Type 2 Diabetes
Principles and Practice
Second Edition
Edited by
Barry J. Goldstein
Dirk Müller-Wieland
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Edited by
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Dirk Müller-Wieland
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To C. Ronald Kahn, an extraordinary mentor, who fostered our career interests in the molecular pathogenesis of diabetes and its complications.

To our families for their love and support.

To our patients, who suffer with the restrictions imposed by diabetes on their daily lives, with the hope that this book will help alleviate their burden.
The incidence and prevalence of type 2 diabetes mellitus have increased dramatically in modernized and developing nations over the past few decades—and this “epidemic” shows no signs of abating. Physicians and other healthcare professionals worldwide are well aware of this growing burden. The pathogenesis and management of the hyperglycemia of diabetes and its associated risk factors and morbidities, especially involving cardiovascular and microvascular complications, must be fully understood by all of the many providers that care for patients with diabetes worldwide.

Patients are always asking, “Isn’t there anything new to help manage my diabetes?” This reflects the relative inadequacies of many of our attempts at lifestyle change, as well as some of the shortcomings of currently available medications for the long-term management of this disorder. Certainly, changes in lifestyle can be effective, but they are extremely difficult to implement over an extended period of time. Diabetes patient management is often implemented later in the course of the disease, since the disease can be asymptomatic and therefore can go unrecognized for many years. Recent studies have shown clearly that the onset of diabetes can be prevented or delayed and more aggressive, earlier treatment may also help to alter its course and, possibly, its chronic complications. Large clinical trials will help to answer these questions in the future.

In this second edition, we have thoroughly updated all existing chapters and developed new ones vital to the management of diabetes, while maintaining the international perspective and focus on clinical care found in the first edition. The entire clinical field is covered in succinct chapters written by recognized experts. The content spans from a current perspective on diabetes demographics and epidemiology, pathophysiology, disease monitoring, approaches to glucose control, and managing complications. New to this edition are chapters that expand on nonpharmacological management options; diabetes-related macrovascular conditions, including coronary heart disease and peripheral vascular disease; and discussions on rare forms of diabetes, polycystic ovarian syndrome, and non-alcoholic steatohepatitis. As before, this edition closes with a look at the future of new devices for glucose monitoring and diabetes management.

We hope this book will be used frequently and successfully in the management of this complex and widely prevalent disorder.

Barry J. Goldstein
Dirk Müller-Wieland
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DIAGNOSTIC CRITERIA FOR DIABETES AND OTHER CATEGORIES OF ABNORMAL GLUCOSE TOLERANCE

Diabetes mellitus (DM) refers to a number of disorders that share the common feature of elevated blood glucose levels. The classification accepted by the World Health Organization (WHO) (1,2) and the American Diabetes Association (ADA) (3,4) combines both clinical stages of hyperglycemia and the etiological types. Two main subtypes of diabetes are type 1, either autoimmune or idiopathic, and type 2, attributable to insulin resistance, insulin secretion defects, or both. Although diabetes has been known for centuries, our understanding of the etiology and pathogenesis of this disease is still incomplete. Type 1 is characterized by deficiency of insulin due to destructive lesions in pancreatic β-cells. It occurs typically in young subjects, but may affect people of any age. Type 2 diabetes comprises about 80% to 90% of all cases. Type 2 is a heterogeneous, polygenic disorder resulting from interaction between susceptibility genes and lifestyle/environmental factors.

Diabetes affects currently about 5% of the world’s population, and its prevalence is rapidly increasing, particularly in elderly subjects. There is a marked variation in the prevalence of diabetes among many national and ethnic populations. The spectrum ranges from very low prevalence of about 1% in tribes in Papua New Guinea, the Inuit, or the Chinese living in mainland China, to extremely high rates of 20% to 45% in Australian Aborigines, Nauruans of Micronesia, and Pima Indians of Arizona (5). Even within nations, the variation in the prevalence is marked. For example, in the United States, African Americans have a twofold, Mexican Americans a 2.5-fold and Native Americans a fivefold increase in the risk of the development of type 2 diabetes compared with Caucasians (6). Large variation in the prevalence of type 2 diabetes in different populations probably results from environmental as well as genetic determinants.

