program was \$10 870 per well-year gained; a figure comparable to other advocated health care programs
Javitt, 1989 (53)	Cost-effectiveness of treatment and control of diabetic retinopathy in Type 1 diabetes patients	Costs of screening and panretinal photocoagulation per person-year of sight saved = \$966
Allan, 1990 (54)	Costs and effects of glucose self-monitoring in Type 2 diabetes patients	Blood glucose monitoring was no more effective than urine testing, but 8–12 times more expensive
Javitt, 1990 (55)	Efficiency of screening strategies for detecting diabetic retinopathy in Type 1 diabetes patients	Screening for and treating patients with retinopathy realizes a cost savings under many different types of screening programs, ranging from \$62–109 million and saving 71 000–85 000 sight years
Dasbach, 1991 (56)	Screening and treatment strategies for diabetic retinopathy	Costs for screening are recovered by the avoided costs of blindness in insulin-taking persons, but not in non-insulin-taking persons
Javitt, 1991 (57)	Efficiency of current screening conditions and those at higher levels of compliance	At current levels of screening, \$101 million and 47 000 sight years are saved in an incidence cohort. Added savings of \$9500 occur with each new person screened
Sculpher, 1991 (58)	Screening strategies for referring cases of diabetic retinopathy	The efficiency of screening varies by the person doing the screening and the site where it is performed
de Weerd, 1991 (59)	Costs and effects of a diabetes education program for insulin-treated patients	No significant effect of education on metabolic control, use of health services, drug costs, or indirect costs was observed between an experimental and control group.
Fendrick, 1992 (66)	Cost-effectiveness of screening and treatment of diabetic retinopathy among Type 1 diabetes patients in Sweden relative to no screening	Screening for and treating patients with retinopathy may realize a cost savings of 22–37 million SEK and 2300–3200 sight years saved depending upon patient compliance to screening recommendations
Lairson, 1992 (61)	Screening strategies for referring cases of diabetic retinopathy	In a government health care setting, screening with retinal photographs (with dilated pupils) is more cost-effective than ophthalmoscopy
Scheffler, 1992 (62)	Cost-effectiveness of a diabetes pregnancy intervention program	Over \$5 in hospital charges was saved for every \$1 spent in this preconception and early pregnancy program.
Sculpher, 1992 (63)	Additional screening strategies for referring true cases of diabetic retinopathy	Tradeoffs exist such that to increase sensitivity, you have to adopt tests with lower specificities and/or higher costs per case detected
Siegel, 1992 (64)	Screening strategies for early renal disease and treatment with ACE inhibitors in Type 1 diabetes patients	Screening for and treatment of microalbuminuria with ACE inhibitors appears to be cost-effective. This result, though, depends upon the drug effectiveness, screening costs, and the cost of end-stage renal diseases
Bentkover, 1993 (65)	Cost-effectiveness of treating non-healing foot ulcers with platelet releasate in a wound care clinic	Clinic and platelet releasate treatment was more cost-effective (\$22 500 per healed person) than clinic and saline solution treatment (\$36 000 per healed person)
Borch-Johnsen, 1993 (66)	Cost-benefit of screening and treatment for microalbuminurians Type 1 diabetes patients	Screening for microalbuminuria and treatment with antihypertensive drugs would pay for itself if the rate of increase in albuminuria was reduced by 8–10% a year
Elixhauser, 1993 (67)	Preconception care for diabetic women relative to usual prenatal care	Intensive medical care before conception appears to result in costs savings from averted complications compared with prenatal care only

Table 23.5 (continued)

Study	Issue examined	Results
Griffith, 1993 (68)	Screening for retinopathy in a primary care setting	Screening by ophthalmoscope and fundal photography both had high sensitivities for referring patients. Direct ophthalmoscopy was less expensive than retinal photos.
Levy-Marchal, 1993 (69)	Examination of screening strategies to identify early cases of Type 1 diabetes in the population	Cost-benefit ratios (the cost of screening relative to the ability to accurately identify subjects) vary by the population groups examined and the screening test
Simell, 1993 (76)	The costs and effects of shorter hospital stays among children diagnosed with Type 1 diabetes	Direct and indirect costs were reduced among patients with shorter lengths of stay (9 days) compared to those with longer stays (23 days). No difference in metabolic control was observed between the groups up to 2 years
Haardt, 1994 (71)	Cost-benefit analysis of implantable insulin pumps compared to multiple injections	The implantable insulin pump was more effective in metabolic control over 6 months than multiple injection therapy, but direct costs were 3 times higher
Javitt, 1994 (72)	Savings to the federal budget from screening and treatment for eye disease in Type 2 diabetes patients	Screening and treatment for diabetic eye disease saves \$248 million to the federal budget. If all patients are screened, could save up to \$472 million
Le Floch, 1994 (73)	Cost-effectiveness of screening for microalbuminuria	The cost-effectiveness ratio of screening with dipsticks and lab assay for identified positives relative to screening with lab assays alone was £6600 per QALY
Starostina, 1994 (74)	Costs and effects of glucose self-monitoring strategies (urine, blood, none) in Russia	Glucose control was improved and DKA events reduced among subjects in urine or blood monitoring relative to no Both methods were equally effective, but the cost of urine testing strips was markedly lower
Woolridge, 1994 (78)	Cost to a government insurer of paying for therapeutic shoes for patients with foot problems	No difference in future payments for health services up to 1 year was observed between patients with shoes paid for by insurance and patients who bought their shoes
Collins, 1995 (76)	Savings in prescription costs from a weight reduction program	Weight reduction was maintained over a 1 year period after intervention. Prescription drug costs were reduced by \$442 per person over this time.
Eckman, 1995 (77)	Cost-effectiveness of treatments in patients with foot infection and suspected osteomyelitis	Several strategies were examined for Type 2 diabetes patients. In general, those involving long courses of antibiotic therapy were preferable to those involving amputation
Franz, 1995 (78)	Cost-effectiveness of practice guidelines nutrition care in Type 2 diabetes patients	Nutrition interventions that follow practice guidelines can improve metabolic control at a reasonable cost
Kiberd, 1995 (79)	Cost-utility of screening and treatment for diabetic renal disease in Type 1 diabetes patients	Screening for microalbuminuria and treatment with ACE inhibitors is cost-effective relative to screening and treatment for hypertension and macro-proteinuria if certain conditions are satisfied, including screening costs and accuracy, drug costs, and renal disease costs
Steindel, 1995 (80)	Cost and effects of insulin pump treatment in poorly controlled adolescents	Insulin pump treatment did not change metabolic control over one year, but did reduce hospital stays and direct costs compared with treatment in the year before
DCCT Research Group, 1996 (81)	Cost-effectiveness of intensive insulin treatment relative to standard treatments	Intensive insulin therapy represents a good monetary value. The incremental cost per year of life gained with intensive treatment was \$30 400
Javitt, 1996 (82)	Cost-effectiveness of screening and treatment for diabetic eye disease relative to existing disease	The cost of detecting and treating diabetic eye disease is \$3190 per QALY saved; \$1996 for those with Type 1 diabetes, and \$3530 for patients with Type 2 diabetes
Joannou, 1996 (83)	Screening for retinopathy in a diabetes clinic	Screening with 60 degree retinal photography was more effective than with 45 degree photos. Cost was \$6 per patient screened, \$37 for each patient referred
Stern, 1996 (84)	Direct costs of intensive insulin treatment relative to standard treatments in Type 1 diabetes patients	Over 35 years, the cost of intensive treatment is about \$19 000 higher than the cost of standard treatment. No indirect costs of premature mortality are included

these reports, though, is not at the same level as that for retinopathy. Several questions remain regarding the level of 'effectiveness' of ACE inhibitors in a microalbuminuric population, the degree of compliance to pharmaceutical treatments, and the cost of screening in the diabetic population. As Kiberd (79) points out, the cost-effectiveness of screening for microalbuminuria can vary tremendously by the values assigned to each of these issues.

The cost-effectiveness of treatment for diabetic foot ulcers remains muddled. A paper by Eckman et al. (77) examined treatment strategies for foot ulcers with suspected osteomyelitis. The underlying message emerging is that treatment with a long course of antibiotics is more cost-efficient in most situations than amputation. The authors, however, examined several treatment alternatives in their analysis, and as such, one can only draw general conclusions from the work rather than specific recommendations.

Herein lies the crux of most economic analyses. Evaluations are most useful when they elicit specific recommendations regarding the pursuit of a treatment, technology, or program. Such recommendations can be readily put to use by decision-makers in health care. Clear recommendations, though, are not apparent for many of the issues pertaining to diabetes care.

It is equally important that proper interpretations are applied to the existing reports. Two reports have examined the issue of intensive insulin treatment among persons with Type 1 diabetes. Stern and Levy (84) conducted a cost analysis and found that, over 35 years, the cost of intensive treatment was greater than the cost of standard forms of treatment, even after accounting for the greater costs of treating complications in the standard treatment group. Their report, however, did not consider indirect costs or the relative benefit of improved health associated with intensive treatment. Similarly, the DCCT Research Group (81) found that intensive treatment was more costly than standard treatment; the cost per year of life gained with intensive treatment was \$30 400. They concluded, however, that intensive insulin therapy represents a good monetary value.

Are services that reduce costs or save money the only services worth pursuing? Many individuals would answer this second question in the affirmative, but such a response would be shortsighted. For it neglects the clear health benefits of many

interventions that do not save money. Diabetes issues should be viewed in a balanced perspective of costs relative to the improvement in health obtained. When is an intervention cost-effective? The answer here depends upon how one values life or health, but indications from the economic literature suggest that interventions costing \$20 000 per year of life gained are cost-effective, while those costing more than \$100 000 per life year gained are not.

OUTCOMES RESEARCH

An understanding of the appropriate use of health care may also be gathered from health outcomes studies. At present, large variations in health care interventions (and costs) exist by area (85–87). As there are also no apparent differences in health outcomes, it would appear that either there is inappropriate care or inappropriate priorities are being pursued in some areas. The general aim in formal outcomes studies is to identify the practices and results of medical care interventions over large populations, record the outcomes related to specific practices, and suggest modifications to clinical practice on the basis of these observations (91).

There are numerous informal studies that address health outcomes associated with diabetes. Reports of international differences in outcomes, in particular, provide clues towards identifying areas that may have unsuitable care or misplaced priorities. The Diabetes Epidemiology Research International study, for example, illustrated significant differences in mortality among Type 1 diabetes patients in four countries (89). Death rates were highest in Japan, followed by Allegheny County, PA, Finland, and Israel.

