

Chapter

2

CLASSIFICATION AND
DIAGNOSIS*John E. Gerich, MD*

In 1979, the National Diabetes Data Group (NDDG) of US National Institutes of Health (NIH) proposed diabetes classifications that were widely accepted and used until recently. In 1995, under the sponsorship of the American Diabetes Association (ADA), an international Expert Committee was established to review current findings on diabetes and determine whether changes in recommendations for classification, diagnostic criteria, screening, and management were necessary. The major changes outlined by these groups have led to currently accepted diabetes classification terminology. Tables 2-1 and 2-2 list the revisions and current definitions of diabetes classifications.

Table 2-1 Revisions in Diabetes Classification Terminology

1979—NDDG	1995—ADA
<ul style="list-style-type: none"> ▲ The terms “juvenile-onset” and “adult-onset” diabetes were discarded as inappropriate and retermed “insulin-dependent diabetes mellitus (IDDM)” and “non-insulin-dependent diabetes mellitus (NIDDM),” respectively. 	<ul style="list-style-type: none"> ▲ The terms “insulin-dependent” and “non-insulin-dependent” and their acronyms were eliminated as confusing and treatment-based rather than etiology-based. ▲ The terms “type 1” and “type 2” diabetes were retained, using arabic numerals rather than roman numerals, also to eliminate confusion.

NDDG, National Diabetes Data Group⁹; ADA, American Diabetes Association.³

Table 2-2 Classification of Diabetes Mellitus

Current Classification	Also Called
Type 1 diabetes	IDDM, juvenile-onset diabetes
Type 2 diabetes	NIDDM, adult-onset diabetes
Gestational diabetes	GDM
Latent autoimmune diabetes in adults (LADA)	Slow-onset type 1 diabetes; type 1½ diabetes
Maturity-onset diabetes of the young	MODY
Other types	
Pre-diabetes	Impaired fasting glucose (IFG), impaired glucose tolerance (IGT)

Sources: ADA, 2004;³ Fajans, 1997;⁸
Landin-Olsson, 2002.²⁵

Description

- ▲ A disease of absolute insulin deficiency, brought on by pancreatic β -cell damage
 - ▲ A disease of relative insulin deficiency; etiologic factors are complex and not fully understood, but β -cell dysfunction and insulin resistance are generally present; often associated with obesity
 - ▲ Glucose intolerance first recognized during pregnancy; genetic factors or preexisting unrecognized diabetes may be causative
 - ▲ Seen in non-overweight adults; presence of pancreatic antibodies; may initially respond to oral drugs, but insulin often required within 3 years of diagnosis
 - ▲ Often develops before age 25; inherited as autosomal dominant; usually treated for many years or decades by diet or oral drugs
 - ▲ Genetic defects of the β -cell
 - ▲ Genetic defects in insulin action
 - ▲ Diseases of the exocrine pancreas
 - ▲ Endocrinopathies
 - ▲ Drug- or chemical-induced diabetes
 - ▲ Infections
 - ▲ Uncommon forms of immune-mediated diabetes
 - ▲ Other genetic syndromes associated with diabetes
 - ▲ An intermediate stage between normal glucose metabolism and diabetes
-

PATHOPHYSIOLOGY

Glucose metabolism is regulated on a moment to moment basis by changes in secretion of insulin and glucagon, hormones produced in and released from pancreatic β - and α -cells, respectively, and tissue responses to these hormones. When glucose metabolism is normal, ingested carbohydrate is broken down into glucose in the gastrointestinal tract, enters the bloodstream, and is transported into the body's cells to be stored or used for energy immediately. Insulin is vital to this transport process. Normally, β -cells respond to rising plasma glucose levels with an increase in insulin secretion. This secretion tapers off as blood glucose levels return to normal. Plasma glucagon levels change in the opposite direction of insulin. A decrease in glucagon secretion after meal ingestion decreases the release of glucose stored in the liver. When plasma glucose levels drop (ie, during fasting), a decrease in insulin secretion and an increase in glucagon secretion permits stored glucose to be released into the bloodstream.^{1,2}

All forms of diabetes result from an imbalance between the body's need for insulin and its ability to secrete insulin. When insulin secretion cannot meet the body's demand, there is overproduction of glucose and decreased clearance of glucose from the bloodstream, which leads to increased levels of plasma glucose (hyperglycemia).¹

Type 1 Diabetes Mellitus

Type 1 diabetes accounts for 5% to 10% of all diabetes and is diagnosed most often in children and adolescents, although it can appear at any age. These patients have absolute insulin deficiency and are dependent on insulin replacement for life. Diabetic ketoacidosis is often the presenting symptom in patients with type 1 diabetes.³ There are two subclasses of type 1 diabetes: immune-mediated and idiopathic.

