

Diagnosis and Classification of Diabetes Mellitus

AMERICAN DIABETES ASSOCIATION

DEFINITION AND DESCRIPTION OF DIABETES MELLITUS

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels.

Several pathogenic processes are involved in the development of diabetes. These range from autoimmune destruction of the β -cells of the pancreas with consequent insulin deficiency to abnormalities that result in resistance to insulin action. The basis of the abnormalities in carbohydrate, fat, and protein metabolism in diabetes is deficient action of insulin on target tissues. Deficient insulin action results from inadequate insulin secretion and/or diminished tissue responses to insulin at one or more points in the complex pathways of hormone action. Impairment of insulin secretion and defects in insulin action frequently coexist in the same patient, and it is often unclear which abnormality, if either alone, is the primary cause of the hyperglycemia.

Symptoms of marked hyperglycemia include polyuria, polydipsia, weight loss, sometimes with polyphagia, and blurred vision. Impairment of growth and susceptibility to certain infections may also accompany chronic hyperglycemia. Acute, life-threatening consequences of uncontrolled diabetes are hyperglycemia with ketoacidosis or the nonketotic hyperosmolar syndrome.

Long-term complications of diabetes include retinopathy with potential loss of vision; nephropathy leading to renal failure; peripheral neuropathy with risk of foot ulcers, amputations, and Charcot joints; and autonomic neuropathy causing gastrointes-

tinal, genitourinary, and cardiovascular symptoms and sexual dysfunction. Patients with diabetes have an increased incidence of atherosclerotic cardiovascular, peripheral arterial, and cerebrovascular disease. Hypertension and abnormalities of lipoprotein metabolism are often found in people with diabetes.

The vast majority of cases of diabetes fall into two broad etiopathogenetic categories (discussed in greater detail below). In one category, type 1 diabetes, the cause is an absolute deficiency of insulin secretion. Individuals at increased risk of developing this type of diabetes can often be identified by serological evidence of an autoimmune pathologic process occurring in the pancreatic islets and by genetic markers. In the other, much more prevalent category, type 2 diabetes, the cause is a combination of resistance to insulin action and an inadequate compensatory insulin secretory response. In the latter category, a degree of hyperglycemia sufficient to cause pathologic and functional changes in various target tissues, but without clinical symptoms, may be present for a long period of time before diabetes is detected. During this asymptomatic period, it is possible to demonstrate an abnormality in carbohydrate metabolism by measurement of plasma glucose in the fasting state or after a challenge with an oral glucose load.

The degree of hyperglycemia (if any) may change over time, depending on the extent of the underlying disease process (Fig. 1). A disease process may be present but may not have progressed far enough to cause hyperglycemia. The same disease process can cause impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) without fulfilling the criteria for the diagnosis of diabetes. In some individuals with diabetes, adequate glycemic control can be achieved with weight

reduction, exercise, and/or oral glucose-lowering agents. These individuals therefore do not require insulin. Other individuals who have some residual insulin secretion but require exogenous insulin for adequate glycemic control can survive without it. Individuals with extensive β -cell destruction and therefore no residual insulin secretion require insulin for survival. The severity of the metabolic abnormality can progress, regress, or stay the same. Thus, the degree of hyperglycemia reflects the severity of the underlying metabolic process and its treatment more than the nature of the process itself.

CLASSIFICATION OF DIABETES MELLITUS AND OTHER CATEGORIES OF GLUCOSE REGULATION

Assigning a type of diabetes to an individual often depends on the circumstances present at the time of diagnosis, and many diabetic individuals do not easily fit into a single class. For example, a person with gestational diabetes mellitus (GDM) may continue to be hyperglycemic after delivery and may be determined to have, in fact, type 2 diabetes. Alternatively, a person who acquires diabetes because of large doses of exogenous steroids may become normoglycemic once the glucocorticoids are discontinued, but then may develop diabetes many years later after recurrent episodes of pancreatitis. Another example would be a person treated with thiazides who develops diabetes years later. Because thiazides in themselves seldom cause severe hyperglycemia, such individuals probably have type 2 diabetes that is exacerbated by the drug. Thus, for the clinician and patient, it is less important to label the particular type of diabetes than it is to understand the pathogenesis of the hyperglycemia and to treat it effectively.