Reports also exist that describe situations where persons with diabetes face barriers to care or limits (economic and other) on their access to health services. For example, in the United States, persons with Type 1 diabetes who do not have health insurance visit physicians (90) and test their blood sugars (39) less frequently than those who have insurance. Many researchers believe that inadequate attention to routine diabetes management will lead to poor subsequent health, but there is limited evidence, at this time, to prove it. Recent data from the follow-up study to the DCCT, though, indicate that persons without insurance

coverage have worse levels of glycemic control than those with insurance (91). Thus, the link between access to care and poor health outcomes in diabetes may be legitimate.

Formal outcomes studies specific to diabetes are underway (92). The Medical Outcomes Study (MOS) (93) examined the health outcomes of 170 patients with Type 2 diabetes over a 2-year period of time. Overall, no real differences in health outcomes were observed between patients enrolled in health maintenance organizations (HMOs), independent practice associations (IPAs), and traditional fee for service plans. Foot ulcer and foot infection outcomes, though, were better among patients treated by endocrinologists than among patients treated by family or general practitioners. The Type II Diabetes Patient Outcome Research Team (PORT) Study (94) is currently following the medical care and outcome experience of 4000 patients in the United States. Preliminary findings from this study suggest little difference in outcomes (metabolic control) by type of physician (specialist vs. generalist).

The Supply of and Demand for Diabetes Care

Costs are also involved when there are too few or too many resources in diabetes care. The classic issues in economics are the influences of supply and demand on prices. Although the health care setting is not entirely similar to the business world, several scenarios exist where supply and demand are of concern for their influence on the cost of health care. Excesses or shortages in the number (supply) of health care providers, the availability (supply) of medical technologies and drugs, and the demand for health care may affect the costs of disease or treatments for a disease.

An understanding of the demand for and supply of diabetes care can help to explain current cost structures and diabetes care behaviors. An example of too little resources is the finding that insulin is not available to people who need it in some areas of the world. The cost involved here is the increased morbidity and mortality observed among diabetic patients in these areas, because they cannot get care when they need it.

Unnecessary costs are involved when too many resources or providers are available. Physicians,

for example, may recommend that a patient return for another visit as their salaries or income are dependent upon it. The hazard in this situation is that of unnecessary treatment or an inefficient use of resources.

When too few resources are available, there are costs related to the lack of treatment of disease. When insulin is not available to the patients who need it, the cost is expressed in terms of poor health outcomes; severe hyperglycemia or death (95). The implementation of diabetes treatments, programs, or initiatives (such as the St Vincent Declaration) will also have an associated cost if too few skilled specialists are available to provide intensive insulin treatment as practiced in the DCCT or screening and treatment for diabetic eye disease (96) and other complications. The cost in this scenario is a continued high rate of complications in the diabetes population (97).

CONCLUSIONS

An understanding of the economic issues that both patients and society face in treating diabetes is vitally important. Health care choices are a reality of life throughout the world. Health care payers and providers must make decisions that affect not just diabetes, but other non communicable and communicable diseases.

Today, many decision-makers are seeking to address and contain health care costs. Most of the changes taking place in health systems focus on cost containment. There are several mechanisms by which one can reduce costs, such as limiting access to care, shifting services from inpatient to outpatient settings, reducing the frequency of health care use, reducing the duration of the patient encounter, and reducing the cost of the service (perhaps with more use of allied health professionals). Each of these actions has an associated cost.

The above presentation has briefly introduced the different ways in which the costs of diabetes can be viewed. Yet, given the prevailing mood for cost control, our understanding of the costs of diabetes is limited in many areas. Nearly all aspects of medicine must now address the issue of cost, and the evaluation of most new treatments or technologies commonly includes assessments of costs relative to the benefits obtained. We need

more economic assessments pertaining to diabetes to address these issues.

If not, the danger is that the zeal to control costs may overlook the subtleties in improving the health of persons with diabetes. There are clear health benefits to many interventions that do not save money. We must be concerned that diabetes issues are viewed in the balanced perspective of costs relative to the improvement in health of diabetes patients obtained, rather than the unbalanced perspective that may accompany an emphasis on costs.

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Diabetes Field Surveys: Theory and Practical Aspects

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INTRODUCTION

As the contents of this volume attest, our knowledge of the epidemiology of diabetes has expanded enormously in the two decades since the first book dedicated to this subject was published (1, 2). This has been brought about, in large part, through the contrasting use of two major study variants: the establishment of registers for insulin-dependent diabetes mellitus (Type 1 diabetes) (3, 4), and the widespread use of field survey methodology for the study of non-insulin-dependent diabetes mellitus (Type 2 diabetes) (5, 6).

The relatively low prevalence of Type 1 diabetes, coupled with a clearly defined clinical presentation and the imperative of early diagnosis and treatment for survival, mean that it is ideally suited to study by the establishment of incidence registers. This is most applicable in countries which have high ascertainment of cases by virtue of a moderately sophisticated standard of medical practice which is uniformly accessible to the population. Having defined cases through population-based registers, case-control methods are then often utilized for specific aetiological inquiries in Type 1 diabetes (7, 8).

By contrast, Type 2 diabetes is defined in terms of blood glucose concentrations, and a significant proportion of all cases are asymptomatic, and certainly undiagnosed, for some years prior to clinical recognition of the disease (9). In both developed and developing countries, as many as 50% or more of all cases with Type 2 diabetes may be unknown (10–12). Moreover, these undiagnosed cases are by no means benign: many individuals will be found to have occult microvascular and macrovascular disease at this

stage (9, 13–14). This is not surprising, given that the World Health Organization diagnostic criteria for diabetes were defined on the basis of glucose concentrations at which characteristic microvascular complications of diabetes had been observed to occur (15–17, 52, 53).

The Need for Surveys

Because of the existence of pools of both clinically mild untreated cases and undiagnosed cases, irrespective of the population, studies of Type 2 diabetes and its complications that rely on routine data sources and clinic attenders will be subject to considerable bias. For this reason, population-based surveys are necessary to properly define the spectrum of Type 2 diabetes (15, 18). Such surveys may be prompted by recognition of the growing importance of diabetes as a cause of ill-health, in both social and economic terms, and provide information of use for:

- public health planning purposes
- aetiological inquiry
- facilitating appropriate health education and/or referral for treatment of individuals found to have disease or elevated risk factor levels

The need for field surveys is particularly important in developing countries where Type 2 diabetes is becoming increasingly common, and 'routine' sources of information, such as hospitalisation and mortality data, are either not available or at best incomplete (5, 6, 18). Indeed, surveys performed in the developing world over the years since standardized criteria for diagnosis of diabetes

were promulgated have highlighted the emergence of virtual epidemics of Type 2 diabetes as a significant global public health problem (6, 15, 19).

Measurement procedures which are commonly used in epidemiological field surveys of Type 2 diabetes and cardiovascular disease risk factors have been published previously (18, 20–23) and this information will not be repeated here. Similarly, specific descriptions of how to perform field surveys of diabetes and cardiovascular disease whereby up to 120–150 subjects can be surveyed in a morning, with 2 hour glucose tolerance tests, questionnaires, anthropometry, blood pressure measurement, electrocardiograms and complications assessments, can be found elsewhere (18, 20). Therefore, this chapter attempts to cover different ground, by providing a theoretical and practical framework for planning and performing a field survey to determine the prevalence of diabetes, and of associated lifestyle risk factors and conditions, and complications. The emphasis will be on suggestions of particular relevance to surveys in developing countries and remote locations, although the methods have wide applicability.

It is axiomatic that investigators planning studies should carefully consider the suggestions in this chapter in the context of their own resources and environment, and their objectives. Alderson (24) instructively defined an epidemiologic survey as: ‘a special inquiry which collects planned information from individuals (usually a sample) about their history, habits, knowledge, attitudes or behaviour. In addition to asking questions, the respondents may be examined or various investigations carried out’. Researchers interested in a more comprehensive description of general survey methods should consult Abramson (25).

PLANNING AND PREPARATION FOR A SURVEY

Investigators planning a survey should follow a well-defined set of principles, summarized in Table 24.1, and discussed below. While many of these are common sense, even the most experienced researchers could benefit from checking their progress against such a list. It should also be pointed out that while there is some logical sequence to the steps, in reality many of these will be carried out concurrently.

Table 24.1 Summary check-list of steps in planning and performing a survey

Planning and Preparation
1. Defining the study objectives
2. Choice of research method
3. Selection of study population and sampling method
4. Sample size determination
5. Choice of study variables and measurement instruments
6. Design of questionnaires
7. Preparation of survey manual, data record forms and other documentation
8. Planning analyses and data presentation
9. Funding applications
10. Ethics approval
Organization and Conduct
1. Logistics: dates, staff, survey sites, equipment and supplies
2. Pre-testing, pilot-testing and staff training
3. Census of survey population
4. Promotion and maximizing response
5. Supervision and quality control
After the Survey
1. Public relations and follow-up
2. Packing, transportation and storage of equipment and specimens
3. Safe-keeping of survey forms and other documentation
4. Data processing and reporting

Defining the Study Objectives

The initial steps in planning any survey (or other form of epidemiological study) are to formulate the research question(s) to be addressed and to define the objectives of the study. This may involve preliminary discussions with peers, potential collaborators, and experts in the field, and critical review of the literature and any available routine data. These steps should help to define important gaps in knowledge so that worthwhile research questions can be formulated.

Objectives should be clearly and concisely stated in writing, and should be achievable (20). For example: ‘To define the relationship between physical inactivity and impaired glucose tolerance (IGT) in population x.’ The stated objectives will be critical in determining the type of study which is performed, including the resources (funds, staff, facilities, instruments) and time required to complete the work. Objectives may need to be recast if subsequent steps in planning suggest that they are not achievable.

Choice of Research Method

The nature of the objectives will in large part determine the study design. The simplest observational study is the *cross-sectional population survey*, the subject of this chapter. These are also known as prevalence studies, and are by far the most commonly performed type of epidemiological study of Type 2 diabetes (5, 6, 10–14). As outlined elsewhere, depending on the study hypotheses, additional elements can be added to the cross-sectional design, including rural–urban comparisons, contrasting the experience of migrant groups with those who have not migrated, and serial surveys to monitor trends in prevalence (18, 26–29).

If the objectives include the desire to define the incidence and natural history of disease, and to relate baseline risk factors to incidence of disease and complications, then an initial cross-sectional survey population can form a cohort for a *prospective or longitudinal study*. Although not essential, it is preferable to have planned to perform a longitudinal study from the beginning, as this will influence many aspects of the design of the baseline survey, and it will be possible to put in place procedures for surveillance of the study population. The latter will allow investigators to more readily trace subjects at the time of follow-up studies, and provide important information on patterns and determinants of morbidity and mortality. Longitudinal studies in several populations, including Britons, Pima Indians, Nauruans and Swedes have contributed much to our current understanding of Type 2 diabetes (30–33).

