
CLASSIFICATION OF DIABETES MELLITUS

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ABSTRACT

Diabetes is a heterogeneous, complex metabolic disorder characterized by elevated blood glucose concentrations secondary to either resistance to the action of insulin, insufficient insulin secretion, or both. The most common classifications include Type 1 diabetes mellitus, Type 2 diabetes mellitus, and gestational diabetes. Type 2 diabetes (T2DM) is characterized by insulin resistance and a relative deficiency of insulin secretion. The absolute plasma insulin concentration (both fasting and meal-stimulated) usually is increased, although "relative" to the severity of insulin resistance, the plasma insulin concentration is insufficient to maintain normal glucose homeostasis. Insulin secretion capacity progressively worsens over time in most patients with T2DM. Type 1 DM results in an absolute deficiency in beta-cell function in most. Autoimmune destruction of beta-cells is a common origin, though cases continue to be classified as idiopathic. Gestational diabetes mellitus (GDM) is defined as glucose intolerance which is first recognized during pregnancy. In most

women who develop GDM, the disorder has its onset in the third trimester of pregnancy and patients with GDM have a high risk of developing T2DM later in life. Other causes of diabetes include genetic disorders, diseases that cause damage to the pancreas, as well as an excess of certain hormones such as growth hormone and glucocorticoids. Diabetes mellitus may also be due to drugs, chemicals, or infections. Proper classification of the type of diabetes often helps determine appropriate therapy. For complete coverage of all related areas of Endocrinology, please visit our on-line FREE web-text, WWW.ENDOTEXT.ORG

CLASSIFICATION OF DIABETES (TABLE 1)

Diabetes is a heterogeneous complex metabolic disorder characterized by elevated blood glucose concentration secondary to either resistance to the action of insulin, insufficient insulin secretion, or both [

1]. The major clinical manifestation of the diabetic state is hyperglycemia. However, insulin deficiency and/or insulin resistance also are associated with abnormalities in lipid and protein metabolism, and with mineral and electrolyte disturbances. The vast majority of diabetic patients are classified into one of two broad categories: type 1 diabetes mellitus, which is caused by an absolute or near absolute deficiency of insulin, or type 2 diabetes mellitus, which is characterized by the presence of insulin resistance

with an inadequate compensatory increase in insulin secretion. In addition, women who develop diabetes during their pregnancy are classified as having gestational diabetes. Finally, there are a variety of uncommon and diverse types of diabetes, which are caused by infections, drugs, endocrinopathies, pancreatic destruction, and genetic defects. These unrelated forms of diabetes are included in the “Other Specific Types” and classified separately.

Table 1 lists the various disorders that can either cause or contribute to the development of diabetes and the Endotext chapters where these disorders are discussed in detail.

| Table 1. Etiologic Classification Of Diabetes Mellitus | |
|---|---|
| Disorders | Endotext Chapter |
| Type 1 Diabetes | Pathogenesis of Type 1A Diabetes |
| Type 2 Diabetes | Pathogenesis of Type 2 Diabetes |
| Gestational Diabetes | Gestational Diabetes |
| Genetic defects of beta-cell development and function | |
| MODY | Diagnosis and Clinical Management of Monogenic Diabetes |
| Neonatal Diabetes | Diagnosis and Clinical Management of Monogenic Diabetes |
| Mitochondrial DNA | Atypical Forms of Diabetes |
| Genetic defects in insulin action | |
| Type A insulin resistance | Atypical Forms of Diabetes |
| Leprechaunism | Atypical Forms of Diabetes |
| Rabson-Mendenhall syndrome | Atypical Forms of Diabetes |
| Lipoatrophic diabetes | Lipodystrophy Syndromes: Presentation and Treatment* |
| Diseases of the exocrine pancreas | |
| Pancreatitis | Atypical Forms of Diabetes |
| Trauma/pancreatectomy | Atypical Forms of Diabetes |
| Neoplasia | Atypical Forms of Diabetes |
| Cystic fibrosis | Atypical Forms of Diabetes |
| Iron overload (hemochromatosis, thalassemia, etc.) | Atypical Forms of Diabetes |
| Fibrocalculous pancreatic diabetes | Fibrocalculous Pancreatic Diabetes** |
| Endocrinopathies | |
| Acromegaly | Atypical Forms of Diabetes |

