

Diagnosis, Classification, and Pathogenesis of Diabetes Mellitus

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Diabetes mellitus is a metabolic disorder that is characterized by inappropriate hyperglycemia and is associated with both acute and chronic complications. Currently, diabetes mellitus is diagnosed by blood or plasma glucose levels. A random plasma glucose level ≥ 200 mg/dL in an individual with classic symptoms is sufficient to make the diagnosis. Otherwise, a fasting plasma glucose level ≥ 126 mg/dL or a 2-hour plasma glucose level ≥ 200 mg/dL after an oral glucose challenge of 75 g on 2 occasions is sufficient evidence upon which to diagnose diabetes mellitus. The major types of diabetes mellitus are type 1 diabetes (insulin deficient) and type 2 diabetes (combination of insulin resistance and insulin deficiency). In both types, there is a genetic predisposition as well as environmental factors that contribute to the expression of the genetic predisposition. In type 1 diabetes, the primary abnormality is extensive deficiency of beta cell function. In type 2 diabetes, insulin resistance occurs, and the marked compensatory increases in insulin secretion necessary to maintain normal glucose tolerance cannot be achieved or maintained. As beta cell function continues to decrease, the individual progresses from normal glucose tolerance to impaired glucose tolerance to diabetes with primarily postprandial hyperglycemia to diabetes with fasting hyperglycemia. Drugs can cause diabetes by interfering with beta cell insulin secretion, by increasing insulin resistance, or by a combination of both. Atypical antipsychotic drugs have been reported to cause diabetic ketoacidosis, obesity and insulin resistance, type 2 diabetes, and hypertriglyceridemia. A monitoring system should be in place in patients started on treatment with these agents to detect metabolic abnormalities as they are evolving so that adequate and timely treatment can be initiated.

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DIAGNOSIS OF DIABETES MELLITUS

The distribution of blood glucose levels in most populations takes the form of a skewed normal distribution with the skew toward the higher range. This is shown schematically in Figure 1.¹ When a variable does not have a normal distribution, the delineation of abnormal from normal becomes arbitrary. The problem of determining what blood or plasma glucose level is abnormal enough to warrant the diagnosis of diabetes mellitus has always been a dilemma and has undergone a number of changes over the last 40 to 50 years. In 1979, the National Diabetes Data Group convened a meeting to address this issue.¹ They decided that the blood or plasma glucose level that would predict the development of chronic diabetic complications should define diabetes mellitus. The most common and

most closely correlated complication with hyperglycemia known at that time was diabetic retinopathy. Several population-based epidemiologic studies in the 1960s and 1970s had shown that a plasma glucose value ≥ 200 mg/dL 2 hours after a 50-g oral glucose load was associated with the development of diabetic retinopathy.² The committee decided that the gold standard for defining diabetes mellitus should be a 2-hour post glucose challenge plasma glucose level ≥ 200 mg/dL and that the comparable fasting plasma glucose level would be 140 mg/dL.¹ Over the subsequent years, it was observed that a fasting plasma glucose level ≥ 140 mg/dL had very high specificity (100%) but relatively low sensitivity (31%).³

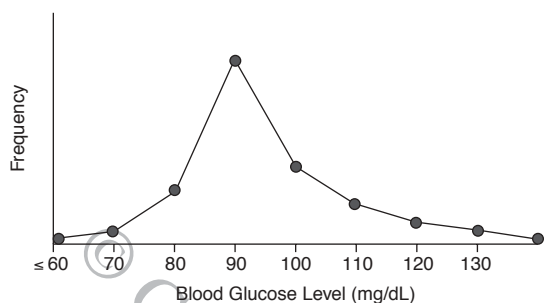
In 1997, the American Diabetes Association convened an Expert Committee to revisit the issues concerning the diagnosis and classification of diabetes mellitus, taking into consideration the extensive new data available since 1979.⁴ That committee had the opportunity to review several large epidemiologic studies that had compared the predictive values of fasting plasma glucose, 2-hour post oral glucose challenge plasma glucose, and hemoglobin A_{1c} for future development of diabetic retinopathy. Figure 2 shows the data from one of those studies.⁴ The conclusions of the deliberations of that committee established the new guidelines for the diagnosis of diabetes mellitus, listed in

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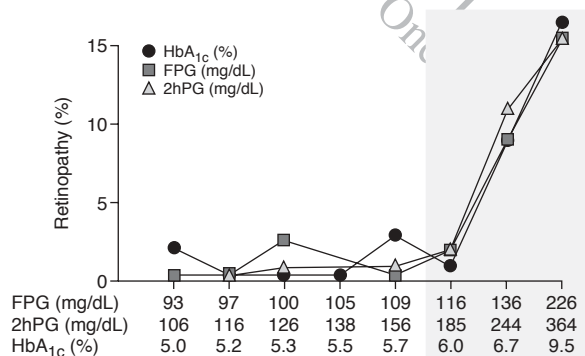
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Figure 1. Schematic Representation of the Distribution of Fasting Blood Glucose Levels in a Population^a



^aAll populations with a low-to-moderate prevalence of diabetes mellitus have a distribution of fasting blood glucose levels that are skewed toward the higher range.