Of course, ‘survey methods’ and the general principles involved in their planning and conduct also contribute to the other major forms of epidemiological study, although these are not ‘surveys’, *per se*. For example, *case-control* methodology has been employed in studies of Type 2 diabetes in Hispanic and non-Hispanic Americans (34) and *experimental* studies have suggested that diet and exercise intervention may prevent Type 2 diabetes (35).

Selection of Study Population and Sampling Method

The study population is usually defined on the basis of characteristics such as geographic loca-

tion, age-range, sex and ethnicity. The choice of the population is determined by the study objectives, available resources, likelihood of cooperation and stability of the population, and logistic factors including topography and ease of transport. Having defined the population for study, a sample is usually selected in some way so as to be representative of that population.

The ideal of a *simple random sample*, whereby all members of the target population are eligible for inclusion, is rarely possible. This requires the existence of a complete sampling frame, such as an electoral roll, and considerable resources, given the likely wide geographic spread of subjects. National estimates of diabetes prevalence in the USA (11) and Australia (36) have been based on randomization of individuals, but the former involved a complex system of stratified sampling, and the latter was limited to residents of large cities and did not use glucose tolerance tests (18).

Many surveys of Type 2 diabetes have been performed in *whole community samples*, with all persons within a defined geographic area who meet certain other criteria, including age, being eligible. Boundaries may reflect local administrative areas (12), whole villages (29), or areas defined by the investigators to suit logistic and sample size considerations, and demarcated by streets, rivers or other landmarks (37). The small Pacific island nation of Nauru represents a unique case, with the entire population of adult ethnic Nauruans being eligible for study (32, 38). In the more usual case, community samples are chosen on the basis of logistic factors (e.g. accessibility and appropriate facilities for establishing a temporary survey site), because they are judged to be typical of the background population, and because their characteristics are compatible with the *a priori* objectives of the study. For example, communities may be selected because their lifestyle is thought to be typically urban or rural (26–29). Where such community samples are studied care must be taken in extrapolating results to the wider population. A case in point is the genetically diverse population of Papua New Guinea, where the prevalence of Type 2 diabetes can vary widely between nearby villages, even where lifestyle appears similar (29).

In some circumstances, it might be feasible to use *random cluster sampling*, whereby the advantages of working in defined communities or areas are retained, but an attempt is made to choose a

study sample more representative of the target population. This involves sampling from many geographical clusters of population which each have an equal chance of being selected: clusters will most usually be defined by existing administrative boundaries, but may be created specifically for the survey, for instance, using street boundaries. If the population size varies between clusters, then sampling should be with 'probability proportional to size' (39). The larger the number of clusters, the more representative the sample is likely to be of the background population. A national survey of Type 2 diabetes prevalence in Mauritius utilized a two-stage random cluster sampling scheme in which 10 clusters of around 500–600 adults were selected (12).

Additional sampling strategies include *stratification*, whereby subgroups (such as an ethnic group or age-group) may be deliberately over- or undersampled, *systematic sampling*, where, for example, every *n*th street, household or individual is selected, and *multi-stage sampling*, whereby a sequence of any of the previously described methods is followed to define the eventual sample (21, 24, 39). However, particularly in unsophisticated populations, response is likely to be optimized where all adult members of a community participate, rather than by singling out individuals from different households and neighbourhoods.

Sample Size Determination

The size of the sample required in any survey must be estimated early in the planning phase in relation to major objectives. Standard formulae are used to calculate sample size estimates, or published tables or computer programs can be consulted (21, 39, 40). The formula used will vary depending on the nature of the study hypothesis, and it is prudent for the inexpert to seek statistical advice. Calculation of sample size will require designation of parameters including an estimate of the major study endpoint(s) (e.g. difference in prevalence or mean values of a continuous variable between two subgroups), the level of statistical significance (usually 0.05) accepted as indicating a real difference, and the power or likelihood of the study demonstrating such a difference if it really does exist. With more elaborate hypotheses, and

the need for greater precision of estimates and power of a study to find a result, sample size requirements can rise dramatically (39).

Of course, surveys of Type 2 diabetes commonly measure many variables, besides the prevalence of the defining condition. These include continuous variables such as blood glucose and cholesterol concentrations, blood pressure, urinary albumin excretion, and body mass index, and a range of categorical variables, including gender, cigarette smoking, ethnicity, presence of retinopathy, hypertension and other conditions, and so on. In turn, many research questions can potentially be studied. It is neither practical nor desirable to make sample size calculations for all possible analytic scenarios. Investigators must decide on their primary objectives, and focus on these in determining the optimal sample size.

While available resources and logistic factors must also be considered in planning the size of a study, and the data to estimate sample size may be limited or inaccurate, there are no excuses for failure to consider whether the sample size in any study is sufficient to give useful information. Funding agencies are usually forthright in requiring demonstration that sample size is adequate.

Choice of Study Variables and Measurement Instruments

Variables to be measured in a survey must be chosen in relation to the objectives of the study and taking consideration of the likely form of analysis. In general, investigators should resist the temptation to measure too much—this tendency is a particular problem in collaborative studies, where participating researchers may have different interests. This impasse can be overcome, at least to some extent, by limiting measurements of secondary importance, and those that are complex or time-consuming, to subgroups of the main study population.

Variables in typical diabetes surveys will be selected from several categories including *demographic characteristics* (e.g. age, sex, ethnicity, place of birth, socio-economic status indicators), *medical and family history indicators* (e.g. past history of diabetes or myocardial infarction, use of medications), *lifestyle risk factors* (e.g. physical

activity, alcohol consumption, cigarette smoking, dietary fat consumption), *physical measurements* (e.g. height, weight, waist and hip circumferences, blood pressure), *clinical examination findings* (e.g. deep tendon reflexes, ophthalmoscopy), *biochemical determinations* (e.g. plasma glucose, serum insulin, urinary albumin concentration), and *special investigations* (e.g. Minnesota codings of electrocardiograms, vibration thresholds, gradings of retinal photographs) (13, 14, 20, 26–34, 41).

Each variable selected for measurement in a survey should have a clear written *operational definition* which can be understood by survey staff and potentially reproduced by other investigators (42). This applies not only to physical measurements such as blood pressure and girth, but also to questionnaire variables. It is the nature of field surveys that compromises in measurement technique are often necessary, compared to what might be performed in a clinical or laboratory study, but it is equally true that particular procedures, or perhaps the whole survey, will not be worth performing if methods are suspect. Good measurements have the characteristics of repeatability and validity. Poor repeatability necessarily also implies poor validity, but a measurement may be highly repeatable, but have poor validity—for instance, repeat measurements made on a glucose analyser or a weighing scale may be very similar, but if the instruments are incorrectly calibrated then they will not be valid measures. Armstrong et al (42) have described methods for assessing validity and repeatability of measurements before and during surveys.

Important characteristics of a measurement in the context of a field survey are as follows:

1. *Validity*—refers to the extent to which a method measures what it is supposed to: its ‘truthfulness’ (42). Valid measures should be both *sensitive and specific* (43). Particular care should be taken to check that measurement instruments adopted from elsewhere are valid. For example, established questionnaires may not be valid in different cultures, and glucose analysers may not perform well under conditions of high humidity or temperature.
2. *Repeatability or reliability*—is the level of agreement between replicate measurements (42). It is influenced by two main components:
 - a. *Within-subject variability*: this is usually random, but may be subject to bias by factors such as exertion, cigarette smoking, stress and temperature. For example, the well-known variability in glucose tolerance test results in individuals, even when repeated within a few days, is likely to reflect both random and non-random forces (44).
 - b. *Observer or measurement variability*: within single observers and/or instruments variability tends to be random, but between observers and/or instruments bias is introduced to measurements. Random measurement errors diminish true associations in epidemiological studies, but are not inherently fatal as they tend to average out. However, the systematic errors introduced by different observers and/or instruments can invalidate a study (42, 43). For example, even where standardized training of blood pressure observers and calibration of sphygmomanometers has been meticulous, it is important to ensure that subjects present to the observers randomly (21). Otherwise, if a difference between subgroups is found it will be difficult to tell if this is real or due to observer variation.
3. *Robustness*—particularly if working in under-developed country settings, measurement instruments must be chosen taking into account aspects such as their portability, durability, ability to withstand electricity fluctuations and extremes of temperature and humidity, and availability of spare parts and ease of repair under field conditions.
4. *Acceptability to subjects*—bad news travels fast, and it is important not to use methods that might prejudice the cooperation of study subjects. Initially, considerable time should be spent explaining the purpose of the study and the procedures it will entail to the population, by means such as community meetings, house-to-house visits and, if subjects are literate, written explanations. Methods may need to be modified to suit local cultural factors. For instance, venesection may need to be replaced by finger pricks, or multiple samples sacrificed in favour of a single fasting or 2-hour post-load sample (20, 45). Similarly, in some cultures

questions regarding sensitive matters such as stillbirths and miscarriages are best avoided. In general, time-consuming and invasive procedures should be avoided in field surveys.

5. *Acceptability to researchers*—factors including cost, time to perform the measurement and ease of use under field conditions must be considered. The time needed to complete each measurement procedure, the number of procedures to be undertaken and the number of staff/measurement instrument combinations available are critical in determining the number of subjects that can be invited to a diabetes field survey in any one day (18,20). This is especially so in surveys utilizing glucose tolerance tests in subjects who have fasted overnight, where it is advisable that all procedures, including the final 2-hour blood collection, should be completed by midday at the latest. As has been described previously, with good planning and sufficient staff it is possible to survey 120–150 subjects per morning in a quite comprehensive diabetes and cardiovascular disease risk factor survey (18,20,27,41,46). The procedures included in such a survey are listed in Table 24.2.

Table 24.2 Sequence of procedures included in a large-scale Type 2 diabetes field survey, requiring 15–20 team members and allowing 120–150 subjects to undertake ‘core’ procedures

Procedure	Number of staff
Core Activities	
1. Registration	2–3
2. Venesection (fasting and 2-hour)	3
3. Glucose load	1
4. Height and weight	1
5. Waist and hip girth	1
6. General questionnaire	1
7. Activity/dietary questionnaire*	1
8. Blood pressure	2
9. Electrocardiogram*	2
10. Laboratory	2–4
Complications Screening* (all diabetic subjects and sample of IGT and normals: performed on day following core procedures)	
1. Early morning urine	—
2. Visual acuity & mydriasis	1
3. Foot examination/sensory testing	1
4. Eye examination/retinal photography	2

*Non-essential procedures, depending on population and resources. For further details see reference (20).