| | |
|---|---|
| Cushing's syndrome Glucagonoma Pheochromocytoma Hyperthyroidism Somatostatinoma Primary Hyperaldosteronism | |
| Diabetes Mellitus After Solid Organ Transplantation | Diabetes Mellitus After Solid Organ Transplantation |
| Drug- or chemical-induced hyperglycemia | |
| Vacor Pentamidine Nicotinic acid Glucocorticoids Growth Hormone Diazoxide Check point inhibitors Dilantin Interferon alpha Immune suppressants Others (statins, psychotropic drugs, b-Adrenergic agonists, thiazides, etc.) | Atypical Forms of Diabetes |
| Infections | |
| Congenital rubella | Atypical Forms of Diabetes |
| HCV | Atypical Forms of Diabetes |
| COVID-19 | Atypical Forms of Diabetes |
| HIV | Diabetes in People Living with HIV |
| Immune-mediated diabetes | |
| Latent Autoimmune Diabetes in Adults (LADA) | Atypical Forms of Diabetes |
| Stiff-man syndrome | Atypical Forms of Diabetes |
| Anti-insulin receptor antibodies | Atypical Forms of Diabetes |
| Autoimmune Polyglandular Syndromes | Autoimmune Polyglandular Syndromes*** |
| Diabetes of unknown cause | |
| Ketosis-prone diabetes (Flatbush diabetes) | Atypical Forms of Diabetes |
| Other genetic syndromes sometimes associated with diabetes | |
| Down syndrome Klinefelter syndrome Turner syndrome Wolfram syndrome Friedreich ataxia Huntington chorea | Atypical Forms of Diabetes |

| | |
|--|--|
| Bardet-Biedl syndrome (Laurence-Moon-Biedl syndrome) Myotonic dystrophy Porphyria Prader-Willi syndrome Alström syndrome Others | |
|--|--|

Unless indicated chapters are located in the

*Chapter in Diagnosis and Treatment of Diseases of Lipid and Lipoprotein Metabolism section

**Chapter in Tropical Medicine section

***Chapter in Disorders that Affect Multiple Organs section

TYPE 1 DIABETES MELLITUS

Type 1 diabetes results from autoimmune destruction of the pancreatic beta-cells [3, 4]. Markers of immune destruction of the beta-cell are present at the time of diagnosis in 90% of individuals and include antibodies to the islet cell (ICAs), to glutamic acid decarboxylase (GAD65), tyrosine phosphatases IA-2 and IA-2b, ZnT8, and insulin auto-antibodies (IAAs). Individuals may convert to negative if only one marker is positive, but individual risk of developing type 1 DM increases with the number of positive markers. Two positive antibodies are associated with a 75% chance of developing diabetes in the next 10 years [4a]. Diagnostic staging is now available for individuals with autoimmunity, even prior to diagnosis of type 1 DM. (Table 2) [4b]. While this form of diabetes usually occurs in children and adolescents, it can occur at any

age. Younger individuals typically have a rapid rate of beta-cell destruction and present with ketoacidosis, while adults often maintain sufficient insulin secretion to prevent ketoacidosis for many years [5]. The more indolent adult-onset variety has been referred to as latent autoimmune diabetes in adults (LADA). There is still controversy whether adult type 1 DM and LADA are the same clinical entity, but LADA patients are antibody positive and often require insulin therapy within years of diagnosis. Idiopathic forms of type 1 DM often are of African or Asian descent. An intermittent risk of diabetic ketoacidosis, based on their varying insulinopenia, is present [4a]. Eventually, all type 1 diabetic patients will require insulin therapy to maintain normoglycemia. For additional information see the chapters that discuss in detail the pathogenesis of type 1 diabetes [5a, 5b].

| | Stage 1 | Stage 2 | Stage 3 |
|-----------------------------------|---|--|--|
| Phenotypic characteristics | -Autoimmunity -Normoglycemia -Presymptomatic | -Automimmunity -Dysglycemia -Presymptomatic | -New onset Hyperglycemia -Symptomatic |
| Diagnostic criteria | -2 or more islet autoantibodies -No impaired glucose tolerance or impaired fasting glucose | -2 or more islet autoantibodies -Dysglycemia: impaired fasting glucose and/or impaired glucose tolerance: FPG 100-125mg/dl and/or 2-hour plasma glucose 140-199mg/dl A1C 5.7-6.4% or a ≥10% increase in A1C | -Clinical symptoms -Diabetes by standard criteria |