Type 2 diabetes is usually preceded by a long period of asymptomatic hyperglycemia that may last for years. In this prediabetic state, postprandial or postglucose levels are mildly elevated whereas fasting blood glucose can usually be maintained within the near-normal range. The elevation of postglucose levels is used for the definition of impaired glucose tolerance (IGT), a nonspecific reversible stage. About 30% of these subjects progress to overt diabetes within 10 years (7). Elevation of fasting glucose is used for the definition of impaired fasting glucose (IFG). In some individuals beta-cells compensate for insulin resistance by increased insulin secretion, and type 2 diabetes does not develop. However, in a large number of prediabetic individuals multiple defects in insulin action and/or insulin secretion gradually lead to sustained hyperglycemia. As a consequence of insulin resistance, the beta-cell produces increased amounts of insulin, and compensatory hyperinsulinemia maintains normoglycemia. When beta-cell compensation to insulin resistance fails, decompensated hyperglycemic state develops. Thus, type 2 diabetic subjects have relative (rather than absolute) insulin deficiency. Usually these individuals do not need insulin treatment to survive.

Criteria for diagnosis of diabetes and other categories of glucose tolerance have changed considerably during the last 20 years (8,9). Table 1 shows the current criteria for normal glucose tolerance (NGT), IFG, IGT, and diabetes. Criteria proposed by the WHO (1,2) and the ADA (3,4) are different. The main difference between these new criteria is that the ADA does not recommend the use of an oral glucose tolerance test. The WHO defined a new subcategory of glucose tolerance, IGT, to describe subjects whose fasting glucose levels were normal but whose 2-hour postglucose challenge levels were elevated, although not diabetic. The 2 hour 75 g oral glucose tolerance test was recommended as the international standard for diabetes diagnosis. The cutoff point between IGT and diabetes was based on an increased risk of developing diabetic complications, primarily retinopathy, for these subjects with diabetes.

The ADA (but not the WHO) recommended that in epidemiological studies, estimates of diabetes prevalence and incidence should be based only on fasting glucose criteria. The fasting
glucose criteria for diagnosis were considered by the ADA to have good reproducibility, small variability, and easy application in clinical practice. IGT is defined by the WHO as a 2-hour plasma glucose concentration between 7.8 and 11.0 mmol/L. The ADA (3) also introduced a category of IFG, defined as fasting plasma glucose between 5.6 and 6.9 mmol/L, to replace IGT. IFG and IGT were considered to be metabolic stages intermediate between normal glucose homeostasis and diabetes. However, it is possible that IFG differs from IGT with respect to the relative contribution of insulin secretion defect and hepatic and peripheral insulin resistance. IFG and IGT are not clinical entities, but rather risk categories for future diabetes and/or cardiovascular disease. Normoglycemia is defined as plasma fasting glucose $< 6.1$ (WHO) (1) and $< 5.6$ mmol/L (ADA) (3) and a 2-hour glucose $< 7.8$ mmol/L in an oral glucose tolerance test. The changes in diagnostic criteria for diabetes recognized results of epidemiological studies indicating that the risks of both retinopathy and cardiovascular disease start to increase at fasting plasma glucose values of about 6.0 mmol/L (10).

Both the ADA and WHO recommend a fasting plasma glucose concentration of 7.0 mmol/L for the diagnosis of diabetes, but according to the WHO criteria (1), diabetes can be also diagnosed if the 2-h glucose concentration is at least 11.1 mmol/L. For the asymptomatic person, at least one additional glucose test result with a value in the diabetic range is essential, from a random (casual) sample, or from the oral glucose tolerance test.

A number of studies summarized by Shawn et al. (11) have compared the WHO and ADA criteria for DM using fasting and 2-h definitions. These studies demonstrate both an increase and a decrease in people as having nearly diagnosed diabetes depending on the population studied. Compared to the WHO criteria, fasting glucose-based ADA criteria may underestimate glucose abnormalities more in older age than in younger age (12). Also the Cardiovascular Health Study demonstrated a 50% underestimation of diabetes prevalence in older adults (> 65 years) comparing the ADA criteria with the WHO criteria (13). Furthermore, IGT may have higher sensitivity over IFG for predicting progression to type 2 diabetes (14).