Design of Questionnaires

Questionnaires should be prepared according to a set of general principles which have been well described by others (42,47). Important aspects are summarized below:

1. Begin by listing the information required, then draft questions based on this list.
2. Questions should be easily understood, unambiguous, and non-judgemental.
3. Avoid leading questions (those that suggest an answer).
4. The questions should occur in a natural order.
5. Easy questions should come first, and more difficult and sensitive questions toward the end.
6. The relative merits of self-administered versus interviewer-administered formats must be considered. Interviewer-administered questionnaires are usually favoured in field surveys.
7. In general, a mixture of open and closed questions are used in field surveys. Closed questions are often preferable as they are more specific and easily analysed. The distinction between open and closed is in fact blurred for simple ‘open’ questions such as, ‘What treatment are you currently taking regularly for diabetes?’, where the interviewer records the answer directly into a coding box based on category options on the questionnaire. Where necessary, supplementary questions will be asked to guide the subject’s response. Categories must be mutually exclusive (for example: yes, no, don’t know; and ≤10, 11–20, 21–30, etc. for cigarettes per day).
8. As far as possible questionnaires should be pre-coded, with responses written directly into boxes ready for computer entry.
9. Questionnaires should be tested for validity and repeatability and modified where necessary (42).
10. Translated questionnaires should be independently back-translated to the original language to ensure original meanings have been retained.
11. Interviewers should have clear written instructions and be trained in the use of the questionnaire.

3. *Survey registration book*—as subjects are registered on arrival at the survey site they should be allocated a unique sequential number, and have their name recorded against that number, which should also be transcribed to the survey names list or census, as described above. The registration book is crucially important, as it is the 'bible' for linking names to survey numbers.
4. *Questionnaires/data record forms*—in surveys where a number of procedures are undertaken sequentially, including a simple questionnaire and measurements such as anthropometry and blood pressure, it is convenient to have a single form which subjects carry with them from station to station (20). Subjects are instructed to return this form to the registration station after they have completed all procedures, where it is checked to ensure nothing has been missed. Where special procedures are undertaken (e.g. retinal photography, electrocardiograms, more elaborate questionnaires) these records are best retained at the station where they are performed, after ensuring that the subject's survey number has been transcribed, and check-boxes on the main form are ticked to indicate that the station has been visited. This allows staff to determine readily at any time which survey stations a subject has or has not visited.

In some situations, such as where groups of subjects may undergo different procedures (e.g. retinal photography only for diabetic subjects, or a systematic subsample of every fifth subject for a dietary questionnaire) it may be convenient to indicate this by using differently coloured primary record forms, or by attaching a coloured sticker to the front of the forms.

Survey record forms should be designed with data processing in mind—this means as much of the information as possible should be pre-coded, preferably into boxes down the right-hand side of the page to facilitate data entry to computer. As far as possible, items on survey forms should follow the sequence in which the data are collected. Particular care must be taken to ensure that the correct number of boxes are shown for measurement variables, decimal points are indicated where relevant, and staff are instructed in how to complete the forms.

Subject Information Forms

A variety of forms are required for keeping subjects informed throughout the phases of a study. These help to ensure both a good response and the collection of optimal data on the subjects who attend. Wherever possible, it is a good idea to have these forms signed by respected and important figures, such as the Minister of Health, the Chief Medical Officer, and/or local civic leaders. In non-literate societies personal visits and/or community meetings will be necessary to give information.

1. *Preliminary information sheet*—this should be distributed well in advance of the survey, with the purpose of explaining the general rationale for the study, and what it will entail for the individual. At least in developing countries, it is usually best for this to be delivered by hand at the time that the house-to-house census is being performed, and accompanied by a verbal description of the survey and its purpose.
2. *Invitation letter*—this should give instructions about fasting, details of where and when to attend, an offer of transport if required, and a contact so that arrangements can be changed if the original appointment is not convenient. It is a good idea to also have a separate *re-invitation letter* to be used for those subjects who do not attend on their scheduled day—this will be of similar format to the invitation letter.
3. *Letter for employer*—it can be an advantage for an official explanatory letter to be sent to the employers of subjects selected for the survey so as to forewarn them and to seek their cooperation in allowing their employees to take time off to attend the survey.
4. *Attendance certificate*—this is given to subjects who subsequently require proof of attendance for their employers.
5. *Consent form*—in literate societies it is usually most convenient to have subjects sign a consent form at the time they arrive at the survey Registration Station. If morbidity/mortality surveillance is contemplated for some time in the future, then it is also useful to include in the consent form the subject's permission for access to his/her medical

records. For non-literate societies, ethics committees will generally accept that attendance at a survey is sufficient indication of consent, providing researchers undertake to give a full verbal description of the purpose and process of the survey to participants. If necessary, thumbprints can be taken.

6. *Special invitations and instructions*—depending on the survey protocol, there may be a requirement to re-invite some survey participants on another occasion for follow-up procedures and/or substudies. For example, glucose tolerance test results may not be available until subjects have left the survey site. In this situation, newly-diagnosed diabetics could be invited back on another day for an eye examination and retinal photography. Similarly, in literate societies subjects selected to provide 24-hour, overnight, or early morning urine samples for albumin measurement should be given written (and verbal) instructions on how to collect the specimen.
7. *Results notification*—As soon as possible after a subject's attendance they should receive a copy of their results, along with recommendations for action, including referral to medical or other practitioners where indicated. In surveys in remote locations it has been the author's habit to write results for those measures immediately available (e.g. obesity, blood pressure, glucose tolerance and retinal examination) into pre-prepared forms in the afternoon following completion of the day's work. These are then handed out by local workers. Results for other measures such as urinary albumin and serum lipids are then distributed as soon as they are available: in some situations only to those subjects requiring follow-up (subjects are told that if they hear no more it means their other results are

satisfactory). Alternatively, and particularly in developed country settings where results for routine biochemistry become available, and data are computerized, within a day or so of the survey, it is possible to print computer-generated results letters.

Equipment and Supplies Documentation

1. *Equipment and supplies list*—this should be formulated well in advance (usually by many months) of the survey. Particularly when working in developing countries and remote locations, it is important to consider all contingencies, including back-ups and spare parts in case of equipment failure, and over-ordering of consumables to circumvent unforeseen events. Unless it is known with certainty that specific items are available in the area in which the survey is to be performed, it is prudent to take everything. This applies equally to items ranging from electric generators and tables and chairs, to elastic bands, string and pencil sharpeners! Depending on circumstances, the list might conveniently be subdivided into sections for equipment, consumables, and stationery, and should detail the exact quantity required, the dates when the item was respectively ordered, received in store, packed, and shipped, and the carton number for ease of location. An example is shown below.
2. *Packing list*—whenever a survey is to be performed at a site distant from the researcher's home base, whether this be in a different suburb or city, a rural region, or in an overseas location, a diverse range of equipment and supplies are likely to be transported. It is essential that all items contained in each

SURVEY EQUIPMENT AND SUPPLY LIST: CONSUMABLES

Survey: Shangri La 1997		Ordered	In store	Packed	Carton no.	Shipped
Quantity	Item					
20 × rolls	Tape—Micropore, 12 mm	24/2/97	27/2/97	5/3/97	7	21/3/97
240 × sachets	YSI buffer, 2357	18/2/97	1/3/97	10/3/97	10	21/3/97
10 × bottle	15 ml/bottle Mydriacyl 1%	27/2/97	4/3/97	5/3/97	7	21/3/97
4,400	Needle, multi, G21 × 1.5 (BD 7213)	20/2/97	29/2/97	5/3/97	6	21/3/97
and so on						

carton, box or container are listed, by carton number. Cartons must be labelled clearly with this number to ensure that items can be readily located when required. No worker will enjoy having to search the contents of 25 cartons to locate an item such as a stethoscope or a pair of scissors, particularly if they are required urgently. The packing list (with a column added for monetary value) may also usually be required for insurance purposes and by shipping and/or customs agents when goods are to be freighted by land, sea or air.

Survey Process and Laboratory Documentation

- 1. *Glucose load book*—as described previously (20), in a field survey scenario where many subjects are being given glucose loads on the same morning, it is necessary to maintain a book which lists subjects in order of the time their post-load blood tests are due, so that a staff-member can locate them and ensure that their blood samples are taken on time. This is essential, irrespective of whether times are also recorded on the subject’s survey form. An example follows for a survey in which the first fasting sample on a given day was taken at 7.01 a.m.:

- 2. *Laboratory results book(s)*—The manner in which laboratory results are recorded and stored will depend on the type of specimens collected, the measurement method and instrument used, and the location of measurement. For instance, if plasma glucose is being measured on collected blood samples in the field, or at a centralized laboratory, using a dedicated glucose analyser with manual recording of results, then they should be listed by survey number in a book dedicated to that purpose (20). This book should also record quality assurance details, including times of calibration of instruments, regular duplicate readings, regular readings for known external controls, and if applicable, information regarding daily temperature and maintenance of equipment, including changes in membranes, buffers, etc., as shown at the bottom of this page.

Results can subsequently be computer entered directly from this book, or from individual survey forms if results are thus transcribed. In less sophisticated surveys using portable reflectance meters on capillary blood, glucose values could potentially be written directly into individual survey forms at the time of sampling. Nevertheless, a systematic record of details such as temperature, calibration, and changes in batch of test strips should be maintained.

Survey No.	Given name	Family name	2-hour due	Taken?	Comments
247	Austin	Robertson	9.01	✓	2 mins late
250	Amy	Parker	9.03	✓	
249	Hurtle	Duffield	9.06	✓	
248	Laura	Trevelyan	—	✗	known diabetes
251	Elyot	Standish	9.07	✓	
and so on					

Date: Monday 9th April		Survey Site: Port Mathurin, Rodrigues			Temp: 27 °C
Survey No.	Fasting	2-hour	Calibration	External controls	Notes
140	5.6 (5.5)	6.2 (6.2)	10.0, 25.1	4.8, 12.5, 28.9	new membrane: batch 4301
141	7.1	13.5			new diabetic
142	4.8	5.7	—	—	known diabetic
143	12.5	—			
144	5.9	9.1	—	—	IGT (fasting slight haemolysis)
and so on					

As an example, consider a survey where all subjects should have: (1) a fasting blood

4. *Other documentation*—depending on circumstances, a range of other information may be recorded, such as lists of subjects recalled for special studies, notes on unusual occurrences (e.g. subjects fainting during venesection, investigations of samples with duplicate survey numbers, times of electricity failures and fluctuations, etc.), and names of individuals and organizations to be acknowledged for assisting with the promotion and conduct of the survey.