TYPE 2 DIABETES MELLITUS

Type 2 diabetes is characterized by insulin resistance and, at least initially, a relative deficiency of insulin secretion [6, 7]. In absolute terms, the plasma insulin concentration (both fasting and meal-stimulated) usually is increased, although "relative" to the severity of insulin resistance, the plasma insulin concentration is insufficient to maintain normal glucose homeostasis [8, 9]. With time, however, there is progressive beta cell failure and worsening insulin deficiency ensues. Recently, more sophisticated analyses of the beta-cell response and regulation revealed that most subjects at risk for developing type 2 diabetes, i.e. those with combined impaired fasting glucose and impaired

glucose tolerance already have a significant loss, close to 80% of the total insulin secretory capacity of the pancreas [10]. In a minority of type 2 diabetic individuals, severe insulinopenia is present at the time of diagnosis and insulin sensitivity is normal or near normal [11] . Most individuals with type 2 diabetes exhibit intra-abdominal (visceral) obesity [12], which is part of the "ectopic fat" deposition pattern closely related to the presence of insulin resistance [13] . In addition, hypertension, dyslipidemia (high triglyceride and low HDL-cholesterol levels; postprandial hyperlipemia), vascular endothelial dysfunction [14] and elevated PAI-1 levels often are present in these individuals. This clustering of abnormalities is referred to as the "insulin resistance syndrome" or the

"metabolic syndrome" [15, 16] . Because of these abnormalities, patients with type 2 diabetes are at increased risk of developing atherosclerotic cardiovascular disease (ASCVD) with macrovascular complications (myocardial infarction and stroke). Type 2 diabetes has a strong genetic predisposition and is more common in minority ethnic groups, e.g. Mexican-Americans, Latinos, African Americans, American Indians, Pacific Islanders, than in individuals of European ancestry. The genetic cause(s) of the common variety of type 2 diabetes is (are) not well defined. A large number of genes have been associated with type 2 DM, but they explain a low percentage of the disease heritability. [4a, 17, 18] . For additional information see the chapter that discusses in detail the pathogenesis of type 2 diabetes [18a].

GESTATIONAL DIABETES MELLITUS (GDM)

Gestational diabetes mellitus (GDM) is defined as glucose intolerance which is first recognized during pregnancy. In most women who develop GDM, the disorder has its onset in the third trimester of pregnancy. At least 6 weeks after the pregnancy ends, the woman should receive an oral glucose tolerance test and be reclassified as having diabetes, normal glucose tolerance, impaired glucose tolerance, or impaired fasting glucose. Gestational diabetes complicates about 8-9% of all pregnancies, though the rates may double in populations at high-risk for type 2 diabetes [19] . Clinical detection is important, since therapy will reduce perinatal morbidity and mortality. Dysglycemia risk in GDM is a continuum, and risk

assessment for GDM should occur at the first prenatal visit. Two groups, the International Association of Diabetes and Pregnancy Study Groups (IADPSG) and the National Institutes of Health (NIH) Consensus Group recommend different testing methods for the diagnosis of GDM. A large-scale (~25,000 pregnant women) multinational epidemiologic study [20] demonstrated that risk of adverse maternal and neonatal outcomes continuously increased as a function of maternal glycemia at 24-28 weeks, even within ranges previously considered normal for pregnancy. These observations led to a revision in the diagnostic criteria recommended by IADPSG for GDM using a "one-step" 75-gram OGTT [1, 20]. A NIH Consensus Development Conference, using the same data, continues to recommend the "two-step" approach to diagnosis. The stated reason was the lack of interventional trials to prove the new criteria could decrease poor outcomes, as it was observational [1, 21]. The two criteria for diagnoses of GDM are summarized in Table 3. The Carpenter Coustan values are lower because they are corrected to account for assays currently in use. All women not known to have diabetes should undergo glucose test screening between weeks 24 and 28 using the "one step" 75 grams of glucose load in the morning after an overnight fasting period of at least 8 hours or the "two-step" method which starts with a non-fasting 50 gram glucose load test (GLT). A fasting 100-gram glucose tolerance test is only performed if the screening 50 gram GLT 1-hour plasma glucose value is ≥ 140 mg/dl (7.8 mmol/L). For additional information see the chapter on Diabetes in Pregnancy [21a].

Table 3-Diagnosis of GDM [1]**“One- Step” Diagnosis- 75 gram glucose tolerance test (IADPSG Consensus)**

| TIME | PLASMA GLUCOSE* |
|---------|-------------------------|
| Fasting | ≥92 mg/dl (5.1 mmol/L) |
| 1-hour | ≥180 mg/dl (10.0mmol/L) |
| 2-hour | ≥153 mg/dl (8.5 mmol/L) |

“Two-Step” Diagnosis- (NIH Consensus)

Step 1: Perform 50 gram glucose load test (nonfasting)

| TIME | PLASMA GLUCOSE |
|--------|-------------------------|
| 1-hour | ≥140 mg/dl (7.8 mmol/L) |