Immune-mediated type 1 diabetes mellitus

Most type 1 diabetes cases are caused by variable rates of autoimmune destruction of β -cells.³ The cause of type 1 diabetes is unknown, but researchers have discovered that most patients with type 1 diabetes have specific immune risk markers³:

- ▲ Islet cell autoantibodies (ICAs)
- ▲ Autoantibodies to insulin (IAAs)
- ▲ Glutamic acid decarboxylase autoantibodies (GAD)
- ▲ Autoantibodies to the tyrosine phosphatases IA-2 and IA-2 β

A combination of genetic and environmental factors is thought to contribute to the development of type 1 diabetes,⁴ as studies involving identical twins indicate that only one-half of twins develop diabetes. Environmental triggers are thought to include certain drugs, chemicals, or viruses. Certain genetic markers have been identified, including specific human lymphocyte antigen (HLA) types and others found in the major histocompatibility complex (MHC) on chromosome 6.

Idiopathic type 1 diabetes mellitus

A small percentage of patients presenting with a phenotype suggesting type 1 diabetes (eg, low C-peptides) do not demonstrate autoimmune destruction of β -cells. Varying degrees of insulin deficiency and episodic ketoacidosis may be present, and the need for absolute insulin replacement may come and go. These patients are often of African or Asian heritage.³

Type 2 Diabetes Mellitus

About 90% to 95% of patients with diabetes have type 2 diabetes. These individuals have impaired insulin secretion but are generally not dependent on insulin therapy in the early stages of the disease. The β -cell function deteriorates over the course of the disease, and therefore therapies designed to control glucose may vary from initial treatment with diet modification only to monotherapy or combination therapy, and later insulin therapy.

Key components of type 2 diabetes are:

- ▲ β -Cell dysfunction causing impaired insulin secretion
- ▲ Increased need for insulin due to insulin resistance

The causes of impaired insulin secretion in type 2 diabetes are not fully understood. Both genetics and environment are involved.³

The insulin resistance associated with type 2 diabetes is largely due to acquired causes such as obesity, physical inactivity, and a high-fat diet. Impaired β -cell function appears to be the primary genetic etiologic component. Since type 2 diabetes is a polygenic disorder, there are probably many causes, but it is clear that a disruption in the normal relationship between β -cell function and insulin sensitivity is present before the time of diagnosis.^{5,6}

Gestational diabetes mellitus

Gestational diabetes mellitus (GDM), defined as any degree of glucose intolerance that is first recognized during pregnancy, affects approximately 4% of all pregnancies. GDM generally resolves postpartum, although women who have experienced gestational diabetes are at higher risk of developing type 2 diabetes.³

Hormones produced during pregnancy cause insulin resistance that is normally compensated for by increased insulin secretion. Similar to individuals with type 2 diabetes, women with GDM are unable to meet the increased demand for insulin due to an underlying insulin secretory defect.⁷

DIAGNOSIS OF DIABETES

Diabetes is diagnosed when a patient displays symptoms of hyperglycemia and/or meets plasma glucose testing diagnostic criteria.³ Tests used to diagnose diabetes and pre-diabetes are found in Table 2-3. Symptoms of hyperglycemia are:

- ▲ Polyuria
- ▲ Polydipsia
- ▲ Unexplained weight loss, sometimes with extreme hunger
- ▲ Blurred vision

Conditions when performing the oral glucose tolerance test (OGTT)^{3,8,9}:

Table 2-2 Diagnostic Tests for Diabetes

Tests Used	Blood Sample(s) Taken and Analyzed for Plasma Glucose
Fasting plasma glucose (FPG)	After fasting (≥ 10 –14 h without food)
Oral glucose tolerance test (OGTT)	At fasting and then 2 h after a 75 g oral glucose drink (in children 1.75 g/kg ideal body weight up to 75 g; in pregnant women a 100-g glucose dose is used and fasting, 1-h, and 3-h samples are taken as well as 2-h samples)
Postprandial plasma glucose (PPG)	2 h after a meal: this measurement is often mistaken for the OGTT; however, it is not clinically reproducible and therefore is less accurate than the OGTT
Random plasma glucose (RPG)	Without regard to time of last meal