<i>Fasting glucose</i>		<i>Fasting serum</i>			<i>2 hour glucose</i>		<i>2 hour serum</i>		<i>Na Citrate</i>	<i>EDTA</i>	
Missing	Aliquot present 1/10 QA	Missing	Aliquots missing			Missing	Aliquot present 1/10 QA	Missing	Aliquot missing 1	Aliquot present	Present
			1	2	3						
167	10	12		✗	✗	38KD	10	38	✗	5	38
	20	45		✗	✗	82KD	20	82	✗	10	56
	30	134			✗	104	30	104	✗	15	82
	50	257			✗	168KD	40	168	✗	20	168
and so on											

Planning Analyses and Data Presentation

Early in the planning phase of a survey it is prudent to consider the type of analyses and form of data presentation (in tables and figures) required to address the major objectives and hypotheses of the study. If the researchers do not have statistical expertise, then a statistician or epidemiologist used to dealing with biomedical and preferably epidemiological data should be consulted. Inexperienced investigators can also be guided by reviewing the nature of data presentation in published papers of related studies, although this will reveal only 'the tip of the iceberg' of analysis which is really required.

It is a useful exercise to draft dummy tables and figures in advance, and to consider whether the data to be collected will be suitable for providing this information. It is possible at this stage to identify problems such as variables which have been inadvertently omitted from the study design, other variables which are unnecessary, over-ambitious objectives, and deficiencies in sample size.

Data entry programs should also be prepared in advance, and designed in relation to the questionnaires and data record forms. Data cleaning and editing procedures should be planned as part of this process. Some of the steps (such as range and logic checks and creation of new variables) can be pre-programmed into data entry programs, whether using available software (e.g. SPSS (48) or Epi Info (49)) or specially prepared programs. However, much of the data cleaning and editing will take place as a dedicated exercise following data entry, and it is wise to have a clear plan in place to facilitate this process.

Funding Applications

Early in the course of planning a survey a preliminary budget should be prepared, taking into account costs including staff salaries (including opportunity cost while away from normal duties), transport and accommodation, equipment and consumables, biochemistry and other laboratory investigations, and data processing and report preparation. Unless funding is already available, it will need to be sought. This will usually require the preparation of a formal grant application, depending

on the scope of the research project, to any of a multitude of potential sources, including a government medical research funding organization (e.g. the National Institutes of Health in the USA, the National Health and Medical Research Council in Australia), a university or private research trust, a diabetes-specific research fund (e.g. from a pharmaceutical company or a national diabetes association), or even the World Health Organization.

Depending on the size and complexity of the application, and the requirements and reviewing process of the granting body, it can take anything from weeks to years to prepare and submit an application, have it reviewed, answer reviewers' concerns, and have a final decision on funding, with no guarantee of success. Investigators must take into account the probability and likely time-line of securing funding when formulating their research questions and study design. One way of limiting the burden is to share costs between collaborating organizations. In this way, it may be possible to proceed, particularly with small-scale studies, without the need for supplementary funding applications. It is vitally important to secure the collaboration of local health departments and other agencies which may be able to provide staff and logistic support (e.g. vehicles, office facilities).

Ethics Approval

Even if funding is already available, researchers have an obligation to have their research design examined and approved by a recognized independent ethics committee—these are usually attached to universities and teaching hospitals. Investigators working in overseas locations should also seek approval from local authorities, whether or not formal ethics committees exist. In developing countries, responsible researchers should assist local authorities to establish ethics review committees if they do not already exist.

The general principles which guide ethics in biomedical research have their foundation in the United Nations Universal Declaration of Basic Human Rights and articulated in the Declaration of Helsinki and by the Council for International Organizations of Medical Sciences (42, 50). Major issues in epidemiological research include the importance of free and informed consent, confidentiality and respect for privacy, avoidance of

physical or psychological damage to the subject, communication of results to subjects, and the necessity that the research has practical and scientific integrity (42).

ORGANISATION AND CONDUCT

Logistics: Dates, Staff, Survey Sites, Equipment and Supplies

1. *Dates and duration*—the time to be set aside for a survey will depend on several factors, including the sample size, the number of staff available, local weather patterns, and the dates of school and other holidays. Based on staffing numbers, sample size, and the time taken to complete each survey procedure per staff/subject unit, it is possible to calculate the number of subjects that can be surveyed in a day, and the number of days required overall. Where surveys are to be performed in overseas locations and/or to involve a number of collaborating investigators, it is absolutely crucial to involve all parties in the decision-making process. There is no glory in organizing a field survey during the cyclone season in a tropical country, during Ramadan in a Muslim country, or when necessary staff cannot be released from normal duties.

The duration of the survey must be long enough for the sample size to be surveyed using available resources. It is important to factor spare days into the schedule so that time can be made up for days lost due to unforeseen circumstances, such as local funerals, transport breakdowns, and so on. A clear schedule of dates and locations must be prepared and written into the survey protocol in situations where there are multiple survey sites (20).

2. *Survey staff*—it is necessary to determine that a sufficient number of appropriately qualified staff are available and 'booked' early in the planning phase. For surveys performed in overseas countries or remote from the investigator's home base this usually requires a heavy reliance on staff from the local health department, university, or the like—most importantly for fostering local participation in and ownership of the research, for their familiarity with customs and/or language, and for a positive

effect on response—but also for cost reasons. Equally, however, it is usually important that a nucleus of key staff from organizing institutions be in the team to undertake critical procedures and coordinate other staff. Depending on the scope of the survey, a range of nurses and other health workers, laboratory technicians, clerks, drivers, and so on, may be required. Nevertheless, many procedures (such as measuring height, weight and circumferences, interviewing, and marshalling subjects) can be undertaken by anyone with reasonable literacy and numeracy skills. It is often therefore possible, and even advantageous, to employ persons directly from the community being surveyed (such as unemployed school leavers, retired persons, civic leaders) to work as part of the survey team.

Where appropriate, flights, accommodation, visas, immunizations, and so on, must be arranged well in advance for staff participating in the survey. Failure to do so may undo much organization.

3. *Survey sites*—survey areas should be visited well in advance, and suitable locations for conducting the survey should be identified and, if necessary, booked. Ideally, the survey site will be centrally located within the residential area of the survey sample, with road access: even if subjects walk to the survey site, some may require assistance with transport, and staff, equipment and supplies will need delivery. Where several clusters or communities are to be studied, unless the distance between them is very small, or transport is to be provided for participants, the survey team should establish a survey site in each area (12, 20, 27, 29). Facilities required will depend on the scope of the survey, but access to reliable electricity (e.g. for centrifuge, glucose analyser, ECG machine, retinal camera), running water and toilets is usually important. In areas where there is no electricity, portable generators may be required to power even sophisticated equipment, or battery-operated instruments can be used.

For large surveys, school buildings (during holidays) are ideal, as procedures can be located in sequence in different classrooms, allowing orderly subject flow. However, community and church halls, health centres, private houses, open verandahs and even outdoor areas can be used, depending on

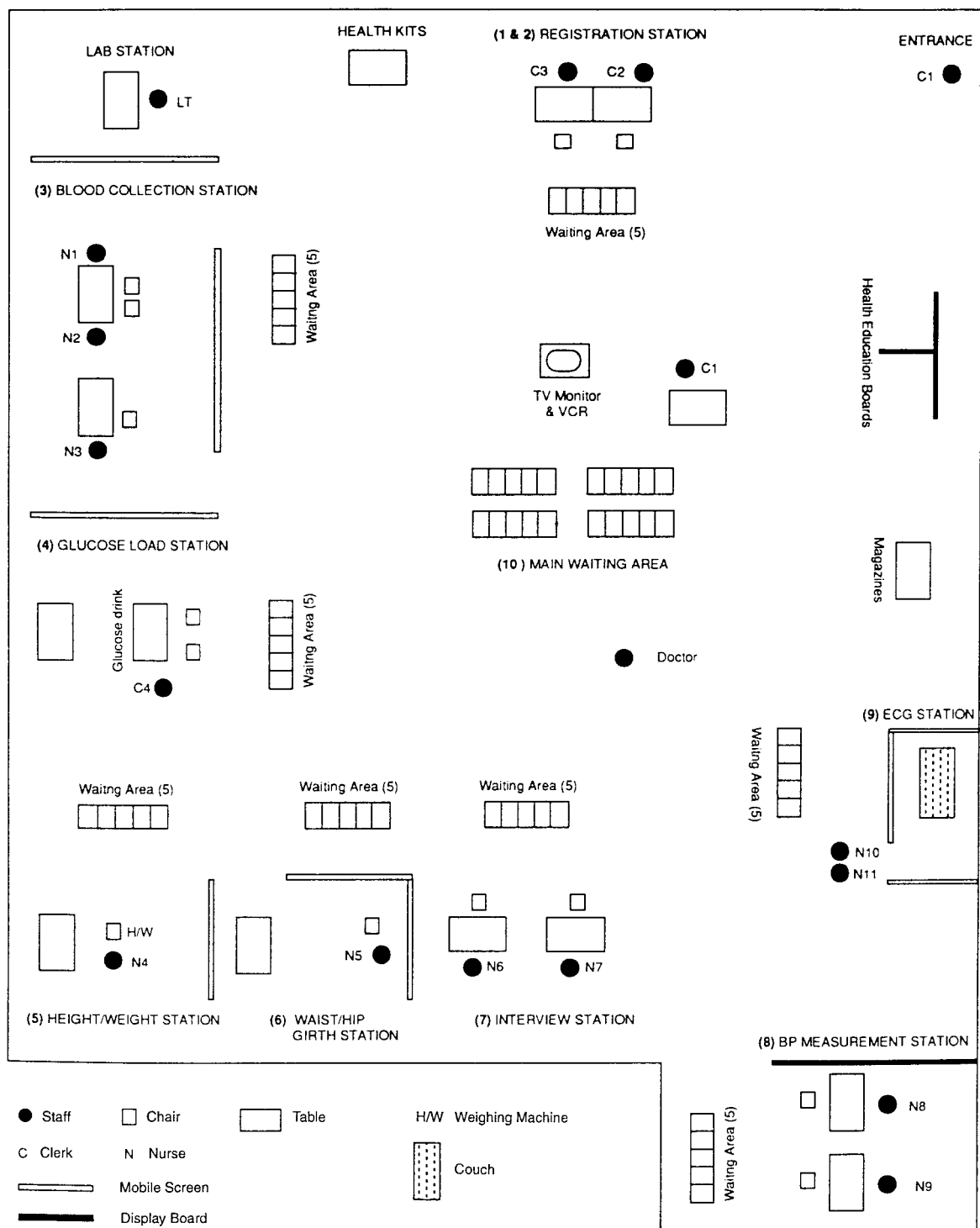


Figure 24.1 Example layout for a field survey of Type 2 diabetes and cardiovascular disease risk factors, as performed in large community halls in Singapore

Source: Singapore: Ministry of Health, 1992 (51). Reproduced by permission

circumstances. It may be necessary to provide temporary screens for privacy for procedures such as venesection, girth measurements and electrocardiograms. A quiet area should also be identified for blood pressure measurement, away from noisy waiting areas. Figure 24.1 shows an example of survey site lay-out for a typical diabetes prevalence study. Figures 24.2–24.5 demonstrate scenes from diabetes field surveys performed in developing countries.