Type 1 diabetes (β -cell destruction, usually leading to absolute insulin deficiency)

Immune-mediated diabetes. This form of diabetes, which accounts for only 5–10% of those with diabetes, previously encompassed by the terms insulin-independent diabetes, type 1 diabetes, or juvenile-onset diabetes, results from a

The information that follows is based largely on the reports of the Expert Committee on the Diagnosis and Classification of Diabetes (*Diabetes Care* 20:1183–1197, 1997, and *Diabetes Care* 26:3160–3167, 2003).

Abbreviations: FPG, fasting plasma glucose; GAD, glutamic acid decarboxylase; GCT, glucose challenge test; GDM, gestational diabetes mellitus; HNF, hepatocyte nuclear factor; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; MODY, maturity-onset diabetes of the young; WHO, World Health Organization.

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ness such as infection. This form of diabetes frequently goes undiagnosed for many years because the hyperglycemia develops gradually and at earlier stages is often not severe enough for the patient to notice any of the classic symptoms of diabetes. Nevertheless, such patients are at increased risk of developing macrovascular and microvascular complications. Whereas patients with this form of diabetes may have insulin levels that appear normal or elevated, the higher blood glucose levels in these diabetic patients would be expected to result in even higher insulin values had their β -cell function been normal. Thus, insulin secretion is defective in these patients and insufficient to compensate for insulin resistance. Insulin resistance may improve with weight reduction and/or pharmacological treatment of hyperglycemia but is seldom restored to normal. The risk of developing this form of diabetes increases with age, obesity, and lack of physical activity. It occurs more frequently in women with prior GDM and in individuals with hypertension or dyslipidemia, and its frequency varies in different racial/ethnic subgroups. It is often associated with a strong genetic predisposition, more so than is the autoimmune form of type 1 diabetes. However, the genetics of this form of diabetes are complex and not clearly defined.

Other specific types of diabetes

Genetic defects of the β -cell. Several forms of diabetes are associated with monogenetic defects in β -cell function. These forms of diabetes are frequently characterized by onset of hyperglycemia at an early age (generally before age 25 years). They are referred to as maturity-onset diabetes of the young (MODY) and are characterized by impaired insulin secretion with minimal or no defects in insulin action. They are inherited in an autosomal dominant pattern. Abnormalities at six 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 . A second form is associated with mutations in the glucokinase gene on chromosome 7p 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 β -cell. Thus, glucokinase serves as the “glucose sensor” for the

β -cell. Because of defects in the glucokinase gene, increased plasma levels of glucose are necessary to elicit normal levels of insulin secretion. The less common forms result from mutations in other transcription factors, including HNF-4 α , HNF-1 β , insulin promoter factor (IPF)-1, and NeuroD1.

Point mutations in mitochondrial DNA have been found to be associated with diabetes mellitus and deafness. The most common mutation occurs at position 3243 in the tRNA leucine gene, leading to an A-to-G transition. 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.

Genetic abnormalities that result in the inability to convert proinsulin to insulin have been identified in a few families, and such traits are inherited in an autosomal dominant pattern. The resultant glucose intolerance is mild. Similarly, the production of mutant insulin molecules with resultant impaired receptor binding has also been identified in a few families and is associated with an autosomal inheritance and only mildly impaired or even normal glucose metabolism.

Genetic defects in insulin action.

There are unusual causes of diabetes that 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 diabetes. Some individuals with these mutations may have acanthosis nigricans. Women may be virilized and have enlarged, cystic ovaries. In the past, this syndrome was termed type A insulin resistance. Leprechaunism and the Rabson-Mendenhall syndrome are two pediatric syndromes that have mutations in the insulin receptor gene with subsequent alterations in insulin receptor function and extreme insulin resistance. The former has characteristic facial features and is usually fatal in infancy, while the latter is associated with abnormalities of teeth and nails and pineal gland hyperplasia.