In general the fasting criterion identifies different people as being diabetic compared to those identified by the 2-h criterion (15). In subjects without previously diagnosed diabetes, the DECODE study group from 16 different European populations (16) found that all subjects diagnosed by either the fasting or 2-h criteria, only 29% qualified as diabetic according to both criteria. This result was confirmed in the DECODA study group (17) including existing epidemiological data from 11 population-based studies collected from Asian people ($n=17,666$) between 30 and 89 years of age. The authors concluded that it would be inappropriate to use the ADA criteria alone for screening diabetes in Asian populations.

### “EPIDEMIC” OF TYPE 2 DIABETES

Epidemiological studies had already identified “diabetes epidemic” in 1970s. The extraordinarily high prevalence of type 2 diabetes was reported in Pima Indians (18) and also in

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**TABLE 1** Criteria for Classification of Glucose Tolerance Status According to World Health Organization and the American Diabetes Association Criteria

<table>
<thead>
<tr>
<th>Glucose tolerance status</th>
<th>Definition</th>
<th>Classification criteria (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal glucose tolerance (NGT)</td>
<td>WHO (1999)</td>
<td>FPG $&lt; 6.1$ and 2 h PG $&lt; 7.8$</td>
</tr>
<tr>
<td></td>
<td>ADA (1997)</td>
<td>FPG $&lt; 6.1$</td>
</tr>
<tr>
<td></td>
<td>ADA (2003)</td>
<td>FPG $&lt; 5.6$</td>
</tr>
<tr>
<td>Impaired fasting glucose (IFG)</td>
<td>WHO (1999)</td>
<td>FPG $\geq 6.1$ and 2 h PG $&lt; 7.8$</td>
</tr>
<tr>
<td></td>
<td>ADA (1997)</td>
<td>FPG $\geq 6.1$ and 7.0</td>
</tr>
<tr>
<td></td>
<td>ADA (2003)</td>
<td>FPG $\geq 5.6$ and 7.0</td>
</tr>
<tr>
<td>Impaired glucose tolerance (IGT)</td>
<td>WHO (1999)</td>
<td>FPG $&lt; 7.0$ and 2 h PG $\geq 7.8$ and $&lt; 11.1$</td>
</tr>
<tr>
<td></td>
<td>ADA (1997)</td>
<td>FPG $\geq 7.0$ or 2 h PG $\geq 11.1$</td>
</tr>
<tr>
<td></td>
<td>ADA (2003)</td>
<td>FPG $\geq 7.0$</td>
</tr>
</tbody>
</table>

Abbreviations: DM, diabetes mellitus; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NGT, normal glucose tolerance. Source: From Refs. 1, 3, and 4.
the Micronesian Nauruans in the Pacific (19), and subsequently in other Pacific and Asian island populations (20). These studies showed that transition from traditional lifestyle to Western way of life resulted in obesity, lack of exercise, profound changes in the diet, and finally to type 2 diabetes. Potential for a future global epidemic of diabetes were highlighted. Since the 1970s several other studies have shown that type 2 diabetes has reached epidemic proportions in several developing countries as well as in Australian Aboriginals (21), African-Americans, and Mexican Americans (22).

Table 2 shows the trends in the number of diabetic patients worldwide (23). Significant increase in the number of type 1 diabetic patients is expected, but the doubling of the number of diabetic subjects in the following 20 years is due to a huge increase in the number of type 2 diabetic patients. According to the estimation of the International Diabetes Federation (IDF) about 194 million people worldwide, or 5.1%, were estimated to have diabetes in the age group 20 to 79 years in 2003 (23). This estimate is expected to increase to some 333 million by 2025, or 6.3% of the adult population. Thus, the increase in the number of diabetic subjects will be almost twofold in the forthcoming 20 years. South East Asia has the most of the increase considering the size of the population (705 million in 2003 and 1081 million in 2025). People in Asia tend to develop diabetes with a lesser degree of obesity at younger ages. Similarly, childhood diabetes has increased substantially (24). The highest prevalence of diabetes was in 2003 in North America, and in 2025 about 10% of the people will have diabetes in this area of the world. Southeast Asia had the highest prevalence of IGT in 2003, and the percentage of people having IGT will be 13.5% in 2025. About 15% to 20% of people in different regions will have either DM or IGT in 2025.