4. *Equipment and supplies*—the principles involved in the choice of measurement instruments and the importance of maintaining accurate documentation of equipment and supplies have been discussed earlier in this chapter. Of no less importance is the practical process of defining exactly what is required to undertake the survey, assuming the critical measurement instruments have already been defined. This entails detailed consideration of

each procedure to be undertaken, and meticulous recording of all items necessary to carry out that procedure. Pilot testing will help to identify missing items. For example, for the Registration Station the list may entail: a descriptive sign; a large table with 4 chairs (sufficient for 2 staff and 2 subjects at a time); pencils, erasers, and pencil sharpeners; paperweights; sufficient survey forms, employer certificates, consent forms, reminder forms, etc. for all subjects; coloured stickers to identify subjects selected for substudies; the census list; the registration book, rubber bands for separating each day's survey forms; and a wastepaper bin. Each time a survey site is established, the checklist of items required for each procedure should be used to ensure readiness.

As for measurement instruments, cost, robustness, and acceptability to subjects and staff must be considered when choosing



Figure 24.2 Subjects sitting awaiting blood pressure measurement during a survey performed at a school building in the Indian Ocean island of Rodrigues



Figure 24.3 Venesection station established in a community hall during a field survey in the Indian Ocean island of Mauritius. At a busy time of the morning, four staff are collecting blood samples

supplies. For example, the relative merits of needles and syringes versus vacuum tubes with multi-sample needles must be weighed up for venesection—certainly for busy surveys a reliable brand of the latter are favoured, even if they may be more expensive. Similarly, the choice between glass and plastic disposable pipettes will likely be decided in favour of the latter when a field laboratory is to be established in a remote area involving transport over rough terrain, and higher quality serum storage tubes will be selected where samples are to be stored for long periods at very low temperatures.

When performing surveys away from home territory, unless it is known with certainty that specific items are available at the destination, it is wise to err on the side of caution, and take absolutely everything required. Moreover, sufficient spare parts and extra supplies should be packed to cover misadventure.

Pre-testing, Pilot-testing and Staff Training

Pre-testing is performed during the early stages of planning when measurement instruments (e.g. sphygmomanometers, height and weight scales, questionnaires, glucose analysers) are being selected and survey procedure is being defined. Instruments will be assessed for their validity, repeatability, robustness and acceptability to subjects and staff, as discussed earlier. Where there are clear options different types of instruments should be compared, and/or assessed in relation to a 'gold-standard'.

Staff must be *trained* assiduously in the standardized methods of the task(s) which they will undertake in the survey, following the instructions detailed in the survey manual (18, 20, 21, 42). No procedure should be exempted from strict standardization and training, including venesection, measurement of height and weight and blood pressure, and laboratory processing of samples. Variation



Figure 24.4 Glucose load station in a vacant hospital ward used as a survey site in the Pacific Island nation of Western Samoa. Glucose monohydrate solution prepared in bulk is dispensed into cups for subjects

within and between observers should be assessed, and staff who perform unsatisfactorily in training should be replaced (42). Measurements which are subject to a large amount of observer variation, such as blood pressure, require relatively more effort to achieve standardization (21). Methods for training blood pressure observers have been devised which use standard audiotapes and/or videotapes, and double-headed stethoscopes.

Of course, variation due to differences between observers can be limited by having as few observers as possible performing each measurement or procedure. Where there must be more than one observer, it is important to ensure that different groups of subjects (e.g. defined by village, gender, ethnicity or age-group, etc.) do not present preferentially to one observer or another. If this is the case, even with proper training and standardization, if a difference is subsequently found between the groups in the measured parameter it may be difficult to exclude systematic measurement bias between observers as being responsible.

Staff training should also include an understanding of the overall goals and structure of the survey, the importance of maintaining subject confidentiality, and an emphasis on the benefits of being professional, but courteous to participating subjects.

Once staff have been trained, equipment has been selected, and all is in readiness, it is important to have a formal *pilot-test* of the survey procedure. This should not be undertaken on subjects eligible for the real survey. The pilot test is a dress rehearsal for the actual survey, and is a final opportunity to refine techniques, to identify and correct bottlenecks in the flow of subjects through the procedures, and to reassess practical matters such as space requirements, placement of chairs and tables, and adequacy of directional signs.

Census of Survey Population

Unless a pre-existing sampling frame is available, such as a current electoral roll, it is usually



Figure 24.5 Glucose measurement at a temporary laboratory established at a school building during a field survey

necessary to perform a census prior to the conduct of a survey. In whole community or cluster surveys this necessitates systematically visiting houses one by one, and recording details for all individuals who are eligible for the survey (20). This may require several visits. In rural and remote areas, and even in urban areas of developing countries, it may be necessary to allocate numbers to dwellings and draw schematic maps which show houses in relation to each other and landmarks such as roads, churches, school-buildings, trees and rivers. This information is then used during the survey for issuing invitations and giving results, and is invaluable if follow-up studies are to be performed. These methods have been applied often in surveys of Type 2 diabetes in South Pacific island nations (5, 26, 27, 29).

The household census also becomes the sampling frame should there be any additional random or systematic sampling stages, and defines the denominator for assessment of response and representativeness of the eventual survey population. The preparation and use of the nominal roll

for participation in the survey, based on the original household survey, has been described earlier.

Promotion and Maximizing Response

The value of a survey's findings depends to a large extent on achieving a high response rate, such that significant bias in results will not occur even if the non-responder group are not representative (21, 42). Response rates of 80–100% have commonly been achieved in diabetes field surveys in rural areas of developing countries, but in general response tends to be lower in more urbanized subgroups and developed populations where the pace of life is faster and opportunity for distraction is greater (5, 10–12, 26, 27, 37, 38).

To maximize response it is important to plan and implement a promotional campaign aimed at explaining to the study population the overall goals of the survey, what it will entail for them, and what benefits it might bring to the community

and to themselves. Prominent members of the community such as politicians, health officials, and religious and civic leaders should be approached for support. It is also important to involve the local medical profession in the study, as otherwise resentment at perceived 'invasion of their patch' may adversely affect response.

A local 'motivator' should be appointed for each survey area, preferably somebody who knows the community well and who has wide respect. This person may conduct the initial census, and then continue in the role of raising awareness and distributing invitations, reminders, results letters, and so on, throughout the period of the study.

Where feasible, all available avenues of the media (variably including garamut drum, newspapers, newsletters, radio and television) should be used, including free media releases and interviews, and paid advertisements. Posters and banners can be placed in prominent locations. Eligible households and/or individuals should receive a clear and honest explanation of the nature of the survey well in advance, both written and verbally. This should provide details such as the time required, the procedures to be undertaken and any risks involved, and special requirements such as the need for fasting and abstention from smoking. Positive aspects should also be highlighted, including: the availability of free medical investigations; the promise that results will be returned to subjects promptly, and that treatment or referral will be arranged wherever necessary; the availability of transport to and from the survey site if required; and the issuing of medical certificates for employers. The information should then be reinforced a few days prior to the actual day of the individual's scheduled attendance, and perhaps again on the preceding evening.

In general, it is best not to offer financial or other rewards for attendance. However, in a survey in which subjects have fasted and probably given up 2 or more hours of their time, it is quite acceptable to offer them a light meal or refreshment once they have completed all their procedures. It is important, however, that this be kept away from the general survey area and carefully 'policed', lest subjects eat or drink something prior to completion of their glucose tolerance test.

It is reasonable to give non-responders one personal reminder while the survey team remains in the area. Additional reminders are unlikely to be

very fruitful. If response is found to be poor at the beginning of a survey, discussions should be held promptly with local team members, community leaders and non-responders to try to determine whether any particular fears, problems (e.g. lack of transport or babysitting,) or miscommunication might be responsible that can be corrected.

At conclusion of the survey known demographic characteristics of responders and non-responders (as determined in the household census) should be compared in order to detect any obvious response bias (e.g. in relation to gender, age, ethnicity or occupation). Moreover, all or at least a subsample of non-responders should be contacted and asked: (1) to identify their reason for non-attendance (e.g. dead, too ill, unable to take time off work, not interested); and (2) whether they have a history of any of the endpoints of major interest within the survey (e.g. history of smoking, diabetes, hypertension, or myocardial infarction). Such information can then be compared with that of the responding sample, and judgement made as to whether any differences found might be sufficient to significantly bias the survey results (21, 42).

Supervision and Quality Control

The survey team should have a clearly designated coordinator, who must be intimately aware of the survey protocol and the requirements for each procedure. Ideally, the coordinator should have a roving commission to answer questions from staff and participants, to observe the performance of staff and the flow of subjects at each measuring station, to correct problems as they are identified, and to offer encouragement to staff. It is best that the coordinator is not allocated to one of the measurement procedures, although they should be trained, certified and able to fill in at any position in case of emergency (e.g. allocated staff taken sick).

Survey forms and other records, including registration and glucose load books and laboratory documentation, should be examined regularly—certainly at the end of each day of the survey—to ensure completeness, to perform any secondary coding required, and to identify any problems which can be corrected. This includes difficulties with legibility, accidental errors and omissions, and systematic errors. Where more than one

observer performs a particular measurement procedure, they should each be allocated a unique *observer number* which is recorded on the survey form adjacent to the measurement; in this way problems can be traced back to the observer and appropriate action, including retraining and re-standardization, undertaken.

If data are being computer entered while the survey is in progress, more formal observer checks can also be performed. For example, terminal digit preference can be assessed, and assuming random allocation of subjects, systematic differences between observers and drift over time can be imputed if there are significant differences in mean values and distributions of measured variables, such as blood pressure.

Reliability of data can also be assessed by repeating at least some measurements on a random sample of subjects. This includes the use of duplicate split samples, unidentifiable to the laboratory, for biochemical measurements. Armstrong et al. (42) have outlined the importance of ongoing quality control at all stages of survey preparation and conduct, including data processing.

It is advisable for team meetings to be held at intervals during a survey, when matters of concern and possible solutions can be discussed. Positive reinforcement and encouragement should be offered freely to staff, particularly in long and arduous surveys. Moreover, days off and social occasions should be scheduled at regular intervals to help foster team spirit and enthusiasm. In field surveys of glucose tolerance where work usually begins early in the morning, many members of the survey team may in fact finish work around midday, allowing time for preparations to be made for the following day, and for recreation (18, 20).