Alterations in the structure and function of the insulin receptor cannot be demonstrated in patients with insulin-resistant lipotrophic diabetes. Therefore, it is assumed that the lesion(s) must reside in the postreceptor signal transduction pathways.

Diseases of the exocrine pancreas. Any process that diffusely injures the pancreas can cause diabetes. Acquired processes include pancreatitis, trauma, infection, pancreatectomy, and pancreatic carcinoma. With the exception of that caused by cancer, damage to the pancreas must be extensive for diabetes to occur; adenocarcinomas that involve only a small portion of the pancreas have been associated with diabetes. This implies a mechanism other than simple reduction in β -cell mass. If extensive enough, cystic fibrosis and hemochromatosis will also damage β -cells and impair insulin secretion. Fibrocalculous pancreatopathy may be accompanied by abdominal pain radiating to the back and pancreatic calcifications identified on X-ray examination. Pancreatic fibrosis and calcium stones in the exocrine ducts have been found at autopsy.

Endocrinopathies. Several hormones (e.g., growth hormone, cortisol, glucagon, epinephrine) antagonize insulin action. Excess amounts of these hormones (e.g., acromegaly, Cushing's syndrome, glucagonoma, pheochromocytoma, respectively) can cause diabetes. This generally occurs in individuals with preexisting defects in insulin secretion, and hyperglycemia typically resolves when the hormone excess is resolved.

Somatostatinoma- and aldosteronoma-induced hypokalemia can cause diabetes, at least in part, by inhibiting insulin secretion. Hyperglycemia generally resolves after successful removal of the tumor.

Drug- or chemical-induced diabetes.

Many drugs can impair insulin secretion. These drugs may not cause diabetes by themselves, but they may precipitate diabetes in individuals with insulin resistance. In such cases, the classification is unclear because the sequence or relative importance of β -cell dysfunction and insulin resistance is unknown. Certain toxins such as Vacor (a rat poison) and intravenous pentamidine can permanently destroy pancreatic β -cells. Such drug reactions fortunately are rare. There are also many drugs and hormones that can impair insulin action. Examples include nicotinic acid and glucocorticoids. Patients receiving α -interferon have been reported to develop diabetes associated with islet cell antibodies and, in certain instances, severe insulin deficiency. The list shown in Table 1 is not all-inclusive, but reflects the more commonly recog-

Table 1—Etiologic 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 12, HNF-1 α (MODY3)
2. Chromosome 7, glucokinase (MODY2)
3. Chromosome 20, HNF-4 α (MODY1)
4. Chromosome 13, insulin promoter factor-1 (IPF-1; MODY4)
5. Chromosome 17, HNF-1 β (MODY5)
6. Chromosome 2, <i>NeuroD1</i> (MODY6)
7. Mitochondrial DNA
8. Others
B. Genetic defects in insulin action
1. Type A insulin resistance
2. Leprechaunism
3. Rabson-Mendenhall syndrome
4. Lipotrophic diabetes
5. Others
C. Diseases of the exocrine pancreas
1. Pancreatitis
2. Trauma/pancreatectomy
3. Neoplasia
4. Cystic fibrosis
5. Hemochromatosis
6. Fibrocalculous pancreatopathy
7. Others
D. Endocrinopathies
1. Acromegaly
2. Cushing's syndrome
3. Glucagonoma
4. Pheochromocytoma
5. Hyperthyroidism
6. Somatostatinoma
7. Aldosteronoma
8. Others
E. Drug- or chemical-induced
1. Vacor
2. Pentamidine
3. Nicotinic acid
4. Glucocorticoids
5. Thyroid hormone
6. Diazoxide
7. β -adrenergic agonists
8. Thiazides
9. Dilantin
10. α -Interferon
11. Others
F. Infections
1. Congenital rubella
2. Cytomegalovirus
3. Others
G. Uncommon forms of immune-mediated diabetes
1. "Stiff-man" syndrome
2. Anti-insulin receptor antibodies
3. 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.

nized drug-, hormone-, or toxin-induced forms of diabetes.