Sources: Fajans, 1997;⁸ ADA, 2004.³

- ▲ Test should be performed in the morning.
- ▲ Subject should have fasted for at least 10 hours.
- ▲ Patients should be seated during the test and should not smoke.
- ▲ Subjects should be otherwise healthy and ambulatory; the test should not be performed on those on prolonged bed rest or who are hospitalized.
- ▲ Patients who have been on restrictive diets or have low carbohydrate intake (≥ 150 g/day) for other reasons should be put

on a diet of ≥ 200 g of carbohydrates per day for at least 3 days before the test.

Steps for performing the OGTT:

- ▲ A blood sample should be collected at baseline (fasting) and plasma glucose concentrations analyzed.
- ▲ A 75-g oral glucose drink should be consumed within 5 minutes (the timing of the test begins at the first swallow; in children a glucose drink of 1.75 g/kg ideal body weight up to 75 g should be given; in pregnant women a 100-g glucose dose is used).
- ▲ A blood sample is taken at 2 hours post-glucose load and plasma glucose concentrations analyzed (pregnant women should be tested at 1-, 2- and 3-hours post-glucose).

Criteria for Diagnosis of Diabetes Mellitus

▲ Symptoms of diabetes plus random plasma glucose (RPG) (≥ 200 mg/dL (11.1 mmol/L)

or

▲ Fasting plasma glucose (FPG) ≥ 126 mg/dL (7.0 mmol/L)

or

▲ 2-hour OGTT value ≥ 200 mg/dL (11.1 mmol/L)

To establish a diagnosis of diabetes, the testing method used must be confirmed on a subsequent day by any one of the procedures.

Before 1997, an FPG of ≥ 140 mg/dL (7.8 mmol/L) or a 2-hour PG ≥ 200 mg/dL in an OGTT was considered diagnostic of diabetes by the NDDG in 1979 and accepted by the World Health Organization (WHO).^{8,9} In 1997, the ADA released new diagnostic criteria with a few significant changes. The FPG level indicating diabetes was lowered to ≥ 126 mg/dL, and a new classification titled "impaired fasting glucose" (IFG) was introduced (now fasting glucose ≥ 100 mg/dL and ≤ 126 mg/dL). In addition, the ADA recommended that the FPG be used instead of the OGTT in routine

Table 2-4 Diagnostic Criteria for FPG and OGTT

Classification	FPG	OGTT
Diabetes	≥126 mg/dL	≥200 mg/dL
Pre-diabetes	Impaired fasting glucose (IFG) ≥100 mg/dL to <126 mg/dL	Impaired glucose tolerance (IGT) ≥140 mg/dL to <200 mg/dL
Normal	<100 mg/dL	<140 mg/dL

FPG, fasting plasma glucose; OGTT, oral glucose tolerance test.

Source: ADA, 2004.³

clinical practice. Table 2-4 outlines current diagnostic criteria for FPG and OGTT.

New criteria: ADA stance

The ADA's Expert Committee had several justifications for the 1997 revision:

▲ *Standardization of cutpoint values for the two tests.* Almost all patients with an FPG of ≥140 mg/dL have an OGTT of ≥200 mg/dL; conversely, only about one-fourth of patients without previously known diabetes with an OGTT of ≥200 mg/dL have an FPG of ≥140 mg/dL. Therefore, the cutoff values for the two tests were unequal.¹⁰

▲ *Facilitation of field work.* The OGTT is inconvenient to patients, costly, and time-consuming; it is infrequently used in routine clinical practice.

▲ *Effectiveness in distinguishing glycemic thresholds for serious complications.* Several studies indicated that both values equivalently predicted adverse outcomes, in particular microvascular complications.¹⁰

Response to ADA

Concern was raised because if FPG alone were used to screen asymptomatic individuals, many cases of diabetes or pre-diabetes would remain undiagnosed.

Accurate diagnosis. In the Diabetes Epidemiology: Collaborative Analysis of the Diagnostic Criteria in Europe (DECODE) study, an analysis of FPG and OGTT levels from nearly 50,000 individuals, determined that the two methods identified similar prevalence rates of diabetes, but they did not necessarily identify the same individuals¹¹:

▲ The FPG identified more young and obese patients as having diabetes.