The United States has the highest increase in the prevalence of DM on the basis of several follow-up studies. In the National Health and Nutrition Surveys (NHANES) II (1976–1980) the prevalence of diagnosed plus undiagnosed diabetes was 8.9%, but in the NHANES III (1988–1994) the prevalence was already 12.3% in the population 40 to 74 years of age (25). Prevalence of IFG increased from 6.5% to 9.7%. Figure 1 demonstrates a large difference between ethnic groups in diabetes prevalence in the U.S. population ≥20 years of age. The prevalence of diabetes (known plus undiagnosed) was particularly high in Mexican American men (13.1%) and women (14.5%). IFG or diabetes was present in about 20% of Mexican Americans. Diabetes has become one of the most common chronic diseases in the United States, where in subjects ≥60 years of age the prevalence is already 18.8%.

Until recently, type 2 diabetes was regarded as a disease of the middle-aged and elderly. However, evidence is accumulating that onset in subjects aged under 30 years is increasing. Even children and adolescent are diagnosed to have type 2 diabetes (26). For example, among children in Japan type 2 diabetes is already more common than type 1 and accounts for 80% of childhood diabetes (27). Between 8% and 45% of newly presenting children and adolescents in the United States have type 2 diabetes.

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Estimates of the Prevalence (%) of Diabetes Mellitus and Impaired Glucose Tolerance in the Age Group 20 to 79 Years in Different Regions of the World in 2003 and 2025</th>
</tr>
</thead>
<tbody>
<tr>
<td>Region</td>
<td>2003 DM</td>
</tr>
<tr>
<td>Africa</td>
<td>2.4</td>
</tr>
<tr>
<td>Eastern Mediterranean and Middle East</td>
<td>7.0</td>
</tr>
<tr>
<td>Europe</td>
<td>7.8</td>
</tr>
<tr>
<td>North America</td>
<td>7.9</td>
</tr>
<tr>
<td>South and Central America</td>
<td>5.6</td>
</tr>
<tr>
<td>Southeast Asia</td>
<td>5.6</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>3.1</td>
</tr>
<tr>
<td>Total</td>
<td>5.1</td>
</tr>
</tbody>
</table>

**Abbreviations:** DM, diabetes mellitus; IGT, impaired glucose tolerance.

**Source:** From Ref. 23.
Epidemic of type 2 diabetes is determined not only by an increase in the incidence but also by mortality rates. Although cardiovascular complications in nondiabetic subjects have significantly reduced in the United States during the last decades this is not the case in diabetic patients, particularly among women, as shown recently by Gu et al. (28). No reliable data on mortality rates are available from populations living in developing countries.

CRITERIA FOR TYPE 2 DIABETES AND CARDIOVASCULAR DISEASE

The chronic hyperglycemia of diabetes is associated with long-term complications, especially in the eyes, kidneys, nerves, heart, and blood vessels. Individuals with undiagnosed type 2 diabetes are at high risk of coronary heart disease, stroke, and peripheral vascular disease. More than half of type 2 diabetic patients die of cardiovascular causes (29).

From the perspective of cardiovascular complications of DM the diagnostic criteria have been too high. Already the Whitehall study showed an increased risk of cardiovascular disease when the 2-hour level exceeded 5.5 mmol/L, albeit after a 50 g glucose load (30). This study and several other population-based studies indicated that the risk for macrovascular complications starts at considerably lower levels of glycemia than has been included in the definition of diabetes.

Early diagnosis of diabetes aims to prevent long-term complications. Because cardiovascular disease is the main complication of type 2 diabetes recent studies have investigated the capability of new criteria to predict these complications. The association of hyperglycemia and cardiovascular disease is a crucial one on which to test the validity of the new criteria. The DECODE Study (31) showed that the 2-h criteria more accurately identifies people who are at increased risk of total and cardiovascular mortality compared to the ADA fasting criteria.