AFTER THE SURVEY

Public Relations and Follow-up

The conclusion of a survey, particularly a long one which involves personnel from a number of institutions, can be a sad occasion, and it is appropriate to hold a party as a means of allowing farewells and acknowledging survey staff and other contributors. Depending on circumstances, gifts and/or certificates of participation should be

given. The latter are often highly regarded in developing countries.

Particularly in developing countries and remote locations it is often good public relations, and even practical in terms of transportation costs, to donate leftover consumables (e.g. venesection and laboratory supplies) to local health-care facilities. This may also be extended to equipment items such as sphygmomanometers.

Even if detailed analysis of the survey data may not be available for some months, it is essential to provide preliminary feedback of overall results to local authorities (e.g. medical practitioners, town/village officials, health department officers, politicians) and to the survey population. Depending on circumstances, the latter may involve a newsletter delivered to all subjects, local meetings, or use of the mass media. It is also important that a clear timetable for provision of a final report to local authorities and any other interested parties is defined before the departure of the survey team. Meeting such deadlines may involve the cooperation of a number of collaborating organizations which have responsibility for providing different aspects of the data (e.g. specific biochemical analyses). However, collation and final data analysis should be the task of the coordinating institution.

When the final report is available, the process of consultation with relevant local authorities, and feedback of the general findings to the survey and general population should be repeated. This is especially important where the survey findings are to be used as the basis for development and implementation of specific interventions.

Packing, Transportation and Storage of Equipment and Specimens

Equipment and supplies to be returned to source locations should be packed and labelled carefully, as described earlier. If air transport is required this is crucial to satisfy airline safety standards and customs obligations.

Where specimens are to be transported, painstaking planning is necessary to ensure that they arrive at their destination in good condition. If transport is to take any more than a few hours then ordinary ice bricks will be inadequate to ensure specimens remain at -20°C . For longer

trips, dry ice will be required, or for samples that need to be kept very cold, liquid nitrogen. If using dry ice, whether as bricks or pellets, it is important to ensure that enough is packed in each cool box to last the expected duration of the trip, plus a margin for misadventure: the amount required should be calculated with the assistance of experienced laboratory managers. For example, a missed flight connection may mean that samples take an additional 24 hours or more to be delivered. If the itinerary is of long duration, it may be necessary to arrange in advance for replenishment of the dry ice supply en route. Certainly, wherever there is a change of flight, it is prudent to make personal contact with an individual in the local office of the cargo agency and/or airline company involved to seek their assistance in ensuring the successful transfer of the precious cargo on to the new craft.

If dry ice is to be used, then the precise amount required and time of pick-up should be booked well in advance. In locations where dry ice is not manufactured, it may be necessary to arrange for it to be freighted in from elsewhere; in this case a larger amount than required should be ordered to account for wastage on the in-coming sector. If specimens are to be air-transported then the timing of collecting dry ice and packing specimens will be designed around the departure time of the flight. It is also absolutely essential that arrangements with the airline, cargo agent, and customs officials have been resolved well in advance. There are special requirements in terms of packaging, labelling and documentation that must be fulfilled when transporting biological material, and when using dry ice. If it is possible, duplicate aliquots of crucial specimens should not be transported at the same time: an aliquot should remain in storage as a back-up in case of problems.

Clear instructions should be given in advance to individuals at the home base who are to receive the specimens and/or equipment. This means informing them of the itinerary of the goods, the time of arrival, air waybill numbers, where relevant, and persons to contact in the freight agency and/or airline. Moreover, the freezers in which specimens are to be stored should be identified, checked and prepared. Once the specimens and equipment have been received, their condition should be noted as they are unpacked and stored, and an acknowledgement should be sent forthwith to the despatchers.

Specimens will usually be aliquots of serum, plasma, buffy coats or urine in small plastic storage containers. Each tube should be labelled in such a way as to identify the survey from which it derives, the type of specimen (e.g. plasma, serum, urine), the subject's unique identifier, the time of collection if multiple samples were taken during a glucose tolerance test, and the number of the aliquot where more than one are taken from a particular sample. In this way, an errant tube can be immediately identified. For example, the code K637C might identify a tube as coming from the 1991 Papua New Guinea survey (K), from subject number 637, and the specimen as the second aliquot of fasting serum (C). Care must be also be taken to ensure that labels on tubes are durable and will not fade or wash off.

Specimen tubes are best packed at the time of processing during the survey, transported and stored, in numerical sequence, in clearly labelled (survey descriptor, type of sample, aliquot number, numerical range), multi-compartment (e.g. 100 spaces) cardboard boxes. The latter are available from laboratory and refrigerator suppliers, or can be purpose-made by packaging firms, often for a cheaper price. Specimens stored systematically in this manner are much more amenable to good housekeeping than those stored randomly in plastic bags, or in a motley and bulky array of foam, metal and plastic laboratory trays.

Safe-keeping of Survey Forms and Other Documentation

As for specimens, it is vitally important to ensure that all data and important documentation are safe during transport. If possible, questionnaire and other data should be computer entered at, or close to, the survey location. Thus, back-up copies of the electronic data record can be saved and retained in different locations.

Nevertheless, hard copies of the original questionnaires, laboratory results, and documentation such as census lists, registration books, glucose load books, and so on, must also be kept for reference. If these need to be transported to the home base of investigators, then photocopies of original information should be made and retained by relevant local authorities. Not only does this provide a back-up, but it also ensures that local

investigators have access to the information in the future should they require it—an important consideration when surveys are coordinated by researchers from overseas or distant locations, who despite their best intentions may subsequently lose contact with collaborators at the point of the survey. This is particularly relevant for longitudinal investigations where personnel may move to other jobs.

Vital records are best carried as hand luggage: baggage does get lost and misplaced, whether transport is by private car, train or aircraft. If there are several investigators, the weight can be shared. If it is unavoidable that questionnaires or other information must be transported as baggage or freight, then the importance of ensuring photocopies and/or electronic copies are made prior to departure cannot be overstated.

On return to base, all hard copies of data and other survey documents should be well labelled, and stored safely and securely. Confidentiality of records must also be maintained. Only key investigators should be able to link the identity of survey participants to their data records. As a minimum, name and address data should be stored separately, preferably in a locked cupboard or safe.

Data Processing and Reporting

Data entry, whether performed at the time of the survey, or following it, must be subject to strict quality control, just as for other aspects of the survey (42). Data should be entered twice, independently in time and preferably by different persons. This allows computer programs to identify discordant entries, so that the correct values can be verified from the original data record. In addition, range and logic checks can be pre-programmed into the data entry program to identify improper responses. If data entry clerks cannot resolve these at the time of the data entry, then they should proceed entering data, after noting irregularities on a 'query sheet'. Problems can subsequently be investigated and resolved by the supervisor. Where clearly erroneous values on questionnaires or other records are altered during the checking process, this fact should be recorded on the original record. Additionally, 'manual' changes may need to be made to some variables

for individual subjects (e.g. classification of glucose tolerance made missing for individuals recorded in the glucose load book as having vomited their drink, or having been late for the 2 hour collection).

Programming code used to create new variables (e.g. categorical diabetes or hypertension status variables derived from glucose and blood pressure measurements and clinical history) should be carefully checked to ensure correctness. This includes review by other workers, and listing of a sample of subject records so that manual classification can be compared to the computed variable. A 'coding book', or at least a labelled file of computer printout, should be maintained which clearly describes all variables and value labels, including the programming required to create new variables. Up-dates to the computer file should also be documented here, along with the date of any modifications.

Further cleaning and editing of the dataset involves examining descriptive data such as frequency tables and simple cross-tabulations for categorical variables, and distributions and scatter-plots of continuous variables (39). This is an important stage in identifying remaining errors and inconsistencies in the data, prior to creating the working dataset for definitive analysis.

As discussed earlier, the sort of analyses to be performed for the purposes of initial reporting should have been considered during the planning phase of the survey, and hence once the dataset is cleaned, edited and ready, analysis should proceed promptly. The first priority is often to draft a report for use by health departments and other agencies which documents the magnitude of the problem and identifies areas of need (e.g. large pool of undiagnosed cases suggesting need for raising public awareness of risk factors and symptoms, and for improving medical case-finding; poor management of blood lipids in known diabetics, suggesting need for improved medical care and better dietary education of cases; etc.). The type of analysis required in this context is generally descriptive, and as such reports are meant for politicians and busy health officials they should be kept relatively simple, with clear messages, including the appropriate use of tabular and graphical information.

Once such formal reporting obligations have been met, attention can be turned to more complex

and focused analytic approaches and preparation of scientific articles. The best advice to inexperienced investigators preparing to write up their survey findings for medical journals is to carefully examine journal requirements and previously published articles of similar work. Of course, the major research questions to be addressed should have been defined early in the planning phase of the study, and hence will follow a largely preordained course. However, flexibility must be maintained to allow the pursuit of unexpected findings thrown up by the data, and so that new hypotheses suggested by the scientific literature can be examined.

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The United Kingdom Prospective Diabetes Study: An Epidemiological Perspective

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INTRODUCTION

For several years now, there has been an air of expectancy as the international diabetes community awaited the results of the United Kingdom Prospective Diabetes Study (UKPDS) (1). The results are now in (2–6) and the question is whether the results will change the way that we approach the management of Type 2 diabetes. The UKPDS study also provided, for the first time, information on the long-term natural history of Type 2 diabetes in a European population. The editors felt that a book on the epidemiology of diabetes, indeed any book dealing with diabetes, would be incomplete without reference to this monumental study, the largest and longest yet in diabetes history. Was the wait worthwhile and will the results influence therapy of Type 2 diabetes?

THE UNITED KINGDOM PROSPECTIVE DIABETES STUDY—WHY WAS IT SO IMPORTANT?

Epidemiological studies have shown an increased risk of cardiovascular disease (CVD) with concentrations of fasting glucose or HbA1c just above the normal range (7–9). A previous large-scale randomized trial in Type 2 diabetes, the University Group Diabetes Program (UGDP) (10), had found no evidence that improved glucose control, by any therapy, reduced the risk of cardiovascular endpoints. In fact, the UGDP reported an increased risk of CVD mortality in subjects allocated to tolbutamide and to phenformin (10). This led to an ongoing debate about the safety of sulphonylurea

therapy, and to the withdrawal of phenformin, which had also resulted in a case of fatal lactic acidosis. Another ongoing controversy has been the suggestion that there may be an increased risk of atherosclerosis from insulin therapy, or indeed any therapy that increases hyperinsulinaemia and weight gain (11). It was against this background that, commencing in 1977, the UKPDS was designed to establish whether, in people who presented clinically as having Type 2 diabetes, improving blood-glucose control reduced the risk of macrovascular or microvascular complications, and whether any particular therapy was advantageous. Earlier intervention studies have been of lesser duration and assessed mainly microvascular disease. For example, the Diabetes Control and Complication Trial (DCCT) (12), which lasted 9 years, showed that improved glucose control delays the development and progression of retinopathy, nephropathy, and neuropathy in people with Type 1 diabetes. In the UK, 9% of people with Type 2 diabetes develop micro-vascular disease within 9 years of diagnosis, but 20% had a macrovascular complication, and macrovascular disease accounts for 59% of deaths in these people (2).