▲ The OGTT identified more lean and elderly patients as having diabetes.

In the Diabetes Prevention Program (DPP), the OGTT was found to be more sensitive than the FPG in diagnosing pre-diabetes and diabetes. Because preventive therapy significantly reduces the incidence of diabetes development, it is important to identify those at risk based on the most sensitive test.¹²

Abnormal glucose levels in postprandial testing precede abnormal fasting levels in the development of type 2 diabetes. Therefore, it is unclear why the ADA does not recommend widespread screening.¹³

Cardiovascular disease. Impaired glucose tolerance (IGT), a pre-diabetic state identified by 2-hour PG levels on an OGTT, is associated with increased morbidity and mortality from cardiovascular disease. Several studies analyzing data from large trials have found the ADA's classification of impaired fasting glucose (IFG) less sensitive than the IGT in predicting cardiovascular disease.¹⁴⁻¹⁶

Criteria for diagnosis of gestational diabetes mellitus (GDM)

The OGTT should be used to screen pregnant women for GDM. A 100-g oral glucose drink is used and plasma glucose levels are

Table 2-5 Diagnostic Criteria for Gestational Diabetes

Hours	mg/dL (mmol/L) ^a
Fasting	95 (5.3)
1-h	180 (10.0)
2-h	155 (8.6)
3-h	140 (7.8)

^aTwo or more of these values must be met or exceeded for a positive diagnosis.

Source: ADA, 2004.³

analyzed at baseline (fasting), 1, 2, and 3 hours post-glucose load.⁸ Indications for diagnosis of GDM are found in Table 2-5.

Distinguishing Type 1 From Type 2 Diabetes After Diagnosis

In many cases, the age of the patient and condition at diagnosis will indicate whether type 1 or type 2 diabetes is present. However, more and more frequently, younger people are developing type 2 diabetes and type 1 and type 1½ may occur at any age. Criteria for distinguishing type 1 from type 2 at diagnosis may be found in Table 2-6.

Pre-diabetes

Pre-diabetes is a term that identifies those who have some degree of impaired glucose homeostasis, as defined below, but who do not have diabetes.

Impaired Glucose Tolerance

Under the WHO criteria, impaired glucose tolerance (IGT) includes individuals whose 2-hour PG on an OGTT is ≥ 140 mg/dL and < 200 mg/dL.⁸

Table 2-6 Distinguishing Type 1 From Type 2 Diabetes at Diagnosis

Identifying Feature	Type 1	Type 2
Age at diagnosis	Usually <40	Usually >40
Weight	Usually thin with recent weight loss	Usually obese
Condition at diagnosis	Usually moderately to severely ill	May show only mild or no symptoms
Acute complications	Ketoacidosis	Nonketotic, hyperosmolar, hyperglycemic coma
Plasma insulin/C-peptide	Low to none	Inappropriately low for plasma glucose
Response to therapy		
Insulin	Responsive	Variable
Sulfonylurea	Unresponsive	Responsive

Sources: Beaser 2001;¹ Foster.²⁶

Impaired Fasting Glucose

Impaired fasting glucose (IFG) encompasses those with an FPG level of ≥ 100 mg/dL and < 126 mg/dL.³

Pre-diabetes can occur as an intermediate stage in type 1 or type 2 diabetes development and is a risk factor for diabetes, as well as for cardiovascular disease.¹⁷ Patients who are diagnosed with pre-diabetes should be monitored carefully for the development of diabetes. They should also be screened at diagnosis for existing cardiovascular disease and monitored thereafter. For information on preventing diabetes after diagnosis of pre-diabetes, see Screening and Prevention, below.

Metabolic Syndrome

Metabolic syndrome is a term used to describe a combination of several conditions indicating high risk of cardiovascular disease. Also known as insulin resistance syndrome or syndrome X, it is characterized by the presence of IGT, IFG, or type 2 diabetes and/or insulin resistance (fasting plasma insulin $\geq 10 \mu\text{U/mL}$) and two or more of the following abnormalities^{18,19}:

- ▲ Central obesity (waist-to-hip ratio >0.9 in men and >0.85 in women; and/or body mass index (BMI) >30)
- ▲ Dyslipidemia (serum triglycerides level $\geq 150 \text{ mg/dL}$ [1.69 mmol/L]; high-density lipoprotein [HDL] cholesterol level $<35 \text{ mg/dL}$ [0.9 mmol/L] in men and $<39 \text{ mg/dL}$ [1.0 mmol/L] in women)
- ▲ Hypertension (blood pressure $\geq 140/90 \text{ mm Hg}$)