The DECODE study (31) analyzed 10 prospective European cohort studies including 15,388 men and 7,126 women, aged 30 to 89 years, who all had undergone a 2-h oral glucose tolerance test. The median follow-up was 8.8 years, and hazard ratios for deaths from all causes, cardiovascular disease, coronary heart disease, and stroke were estimated. Multivariate Cox regression analyses showed that the inclusion of fasting glucose did not add significant information on the prediction of 2-h glucose alone, whereas the addition of 2-h glucose to fasting glucose criteria significantly improved the prediction. Table 3 reports adjusted hazard ratios for deaths from cardiovascular disease, coronary heart disease, stroke,
and all causes with fasting and 2-h categories. IFG did not predict mortality. Diabetes based on fasting criteria predicted total mortality, but 2-h glucose criteria predicted mortality much better than fasting glucose criteria. IGT and diabetes predicted cardiovascular and coronary heart disease mortality as well as coronary heart disease mortality and total mortality. The highest hazard ratios for all categories of death were observed in known diabetic patients. The largest number of excess cardiovascular deaths was found in subjects with IGT who had a normal fasting glucose level, supporting the notion that IGT has prognostic importance. Also the Funaka Diabetes Study in Japan demonstrated that subjects with IGT had higher cardiovascular disease mortality than subjects with IFG (32). In contrast to these findings the Hoorn Study reported no clear differences in mortality risks for subjects classified as IGT, IFG, or newly diagnosed diabetes according to either set of criteria (33).

**INSULIN RESISTANCE AND IMPAIRED INSULIN SECRETION AS PREDICTORS OF TYPE 2 DIABETES**

Type 2 diabetes is caused by impaired insulin action (insulin resistance) and/or impaired insulin secretion. Insulin resistance is a characteristic metabolic defect in the great majority of patients, and it also precedes the development of frank hyperglycemia. Impaired insulin action is observed in several tissues, e.g., skeletal muscle, adipose tissue, and the liver. It leads to increased insulin secretion from the pancreas to overcome impaired insulin action. Compensatory hyperinsulinemia maintains glucose levels within the normal range but in individuals destined to develop diabetes, beta-cell function eventually declines and leads to hyperglycaemic diabetic state. In a minority of subjects diabetes develops as a consequence of a primary defect in insulin secretion. Between 2% and 14% (on average about 5%) of people with IGT progress to type 2 diabetes each year (34). The progression rate is influenced by age, ethnicity, and the degree of glucose intolerance.

The degree of insulin resistance varies between different ethnic groups. For example, in the Insulin Resistance Atherosclerosis Study (35) including 1100 healthy subjects African-Americans and Mexican Americans had a lower insulin sensitivity than non-Hispanic whites. The first study to demonstrate that a combination of insulin resistance and impaired insulin secretion predicts type 2 diabetes was published on Pima Indians. Lillioja et al. (36) showed that low insulin secretory response and increased insulin resistance were both predictors of type 2 diabetes. Furthermore, both impaired insulin secretion and insulin resistance acted as an independent risk factor. Quite similar results were published on Mexican Americans. During the 7-year follow-up baseline high-fasting insulin level (indicator of insulin resistance) predicted the conversion to diabetes (37). Furthermore, low insulin secretion assessed by insulin response (30 min insulin minus fasting insulin divided by 30 min glucose minus fasting glucose) also predicted the development of diabetes. When these two parameters were combined they had an additive effect on the risk of developing diabetes. High degree of

| TABLE 3 | Adjusted Hazard Ratios from Cardiovascular Disease, Coronary Heart Disease, Stroke, and All Causes with Fasting and Two-Hour Glucose Categories in the Same Model: The DECODE Studya |
|-----------------|-----------------|-----------------|-----------------|-----------------|
|                 | CVD             | CHD             | Stroke          | All causes      |
| Fasting glucose criteria |
| IFG             | 1.01 (0.84–1.22) | 1.01 (0.77–1.31) | 1.00 (0.66–1.59) | 1.03 (0.93–1.14) |
| Diabetes        | 1.20 (0.88–1.64) | 1.09 (0.71–1.67) | 1.64 (0.88–3.07) | 1.21 (1.01–1.44) |
| 2-h glucose criteriab |
| IGT             | 1.32 (1.12–1.56) | 1.27 (1.01–1.58) | 1.21 (0.84–1.74) | 1.37 (1.25–1.51) |
| Diabetes        | 1.40 (1.02–1.92) | 1.56 (1.03–2.36) | 1.29 (0.66–2.54) | 1.73 (1.45–2.06) |
| Known diabetesc | 1.96 (1.62–2.37) | 1.94 (1.51–2.50) | 1.73 (1.12–2.68) | 1.82 (1.60–2.06) |

a Adjusted for age, sex, center, total cholesterol, body mass index, systolic blood pressure, and smoking.