DOES METABOLIC CONTROL MATTER?

A number of epidemiological studies have shown the importance of indices of glycaemic control and duration of diabetes in determining the prevalence and incidence of diabetic microvascular complications (13–15), but this required testing in large-scale clinical trials. The Diabetes Control and

Complications Trial (DCCT) (12) and the Stockholm Study (16) first provided this evidence. The landmark DCCT, a randomized clinical trial, demonstrated that good glycaemic control reduces the risk of microvascular complications in Type 1 diabetes (12). A reduction of approx. 2% in HbA1c level (from a mean of 9–7.2%) resulted in a 50–75% reduction in the risk of microvascular complications developing, or progressing if already present. Because of the small numbers of macrovascular events in young people with Type 1 diabetes after only 9 years, the results were inconclusive. Direct evidence that improving glucose control reduces the incidence of microvascular complications is now available and accepted from this pivotal study, along with the Stockholm study (16). A major question remained. Do these results apply to people with Type 2 diabetes? A smaller study, from Kumamoto in Japan on intensive therapy for Type 2 diabetes (17), produced similar results to the DCCT and suggested that this would be the case. The Japanese study utilized a protocol almost identical to that of the DCCT and similar benefits to the DCCT were noted with a 50–75% reduction in microvascular complications (17).

THE UKPDS FINDINGS

The UKPDS study was part of a long-term diabetes research project in which 3867 newly diagnosed people with Type 2 diabetes were randomly assigned to two treatment groups. The first (conventional) group's initial treatment was dietary restriction. The second (intensive treatment) took one of three oral sulphonylurea agents (chlorpropamide, glibenclamide, or glipizide) or insulin. The intensive therapy group had better blood-glucose control, with a mean HbA1c level of 7.0% compared to 7.9% in the conventional group (2). The outcomes were 'hard' clinical endpoints including severe cardiovascular events, vision loss, and renal failure (2). Even though there are differences in pathogenesis, these outcomes were grouped together as all diabetes-related events, diabetes-related mortality, and all-cause mortality, respectively. Interpretation of the UKPDS results needs to be seen against the background of several changes to the study design over the years due to a number of substudies, e.g. that for hypertension

and acarbose. Intensive-therapy subjects were 12% less likely to develop a diabetes-related complication, e.g. myocardial infarction, stroke, and microvascular complications such as retinopathy (2). There was a 25% reduction in risk of microvascular disease (mainly retinopathy.) This reduction was very similar to that seen in the DCCT (12) when adjusted for the difference in HbA1c reduction. Nevertheless, intensive therapy did not significantly reduce the risk of death from diabetes-related causes, or overall risk of death. There was also a significant reduction in need for cataract extraction in the intensive group. All intensive treatments produced similar results, and all resulted in weight gain and increased risk of hypoglycaemia. Of practical interest was the finding that the hyperinsulinaemia and weight gain associated with intensive therapy did not translate into an increased risk of macrovascular disease (2). Indeed the trend appeared to be the reverse, with a 16% reduction in risk of macrovascular disease that bordered on statistical significance ($p = 0.052$). In overweight people with Type 2 diabetes, the UKPDS showed similar results, with the important additional finding that treatment with metformin (which did not increase hyperinsulinaemia or weight gain) produced better results than sulphonylureas or insulin (3). Reduction in mean HbA1c level from 8.0% in the conventional group to 7.4% in the metformin group was associated with a reduction in the risk of diabetes-related death by 42%, death from any cause by 32% and any diabetes-related endpoint by 32%. Metformin was not tested in lean people. The maintenance of blood glucose as close to the normal range as possible required a stepwise addition of hypoglycaemic agents when the glycaemic goals were not met (2). Subjects assigned to any of the sulphonylureas could be given metformin, and these oral agents could later be replaced by insulin. In addition, the dietary policy allowed subjects to be given hypoglycaemic agents when the glycaemic goal (FPG <15 mmol/l) was not maintained, and indeed, 44% required such therapy. Thus, the failure of diet and the gradual failure of the hypoglycaemic drugs to maintain glycaemic goals resulted in substantial therapeutic overlap between comparison groups (2). Indeed, one of the main findings was that regardless of initial therapy, glucose control progressively deteriorated and subjects required increasing doses, and combinations of medication. Thus, the

'intention to treat' analysis often differed from the analysis based on actual treatment received (referred to in the UKPDS publications as 'epidemiological' analysis). For example, intention-to-treat analysis showed a marked increase in mortality in the combined sulphonylurea/metformin group that was not present in the actual therapy analysis. Three other factors need to be taken into account before accepting that the natural history of Type 2 diabetes is as reported in the UKPDS, i.e. a steady deterioration in control and an inevitable progression to increasing medication including insulin (2). First, the age range selected at entry of 25–65 years is younger than the typical patient with Type 2 diabetes seen in community practice. Second, the diagnostic criteria used were not those currently in use, as the World Health Organization first promulgated these in 1980 (18). Subjects entered the study only if their FPG was above 6 mmol/l after 3 months treatment with diet (2). Whilst this was designed to exclude people with impaired glucose tolerance (IGT), many people with Type 2 diabetes who were well controlled with diet (and may have remained so for many years) may have been excluded.

CLASSIFICATION ISSUES IN THE UKPDS

The third factor is that as many as 10% of the UKPDS cohort may have had slow onset Type 1 diabetes (19), a condition we have labelled as latent autoimmune diabetes in adults (LADA) (20). Type 1 diabetes occurs at all ages, and the clinical presentation can vary with age (21). Type 1 diabetes classically has a rapid clinical and biochemical presentation, especially in children. However, in adults, it can masquerade as Type 2 diabetes at presentation with a slow deterioration in metabolic control, and later progress to insulin-dependency (20). This makes the classification of diabetes in adults difficult at times, particularly as the age of onset of Type 2 diabetes appears to have moved several decades to younger age groups and is not uncommon in the 25–35-year age group, particularly in high-prevalence populations (22). This scenario appears to have happened in the UKPDS study (19). Early studies utilizing the anti-GAD assay to assess LADA were clinic-based (20–24). To have any credibility and applicability, particularly for future prediction of Type 1 diabetes and/or

Table 1 Frequency of antibodies to glutamic acid decarboxylase and islet cell antibodies in the UKPDS

Autoantibody	No.	%
ICA positive*	213	5.8
Anti-GAD positive**	361	9.8
Both positive	141	3.9

* ICA positive: ≥ 5 JDF units

** Anti-GAD positive: >20 units

insulin dependency, estimates of LADA prevalence required a population-based epidemiological perspective. The opportunity for this came through the UKPDS (19). The evidence has mounted from a host of studies that anti-GAD has a clear role in diagnosing slow-onset Type 1 diabetes in adults (20, 21, 23), and in predicting future insulin dependency (21). We tested this in the UKPDS by measuring islet cell antibodies (ICA) and antibodies to glutamic acid decarboxylase (anti-GAD) at diagnosis in a sample of the UKPDS cohort (19). We found 6% were positive for ICA, and 10% for anti-GAD, with 12% having either ICA or anti-GAD, and 4% having both (Table 25.1). These subjects appear to be cases of Type 1 diabetes or LADA as judged by both phenotypic (19) and genotypic (25) features. The presence of autoantibodies correlated particularly with phenotypic features consistent with Type 1 diabetes such as early age at diagnosis, lower body mass index (BMI) and reduced beta cell function (19).

In the UKPDS, at all ages, the presence of autoantibodies conferred an increased likelihood of decompensation to insulin therapy (19). Thus 94% of subjects aged under 35 years positive for ICA, and 84% of those positive for anti-GAD at baseline, required insulin therapy after 6 years compared with 14% of seronegative cases. Clearly these findings should be taken into account when interpreting the findings of the UKPDS as an unknown, but significant, proportion of subjects who progressed to insulin therapy had Type 1 rather than Type 2 diabetes, which they initially appeared to have on clinical grounds.

THE UKPDS AND HYPERTENSION

The effect of treating hypertension was also studied in the same subjects (4), and confirmed

that a 'tight blood-pressure control policy' has significant benefits. Lowering mean blood pressure from 155/87 to 144/82 reduced the risk of microvascular complications by 37%, strokes by 44%, cardiac failure by 56% and diabetes-related deaths by 32% (4). This benefit is greater than that achieved by the reduction in mean HbA1c from 7.9 to 7.0%.

This hypertension 'sub-study' showed no difference between the two anti-hypertensive agents used, captopril and atenolol (5). This is not surprising as most subjects required therapy with both agents, and 29% required three or more anti-hypertensive agents. Other studies have shown that ACE inhibitors are the first choice for hypertension therapy in diabetes, and that a blood pressure target of less than 130/80 is appropriate in most cases (26, 27). It appears from the UKPDS that as with diabetes therapy, 'polypharmacy' is required to achieve this target and the improved outcome that results.

The UKPDS has also emphasized that diabetic complications are common, are frequently present by the time of diagnosis, and significantly affect quality of life (2). The study reported that at diagnosis, 35% of subjects had retinopathy, and 15% had neuropathy. In this study, only 2% had proteinuria initially, but this may be because renal impairment was an exclusion criterion. After 12 years in the study, 11% had visual acuity below the level permissible for driving, 1% were legally blind, and 50% of men had erectile dysfunction. This was despite participation in a clinical trial with levels of control better than generally achieved in the community.

SUMMARY

The UKPDS has confirmed the DCCT (12), Stockholm (16) and Kumamoto (17) studies' findings that intensive therapy to improve glycaemic control reduces the risk of microvascular complications. It thus appears that in both Type 1 and Type 2 diabetes, each 1% reduction in HbA1c reduces the risk of microvascular complications by approximately 25%. The reduction in risk for macrovascular disease bordered on statistical significance. Control of blood pressure is even more important than blood glucose control (4). Although not studied in the UKPDS, other studies

have demonstrated the importance of control of dyslipidaemia (28, 29). This is certainly good news for people with Type 2 diabetes in terms of reducing the risk of coronary heart disease and stroke. But it also places a clear obligation on health providers to inform their patients accordingly, and offer treatment that meets targets of blood pressure, lipids and HbA1c levels that are lower than are currently being achieved without intensive therapy.

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