The common denominator of the components of the metabolic syndrome is insulin resistance; the causes of insulin resistance are most commonly obesity, decreased physical activity, and high-fat diets. By decreasing insulin action, insulin resistance leads to increased hepatic glucose and triglyceride release, hypertension (insulin is a vasodilator), and endothelial dysfunction.²⁰ Recent findings from the Third National Health and Nutrition Examination Survey indicate that the metabolic syndrome is highly prevalent in the US population.²¹

SCREENING AND PREVENTION

Identifying patients with diabetes and prediabetes as early as possible is the key to preventing the devastating complications of the disease. Methods of prevention have been the focus of much recent research.

Screening for Type 1 Diabetes

Although it is possible to identify those at high risk of type 1 diabetes due to the presence of certain autoantibodies, there is currently no known prevention for type 1 diabetes. For this reason, and because the incidence of type 1 diabetes is low, routine test-

ing for immune markers in healthy individuals without identified risk factors is not recommended.²²

The risk factors for type 1 diabetes are^{3,4}:

- ▲ First-degree relative (parents, siblings, children) with type 1 diabetes
- ▲ Presence of genetic markers, including certain HLA types and other genes found on chromosome 6
- ▲ Presence of autoantibodies
 - Islet cell autoantibodies (ICAs)
- ▲ Autoantibodies to insulin (IAAs)
- ▲ Glutamic acid decarboxylase autoantibodies (GAD)
- ▲ Autoantibodies to the tyrosine phosphatases IA-2 and IA-2 β
- ▲ Possible environmental factors
 - Exposure to certain drugs or chemicals
 - Viruses (type 1 diabetes is often diagnosed in the spring after the viral season; suspected viruses include mumps, coxsackie, and rubella)

Screening for Type 2 Diabetes

Studies have shown that early detection and treatment can delay the progression or onset of type 2 diabetes and its associated complications. Because type 2 diabetes is more common in those over age 45, the ADA recommends the following³:

- ▲ Screening be considered in all individuals aged 45 and older and repeated every 3 years.
- ▲ Screening should be considered at any age, or more frequently among those with risk factors listed below.

The risk factors for type 2 diabetes are²³:

- ▲ First-degree relative (parents, siblings, children) with diabetes
- ▲ Obesity (BMI ≥ 25 kg/m²)
- ▲ Sedentary lifestyle

- ▲ Race/ethnicity (African, Hispanic, Native American, Asian, or Pacific Islander)
- ▲ Previously diagnosed IGT or IFG
- ▲ Hypertension ($\geq 140/90$ mm Hg in adults)
- ▲ HDL cholesterol ≤ 35 mg/dL (0.90 mmol/L) and/or triglyceride level ≥ 250 mg/dL (2.82 mmol/L)
- ▲ History of GDM or delivery of a baby weighing >9 lb
- ▲ Polycystic ovary syndrome (PCOS)
- ▲ History of vascular disease

Screening for Gestational Diabetes

- ▲ Women at high risk of GDM should be screened for the disease as soon as feasible after the first prenatal visit. If the initial screening results are normal, they should be tested again at 24 to 28 weeks.
- ▲ Women of average risk should be tested at 24 to 48 weeks.³

Only women meeting all of the following criteria should not be tested for gestational diabetes²⁴:

- ▲ Age <25 years
- ▲ Low-risk ethnic group
- ▲ No family history of diabetes
- ▲ No previous history of gestational diabetes or poor obstetric outcome
- ▲ No signs of insulin resistance
- ▲ Normal weight before pregnancy and active lifestyle

The risk factors for gestational diabetes are²⁴:

- ▲ Presence of insulin resistance syndromes (polycystic ovary syndrome, acanthosis nigricans)

- ▲ Previous history of gestational diabetes or delivery of a baby weighing >8 lb
- ▲ Obesity
- ▲ First-degree relative (parents, siblings, children) with diabetes
- ▲ Race/ethnicity (African, Hispanic, Native American, Asian, or Pacific Islander)

Screening for Type 2 Diabetes in Children

Although the incidence of type 2 diabetes in children is on the rise, routine screening of children is not currently recommended. Children who meet the criteria for high risk should be tested with FPG every 2 years beginning at age 10 or at the onset of puberty if earlier.³