b Using fasting plasma glucose < 6.1 mmol/L as reference group.

c Using 2-h plasma glucose < 7.8 mmol/L as reference group.

Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; IFG, impaired fasting glucose; IGT, impaired glucose tolerance.
insulin resistance and normal insulin secretion increased the risk by 4.5-fold, and high insulin sensitivity but low insulin secretion increased the risk by 5.4-fold, whereas the combination of these two increased the risk by 13.9-fold (Fig. 2).

**RISK FACTORS FOR TYPE 2 DIABETES**

The identification of risk factors is essential for the successful implementation of primary prevention programs. Risk factors for type 2 diabetes can be classified as modifiable and nonmodifiable (Table 4). Subjects who subsequently develop diabetes have multiple adverse changes in risk factor levels. A good example is our study of 892 elderly Finnish subjects followed for 3.5 years (38). As shown in Figure 3 the highest risk of developing diabetes was associated with IGT and hyperinsulinemia. Furthermore, hypertriglyceridemia, central obesity, low high-density lipoprotein (HDL) cholesterol, high body mass index, hypertension, and a family history of diabetes were risk factors for diabetes.

**Modifiable Risk Factors**

Hu et al. (39) published results from the Nurses’ Health Study including 84,941 female nurses followed from 1980 to 1996, and who were free of diagnosed cardiovascular disease and diabetes at baseline. During the 16 years follow-up 3300 new cases of type 2 diabetes were diagnosed. As shown in Figure 4 obesity was the single most important predictor of diabetes. Women whose body mass index was at least 35.0 kg/m² had almost 40-fold risk of becoming diabetic compared to women whose body mass index was <23.0 kg/m². Weekly exercised at least 7 h/wk reduced the risk of type 2 diabetes by 39% compared to women who exercise <0.5 h/wk. Smoking of >14 cigarettes/day increased the diabetes risk by 39%, but alcohol intake >10 g/day reduced the risk by 41%. The study also indicated that a diet high in cereal fiber and polyunsaturated fat and low in saturated and trans fats and glycemic load reduced the risk of developing diabetes. A combination of several lifestyle factors, including low body mass index (<25 kg/m²), a diet high in cereal fiber and polyunsaturated fat and low in saturated fat and trans fats and glycemic load, regular exercise, abstinence from smoking and moderate alcohol intake, was associated with a reduction of type 2 diabetes incidence by 90% compared to women without these factors.

![Figure 2](image-url)

**FIGURE 2** The risk of developing type 2 diabetes by fasting insulin concentration and insulin secretion (change in insulin divided by change in glucose concentrations over the first 30 minutes of an oral glucose tolerance test [ΔI/ΔG₃₀]). *Source:* From Ref. 35.
Visceral adiposity precedes the development of type 2 diabetes. Boyko et al. (40) showed in their study of Japanese Americans that intra-abdominal fat area measured by computed tomography (CT) remained a significant predictor of diabetes incidence even after adjustment for body mass index, total body fat area, and subcutaneous fat area and other risk factors for diabetes. Interestingly, high insulin resistance and low insulin secretion predicted diabetes independently of directly measured visceral adiposity suggesting that visceral adiposity could contribute to the development of diabetes through actions independent of its effect on insulin sensitivity. Van Dam et al. (41) showed that in Dutch subjects the association between abdominal obesity (waist circumference) and hyperglycemia was stronger in the presence of a parental history of diabetes.