IF POSITIVE, STEP 2: 100 gram glucose tolerance test

| Carpenter/Coustan | | NDDG | |
|-------------------|-----------------------------|---------|-----------------------------|
| TIME | PLASMA GLUCOSE ⁺ | TIME | PLASMA GLUCOSE ⁺ |
| Fasting | ≥95 mg/dl (5.3 mmol/L) | Fasting | ≥105 mg/dl (5.8 mmol/L) |
| 1-hour | ≥180 mg/dl (10.0 mmol/L) | 1-hour | ≥190 mg/dl (10.6 mmol/L) |
| 2-hour | ≥155 mg/dl (8.6 mmol/L) | 2-hour | ≥165 mg/dl (9.2 mmol/L) |
| 3-hour | ≥140 mg/dl (7.8 mmol/L) | 3-hour | ≥145 mg/dl (8.0 mmol/L) |

*One abnormal value is sufficient to make the diagnosis of GDM. The test should be done in the morning after at least 8 hour fast. ⁺Two abnormal values establishes the diagnosis of GDM. NDDG=National Diabetes Data Group.

SPECIFIC TYPES OF DIABETES**Genetic Defects**

Maturity Onset Diabetes of the Young (MODY) is characterized by impaired insulin secretion with minimal or no insulin resistance [2]. MODY can be subtyped into neonatal and MODY-like. Neonatal diabetes usually has an onset in the first 6 months of life and can be transient or permanent [2, 22]. MODY may affect genes important for beta-cell glucose sensing, development, function, and regulation [2]. Genetic inability to convert proinsulin to insulin results

in mild hyperglycemia [23]. Similarly, the production of mutant insulin molecules has been identified in a few families and results in mild glucose intolerance [24]. MODY5 is most often associated with renal cysts and was not listed on the most recent ADA classification of diabetes, but can rarely cause diabetes [1,2]. The natural history of MODY is highly dependent on the underlying genetic defect and most typically exhibit mild hyperglycemia at an early age. The disease is inherited in an autosomal dominant pattern.

Several genetic mutations have been described in the insulin receptor and are associated with insulin resistance [25]. Type A insulin resistance refers to the clinical syndrome of acanthosis nigricans, virilization in women, polycystic ovaries, and hyperinsulinemia [26]. Leprechaunism is a pediatric syndrome with specific facial features and severe insulin resistance that results from a defect in the insulin receptor [27,28]. Lipoatrophic diabetes results from postreceptor defects in insulin signaling [29] .

A variety of genetic syndromes have been described in which diabetes mellitus occurs with increased frequency. The etiology of the disturbance in glucose homeostasis in these diverse and seemingly unrelated syndromes remains undefined.

Diseases of the Exocrine Pancreas

Damage of the pancreas must be extensive for diabetes to occur [30]. The most common causes are pancreatitis, trauma, and carcinoma. Chronic pancreatitis can cause general inflammatory/fibrotic changes in the pancreas which can cause diabetes. Cystic fibrosis causes a well-recognized pancreatic exocrine function insufficiency, but the same thick, viscous secretions cause inflammation, obstruction, and destruction of small ducts in the pancreas, which can lead to insulin deficiency. Hemochromatosis has also been associated with impaired insulin secretion and diabetes.

Endocrinopathies

Since growth hormone, cortisol, glucagon, and epinephrine increase hepatic glucose production and induce insulin resistance in peripheral (muscle) tissues, excess production of these hormones can cause or exacerbate underlying diabetes [31, 32, 33]

. Although the primary mechanism of action of these counter regulatory hormones is the induction of insulin resistance in muscle and liver, overt diabetes mellitus does not develop in the absence of beta cell failure.

Infections

A variety of infections have been etiologically related to the development of diabetes mellitus. Of these, the most clearly established is congenital rubella [34] . Approximately 20% of infants who are infected with the rubella virus at birth develop autoimmune type 1 diabetes later in life. These individuals have the typical type 1 susceptibility genotype, DR3/DR4.

Drugs

A large number of commonly used drugs have been shown to induce insulin resistance and/or impair beta cell function and can lead to the development of diabetes mellitus in susceptible individuals. An extensive review of these drugs and their mechanism of action has been published [35,36]. Drug classes which have been extensively associated with elevating glucose levels include: beta-blockers, thiazide diuretics, fluoroquinolones, atypical or second generation anti-psychotics, calcineurin inhibitors, protease inhibitors, nicotinic acid, and corticosteroids. In addition, HMG-CoA reductase inhibitors (statins) have been shown to cause a small increase in the risk of diabetes, though the exact mechanisms of how it may increase the risk of diabetes are not completely understood [37].

For additional information on these unusual etiologies of diabetes see the chapter on Atypical Forms of Diabetes and Diabetes Mellitus After Solid Organ Transplantation [37a, 37b].

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