The risk factors for type 2 diabetes in children are³:

- ▲ Overweight, indicated by:
 - BMI >85th percentile for age and sex
 - Weight for height >85th percentile
 - Or weight >120% of ideal for height

And any two of the following:

- ▲ Family history of type 2 diabetes in first- or second-degree relative
- ▲ Race/ethnicity (Native American, African, Hispanic, Asian, or Pacific Islander)
- ▲ Signs of insulin resistance or conditions associated with insulin resistance, such as acanthosis nigricans, hypertension, dyslipidemia, or polycystic ovary syndrome (in adolescents)

Prevention of Diabetes

Much research has concentrated on prevention of type 2 diabetes. Recent studies and their outcomes are summarized in Table 2-7.

Table 2-7
Diabetes Prevention Trials

Study Name	Study Design	Therapy Used	Results
Troglitazone for the Prevention of Diabetes (TRIPOD) Trial ²⁷	Randomized, placebo-controlled trial with 235 Hispanic women previously diagnosed with GDM	Treatment with troglitazone (see Chapter 6) or placebo.	Troglitazone therapy was associated with a 56% relative reduction in development of type 2 diabetes over placebo
STOP-NIDDM Trial (2002) ²⁸⁻²⁹	Randomized, double-blind, placebo-controlled trial with 1429 participants with IGT	Treatment with acarbose (See Chapter 6) or placebo.	<p>▲ A 36% relative diabetes risk reduction was observed in the acarbose-treated group over placebo (confirmed by 2 OGTTs)</p> <p>▲ An absolute risk reduction of 9% was observed in the acarbose-treated group over placebo</p>
Diabetes Prevention Program (2002) ¹²	Multicenter, randomized, placebo-controlled trial with 3234 participants with IGT or elevated fasting glucose values	Lifestyle interventions (weight reduction of 7% or more and at least 150 min of physical activity a week) or treatment with metformin (See Chapter 6)	<p>Both therapies effective in delaying the onset of diabetes: lifestyle modification = 58% reduction in incidence of diabetes; metformin = 31% reduction in development of diabetes</p>

(table continues)

Table 2-7
(continued)

Study Name	Study Design	Therapy Used	Results
Finnish Study (2001) ³⁰	Randomized trial with 522 obese middle-aged participants with IGT	Brief diet and exercise counseling (control group) vs intensive individualized instruction on diet and exercise (intervention group)	Risk of diabetes was reduced by 58% in the intervention group
Da Qing Trial (1997) ³¹	Multicenter, randomized, placebo-controlled trial with 577 patients with IGT	Diet and/or exercise	Diet and/or exercise groups experienced a significant decrease in incidence of diabetes

IGT, gestational diabetes mellitus; IGT, impaired glucose tolerance.

REFERENCES

1. Beaser RS. Definition and pathophysiology. In: Beaser RS, ed. *Joslin's Diabetes Deskbook*. Boston, Mass: Joslin Diabetes Center; 2001:1-22.
2. Dinneen S, Gerich J, Rizza R. Carbohydrate metabolism in non-insulin-dependent diabetes mellitus. *N Engl J Med*. 1992;327:707-13.
3. American Diabetes Association. Clinical Practice Recommendations 2004. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2004;27:S5-S10.
4. Palmer JP, Lernmark A. Pathophysiology of type 1 (insulin-dependent) diabetes. In: Porte D Jr, Sherwin RS, eds. *Ellenberg and Rifkin's Diabetes Mellitus*. 5th ed. New York, NY: McGraw-Hill; 1997:357-372.
5. Gerich JE. Insulin resistance is not necessarily an essential component of type 2 diabetes. *J Clin Endocrinol Metab*. 2000;85:2113-2115.
6. Kahn SE. The importance of the β -cell in the pathogenesis of type 2 diabetes mellitus. *Am J Med*. 2000;108:2S-8S.
7. Beaser RS. Pregnancy and diabetes. In: Beaser RS, ed. *Joslin's Diabetes Deskbook*. Boston, Mass: Joslin Diabetes Center; 2001:503-521.
8. Fajans SS. Classification and diagnosis of diabetes. In: Porte D Jr, Sherwin RS, eds. *Ellenberg and Rifkin's Diabetes Mellitus*. 5th ed. New York, NY: McGraw-Hill; 1997:357-372.
9. National Diabetes Data Group (NDDG). Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. *Diabetes*. 1979;28:1039-1057.
10. American Diabetes Association. Clinical Practice Recommendations 2003. Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2003;25:S5-S20.
11. DECODE Study Group. European Diabetes Epidemiology Group. New diagnostic criteria for diabetes mellitus-will they change the phenotype of the diabetic subjects? *BMJ*. 1998;317:371-375.
12. Diabetes Prevention Program Research Group (DPP). Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;346:393-403.