Physical inactivity is a major risk factor for the development of type 2 diabetes. For example, sedentary lifestyle, indicated by television viewing time, worsens glucose tolerance (42). Physical activity reduces insulin resistance and total and visceral fat mass (43). In contrast, the association of total dietary fat with type 2 diabetes or insulin sensitivity is less

TABLE 4 Risk Factors for Type 2 Diabetes

<table>
<thead>
<tr>
<th>Modifiable</th>
<th>Nonmodifiable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
<td>Ethnicity</td>
</tr>
<tr>
<td>Central obesity</td>
<td>Age</td>
</tr>
<tr>
<td>Lack of physical activity</td>
<td>Sex</td>
</tr>
<tr>
<td>Smoking</td>
<td>Genetic factors</td>
</tr>
<tr>
<td>Alcohol abstinence</td>
<td>Family history of type 2 diabetes</td>
</tr>
<tr>
<td>Low fiber in the diet</td>
<td>Prior gestational diabetes</td>
</tr>
<tr>
<td>High saturated fat in the diet</td>
<td>Prior glucose intolerance</td>
</tr>
<tr>
<td></td>
<td>History of cardiovascular disease</td>
</tr>
<tr>
<td></td>
<td>History of hypertension</td>
</tr>
<tr>
<td></td>
<td>History of dyslipidemia</td>
</tr>
<tr>
<td></td>
<td>Low birth weight</td>
</tr>
</tbody>
</table>

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FIGURE 3 Odds ratio of developing type 2 diabetes in elderly Finnish subjects. Source: From Ref. 38.
consistent. Meyer et al. (44) studied the relation between dietary fatty acids and diabetes in a prospective cohort study of 35,988 older women who initially did not have diabetes. Altogether 1890 new cases of diabetes occurred during 11 years of follow-up. Diabetes risk was negatively associated with dietary polysaturated fatty acids, vegetable fat, and trans fatty acids. Even after adjustment for confounding factors vegetable fat remained a significant predictor of new diabetes. Many studies show that high coffee consumption may protect from type 2 diabetes (45).

Nonmodifiable Risk Factors

The prevalence and incidence of type 2 diabetes are strongly related to age. In fact, about 50% of all type 2 diabetic patients are over 60 years old. Ethnicity is a strong determinant of diabetes occurrence. In Chinese the prevalence of type 2 diabetes is 1% whereas in Pima Indians it is >50% in adult population probably due to genetic influence or due to interaction between genes and environment. No systematic effect of gender on the prevalence and incidence of type 2 diabetes is observed but in some ethnic groups the occurrence of diabetes might depend on gender. Previous abnormality of glucose tolerance, a history of gestational diabetes and a family history of type 2 diabetes are all strong predictors of type 2 diabetes. Interestingly, also the presence of other disease states or conditions, for example hypertension and dyslipidemia increase the risk of type 2 diabetes. In recent years interest has been focused also on low birth weight as a risk factor for type 2 diabetes. Associations between low birth weight and increased risk of type 2 diabetes in adult life have been reported in various populations (46). Several explanations for this relationship have been presented. Long-term effects of nutritional deprivation in utero could affect fetal growth and the development of the endocrine pancreas. Genetic factors could cause both low birth weight and later abnormalities of insulin secretion or insulin sensitivity. Whether the relationship between diabetes and low birth weight is mediated through impaired insulin sensitivity or impaired insulin secretion remains to be determined.
PREVENTION OF TYPE 2 DIABETES: IMPLICATIONS FOR SCREENING

Screening for diabetes may be appropriate under certain circumstances because early detection and prompt treatment may reduce the burden of type 2 diabetes and its complications. However, widespread screening for asymptomatic individuals for type 2 diabetes cannot be recommended. Screening may be appropriate if the subjects have one or more of the risk factors listed in Table 4.

The rationale for screening of type 2 diabetes must be based on the presence of factors having a significant effect on the risk of developing diabetes. Second, screening for diabetes is rational only if diabetes can be prevented by normalizing modifiable risk factors. Clinical trials have demonstrated the efficacy of lifestyle–intervention programs in the prevention of type 2 diabetes. Da Qing study from China (47) showed that exercise and diet resulted in a decrease of 42% to 46% an incidence of type 2 diabetes among 577 subjects with IGT. The Finnish Diabetes Prevention Program demonstrated that weight loss and regular exercise reduced the incidence of type 2 diabetes by 58% (48), and this preventive effect was observed even 3 years after the stopping the intervention (49). Similarly, the Diabetes Prevention Study in the United States showed that diet and regular exercise reduced the incidence of type 2 diabetes by 58% among 3234 subjects with IGT (50). Lifestyle intervention works as well in men and women and in all ethnic groups. Lifestyle was also effective in the Japanese (51) and Indian (52) trials. Accumulating evidence implies that lifestyle intervention is highly successful and screening should be targeted to subjects with high risk of developing diabetes.