Infections. Certain viruses have been associated with β -cell destruction. Diabetes occurs in patients with congenital rubella, although most of these patients have HLA and immune markers characteristic of type 1 diabetes. In addition, coxsackievirus B, cytomegalovirus, adenovirus, and mumps have been implicated in inducing certain cases of the disease.

Uncommon forms of immune-mediated diabetes. In this category, there are two known conditions, and others are likely to occur. The stiff-man syndrome is an autoimmune disorder of the central nervous system characterized by stiffness of the axial muscles with painful spasms. Patients usually have high titers of the GAD autoantibodies, and approximately one-third will develop diabetes.

Anti-insulin receptor antibodies can cause diabetes by binding to the insulin receptor, thereby blocking the binding of insulin to its receptor in target tissues. However, in some cases, these antibodies can act as an insulin agonist after binding to the receptor and can thereby cause hypoglycemia. Anti-insulin receptor antibodies are occasionally found in patients with systemic lupus erythematosus and other autoimmune diseases. 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 sometimes 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 β -cells at autopsy. Additional manifestations include diabetes insipidus, hypogonadism, optic atrophy, and neural deafness. Other syndromes are listed in Table 1.

Gestational diabetes mellitus (GDM)

GDM is defined as any degree of glucose intolerance with onset or first recognition during pregnancy. The definition applies regardless of whether insulin or only diet modification is used for treatment or whether the condition persists after pregnancy. It does not exclude the possibility that unrecognized glucose intolerance may

Table 2—Criteria for the diagnosis of diabetes mellitus

1. Symptoms of diabetes plus casual plasma glucose concentration ≥ 200 mg/dl (11.1 mmol/l). Casual is defined as any time of day without regard to time since last meal. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.
OR
2. FPG ≥ 126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h.
OR
3. 2-h postload glucose ≥ 200 mg/dl (11.1 mmol/l) during an OGTT. The test should be performed as described by WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.

In the absence of unequivocal hyperglycemia, these criteria should be confirmed by repeat testing on a different day. The third measure (OGTT) is not recommended for routine clinical use.

have antedated or begun concomitantly with the pregnancy. GDM complicates ~4% of all pregnancies in the U.S., resulting in ~135,000 cases annually. The prevalence may range from 1 to 14% of pregnancies, depending on the population studied. GDM represents nearly 90% of all pregnancies complicated by diabetes.

Deterioration of glucose tolerance occurs normally during pregnancy, particularly in the 3rd trimester.

Impaired glucose tolerance (IGT) and impaired fasting glucose (IFG)

The Expert Committee (1,2) recognized an intermediate group of subjects whose glucose levels, although not meeting criteria for diabetes, are nevertheless too high to be considered normal. This group is defined as having fasting plasma glucose (FPG) levels ≥ 100 mg/dl (5.6 mmol/l) but < 126 mg/dl (7.0 mmol/l) or 2-h values in the oral glucose tolerance test (OGTT) of ≥ 140 mg/dl (7.8 mmol/l) but < 200 mg/dl (11.1 mmol/l). Thus, the categories of FPG values are as follows:

- FPG < 100 mg/dl (5.6 mmol/l) = normal fasting glucose;
- FPG 100–125 mg/dl (5.6–6.9 mmol/l) = IFG (impaired fasting glucose);
- FPG ≥ 126 mg/dl (7.0 mmol/l) = provisional diagnosis of diabetes (the diagnosis must be confirmed, as described below).

The corresponding categories when the OGTT is used are the following:

- 2-h postload glucose < 140 mg/dl (7.8 mmol/l) = normal glucose tolerance;
- 2-h postload glucose 140–199 mg/dl (7.8–11.1 mmol/l) = IGT (impaired glucose tolerance);
- 2-h postload glucose ≥ 200 mg/dl (11.1 mmol/l) = provisional diagnosis of di-

abetes (the diagnosis must be confirmed, as described below).