13. Borch-Johnsen K. The new classification of diabetes mellitus and IGT: a critical approach. *Exp Clin Endocrinol Diabetes*. 2001;109:S86-S93.
14. Barzilay JI, Spiekerman CF, Wahl PW, et al. Cardiovascular disease in older adults with glucose disorders: comparison of American Diabetes Association criteria for diabetes mellitus with WHO criteria. *Lancet*. 1999;354:622-625.
15. DECODE Study Group. European Diabetes Epidemiology Group. Diabetes epidemiology: collaborative analysis of diagnostic criteria in Europe. Glucose tolerance and mortality: comparison of WHO and American Diabetes Association diagnostic criteria. *Lancet*. 1999;354:617-621.
16. Tominaga M, Eguchi H, Manaka H, et al. Impaired glucose tolerance is a risk factor for cardiovascular disease, but not impaired fasting glucose. The Funagata Diabetes Study. *Diabetes Care*. 1999;22:920-924.
17. Hu FB, Stampfer MJ, Haffner SM, et al. Elevated risk of cardiovascular disease prior to clinical diagnosis of type 2 diabetes. *Diabetes Care*. 2002;25:1129-1134.
18. Hauner H. Insulin resistance and the metabolic syndrome—a challenge of the new millennium. *Eur J Clin Nutr*. 2002;56:S25-S29.
19. World Health Organization (WHO). Definition, diagnosis and classification of diabetes mellitus and its complications. *Report of a WHO Consultation, Part 1: Diagnosis and Classification of Diabetes Mellitus*. Lyons: World Health Organization; 1999.
20. Ostgren CJ, Lindblad U, Ranstam J, et al. Skaraborg hypertension and diabetes project. Glycaemic control, disease duration and beta-cell function in patients with type 2 diabetes in a Swedish community. Skaraborg Hypertension and Diabetes Project. *Diabet Med*. 2002;19:125-129.
21. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults. *JAMA*. 2002;287:356-359.
22. American Diabetes Association. Clinical Practice Recommendations 2004. Prevention of type 1 diabetes. *Diabetes Care*. 2004;27:S133.
23. American Diabetes Association. Clinical Practice Recommendations 2004. Prevention or delay of type 2 diabetes. *Diabetes Care*. 2004;27:S47-S54.

24. Hellman R. Screening and diagnostic testing for diabetes and related conditions. ACE Diabetes Mellitus Consensus Conference. *Endocr Pract.* 2002;8(suppl 1):21-24.
25. Landin-Olsson M. Latent autoimmune diabetes in adults. *Ann NY Acad Sci.* 2002;958:112-116.
26. Foster DW. Diabetes Mellitus. In: Fauci AS, Braunwald E, Iffelbacher KJ, et al, eds. *Harrison's Principles of Internal Medicine*, 14th edition. New York: McGraw-Hill;1998:2060-2081.
27. Buchanan TA, Xiang AH, Peters RK, et al. Prevention of type 2 diabetes: the role of pancreatic B-cell rest. (Submitted for publication, 2003.)
28. Chiasson JL, Gomis R, Hanefeld M, et al. The STOP-NIDDM Trial: an international study on the efficacy of an alpha-glucosidase inhibitor to prevent type 2 diabetes in a population with impaired glucose tolerance: rationale, design, and preliminary screening data: Study to Prevent Non-Insulin Dependent Diabetes Mellitus. *Diabetes Care.* 1998;21:1720-1725.
29. Chiasson JL, Josse RG, Gomis R, et al, for the STOP-NIDDM Trial Research Group. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM Trial. *Lancet.* 2002;359:2072-2077.
30. Tuomilehto J, Lindstrom J, Eriksson JG, et al. Finnish Diabetes Prevention Study Group. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med.* 2001;344:1343-1350.
31. Pan XR, Li GW, Hu YH, et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. *Diabetes Care.* 1997;20:537-544.