The ADA has recommended the plasma fasting glucose measurements as a screening test because it is easier and faster to perform, more convenient and acceptable to patients, and less expensive (53). In contrast, the WHO criteria for diabetes still include a 2-h oral glucose tolerance test, which might be used in the screening of high-risk individuals. Recent studies indicating that 2-h glucose identifies better than fasting glucose values individuals with high risk of cardiovascular disease favors the use of a 2-h oral glucose tolerance test. However, the 2-h glucose tolerance test has the high within-test variability up to 25%. According to different studies when subjects were retested after an interval of up to 3 months 35% to 75% of the subjects who were IGT an the first test had reverted to normal when retested (54).

CONCLUDING REMARKS

In the next 20 years we will face a global epidemic of type 2 diabetes. Although the new cases of diabetes depend somewhat on the glucose criteria used to define diabetes, there has already been a true increase in the incidence and prevalence of type 2 diabetes. With increasing prevalence of obesity worldwide the epidemic of type 2 has emerged, and an “epidemic” of diabetes-related cardiovascular disease will follow (55). Incidence of diabetes in a population is tightly linked to the average weight of that population. Type 2 diabetes does not only cause micro- and macrovascular complications, excess mortality and morbidity, but it is also an expensive health problem. Therefore, socioeconomic, behavioral, nutritional, and public health issues relating to the epidemic of obesity and type 2 diabetes should be addressed. Furthermore, more funds are needed for continuing research aiming to reveal the unsolved issues in the pathophysiology and genetics of type 2 diabetes. Extremely important areas of research will be the identification of the genes responsible for the predisposition to type 2 diabetes, and the identification of environmental factors, which bring out this predisposition. Once these issues have been solved we will better understand the “epidemic” of type 2 diabetes, and target our nonpharmacological and pharmacological treatment modalities more effectively to prevent this continuously growing health problem and its devastating complications.

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TABLE 6 Advice to Patients to Overcome Difficulties with AGIs

Start low, go slow

Prefer nutrients with complex carbohydrates (rice, pasta, full bread, vegetables, fruits)
Avoid refined carbohydrates (sugar, sweets). Take only three meals per day.

Avoid laxatives, such as sugar alcohols (sorbitol).

Control your postprandial blood glucose to experience the efficacy of treatment.

In most cases gastrointestinal side effects are transient.


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TABLE 2 Guideline Target Levels for LDL Cholesterol, HDL Cholesterol, and Triglycerides for Patients with Diabetes

<table>
<thead>
<tr>
<th>European Joint Societies (62)</th>
<th>LDL cholesterol (mg/dL)</th>
<th>HDL cholesterol</th>
<th>Triglycerides (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>European Joint Societies (62)</td>
<td>&lt;100</td>
<td>Not a goal</td>
<td>Not a goal</td>
</tr>
<tr>
<td>International Atherosclerosis Society (57)</td>
<td>&lt;100</td>
<td>Not a goal</td>
<td>Not a goal</td>
</tr>
<tr>
<td>ADA (1)</td>
<td>&lt;100</td>
<td>&gt;40</td>
<td>&lt;150</td>
</tr>
</tbody>
</table>

a. Goal of 70mg/dL (1.8mmol/L) is considered a therapeutic option in those with established CVD.

b. According to some authorities if the patient with diabetes has an estimated 10-year risk for CHD <20%, an LDL-C goal <130mg/dL (3.3mmol/L) is acceptable.

c. Current NCEP/ATP III guidelines suggest that in patients with triglycerides $200mg/dL (2.2mmol/L), the "non-HDL cholesterol" (total cholesterol minus HDL) be utilized. The goal is £ 130mg/dL.

d. For women it has been suggested that the HDL goal be
increased by 10mg/dL.


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