Patients with IFG and/or IGT are now referred to as having “pre-diabetes” indicating the relatively high risk for development of diabetes in these patients. In the absence of pregnancy, IFG and IGT are not clinical entities in their own right but rather risk factors for future diabetes as well as cardiovascular disease. They can be observed as intermediate stages in any of the disease processes listed in Table 1. IFG and IGT are associated with the metabolic syndrome, which includes obesity (especially abdominal or visceral obesity), dyslipidemia of the high-triglyceride and/or low-HDL type, and hypertension. It is worth mentioning that medical nutrition therapy aimed at producing 5–10% loss of body weight, exercise, and certain pharmacological agents have been variably demonstrated to prevent or delay the development of diabetes in people with IGT; the potential impact of such interventions to reduce cardiovascular risk has not been examined to date.

Note that many individuals with IGT are euglycemic in their daily lives. Individuals with IFG or IGT may have normal or near normal glycated hemoglobin levels. Individuals with IGT often manifest hyperglycemia only when challenged with the oral glucose load used in the standardized OGTT.

DIAGNOSTIC CRITERIA FOR DIABETES MELLITUS

The criteria for the diagnosis of diabetes are shown in Table 2. Three ways to diagnose diabetes are possible, and each, in the absence of unequivocal hyperglycemia, must be confirmed, on a subsequent day, by any one of the three methods given in Table 2. The use of the hemoglobin A1c

(A1C) for the diagnosis of diabetes is not recommended at this time.

Diagnosis of GDM

The criteria for abnormal glucose tolerance in pregnancy are those of Carpenter and Coustan (3). Recommendations from the American Diabetes Association’s Fourth International Workshop-Conference on Gestational Diabetes Mellitus held in March 1997 support the use of the Carpenter/Coustan diagnostic criteria as well as the alternative use of a diagnostic 75-g 2-h OGTT. These criteria are summarized below.

Testing for gestational diabetes. Previous recommendations included screening for GDM performed in all pregnancies. However, there are certain factors that place women at lower risk for the development of glucose intolerance during pregnancy, and it is likely not cost-effective to screen such patients. Pregnant women who fulfill *all* of these criteria need not be screened for GDM.

This low-risk group comprises women who

- are < 25 years of age
- are a normal body weight
- have no family history (i.e., first-degree relative) of diabetes
- have no history of abnormal glucose metabolism
- have no history of poor obstetric outcome
- are not members of an ethnic/racial group with a high prevalence of diabetes (e.g., Hispanic American, Native American, Asian American, African American, Pacific Islander)

Risk assessment for GDM should be undertaken at the first prenatal visit. Women with clinical characteristics consistent with a high risk of GDM (marked obesity, personal history of GDM, glycosuria, or a strong family history of diabetes) should undergo glucose testing (see below) as soon as feasible. If they are found not to have GDM at that initial screening, they should be retested between 24 and 28 weeks of gestation. Women of average risk should have testing undertaken at 24–28 weeks of gestation.

A fasting plasma glucose level > 126 mg/dl (7.0 mmol/l) or a casual plasma glucose > 200 mg/dl (11.1 mmol/l) meets the threshold for the diagnosis of diabetes. In the absence of unequivocal hyperglycemia, the diagnosis must be

Table 3—Diagnosis of GDM with a 100-g or 75-g glucose load

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

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.

confirmed on a subsequent day. Confirmation of the diagnosis precludes the need for any glucose challenge. In the absence of this degree of hyperglycemia,

evaluation for GDM in women with average or high-risk characteristics should follow one of two approaches.

One-step approach. Perform a diagnostic OGTT without prior plasma or serum glucose screening. The one-step approach may be cost-effective in high-risk patients or populations (e.g., some Native-American groups).

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 used, a glucose threshold value >140 mg/dl (7.8 mmol/l) identifies $\sim 80\%$ of women with GDM, and the yield is further increased to 90% by using a cutoff of >130 mg/dl (7.2 mmol/l).

With either approach, the diagnosis of GDM is based on an OGTT. Diagnostic criteria for the 100-g OGTT are derived from the original work of O'Sullivan and

Mahan (4) modified by Carpenter and Coustan (3) and are shown in the top of Table 3. Alternatively, the diagnosis can be made using a 75-g glucose load and the glucose threshold values listed for fasting, 1 h, and 2 h (Table 2, bottom); however, this test is not as well validated as the 100-g OGTT.

References

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