Figure 2. The Prevalence of Diabetic Retinopathy in Pima Indians Determined by Deciles of Fasting (FPG) and 2-Hour Post Oral Glucose Challenge Plasma Glucose (2hPG) and Hemoglobin A_{1c} (HbA_{1c}) Levels in a Prospective Study^a



^aReprinted with permission from reference 4. Retinopathy is predicted by the fasting plasma glucose decile between 116 and 136 mg/dL, the 2-hour plasma glucose decile between 185 and 244 mg/dL, and the HbA_{1c} decile between 6.0% and 6.7%.

Table 1.⁴ The current guidelines maintain the 2-hour post 75-g oral glucose load plasma glucose level ≥ 200 mg/dL as the gold standard for the diagnosis of diabetes mellitus. They do, however, recognize that a fasting plasma glucose level ≥ 126 mg/dL is a valid diagnostic criterion that is significantly more sensitive in identifying individuals with diabetes and almost as specific as the previous value (≥ 140 mg/dL). The current guidelines recommend the use of fasting plasma glucose level for diagnosis in most patients because of its ease of performance, but do indicate that high-risk patients frequently benefit from 2-hour post oral glucose challenge plasma glucose determinations for early diagnosis of diabetes mellitus. It was recognized that an elevated hemoglobin A_{1c} level is indicative of diabetes mellitus, but the overlap between the upper limit of the normal range and the diabetic range and the lack of a standardized assay limit its value as a diagnostic test for diabe-

Table 1. 1997 American Diabetes Association Criteria for Diagnosis of Diabetes Mellitus From the American Diabetes Association^a

Symptoms plus casual plasma glucose level ≥ 200 mg/dL (11.1 mmol/L)
Fasting plasma glucose level ≥ 126 mg/dL (7.0 mmol/L)
2-h plasma glucose level ≥ 200 mg/dL (11.1 mmol/L) post 75-g oral glucose load

^aBased on reference 4.

Table 2. New Diagnostic Criteria for Classes of Glucose Intolerance^a

Class	FPG (mg/dL)	2hPG (mg/dL)
Normal	< 110	< 140
Impaired glucose tolerance		≥ 140 and < 200
Impaired fasting glucose	≥ 110 and < 126	
Diabetes	≥ 126	≥ 200

^aBased on reference 4. Abbreviations: FPG = fasting plasma glucose level, 2hPG = 2-hour post 75-g oral glucose load plasma glucose level.

Table 3. 1997 American Diabetes Association Etiologic Classification of Diabetes Mellitus^a

Type 1 diabetes (beta cell destruction)
Immune mediated
Idiopathic
Type 2 diabetes (insulin resistance and/or relative insulin deficiency)
Other types
Genetic defects
Diseases of exocrine pancreas
Endocrinopathies
Drug- or chemical-induced
Infections
Uncommon forms
Other genetic syndromes
Gestational diabetes

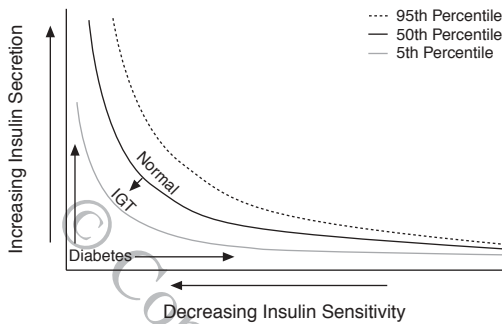
^aBased on reference 4.

tes mellitus. The new diagnostic criteria maintain the category of impaired glucose tolerance as a risk factor for the development of both diabetes and cardiovascular disease (Table 2). Impaired fasting plasma glucose (see Table 2) is a new category of glucose intolerance that was introduced. It has been somewhat confusing, and its usefulness is being evaluated.⁵

CLASSIFICATION OF DIABETES MELLITUS

The new classification of diabetes mellitus that was established by the Expert Committee in 1997 is based on etiology.⁴ The categories of diabetes mellitus are listed in Table 3. The 2 major categories are type 1 and type 2 diabetes. In both types we have considerable knowledge about the pathophysiology, but the exact genetic and etiologic bases of the disorders are not known. Type 1 diabetes is characterized by almost total loss of beta cell insulin secretory function. The absence of insulin leads to ketoacidosis and death if untreated with exogenous insulin. The

Figure 3. The Hyperbolic Relationship Between Decreasing Insulin Sensitivity and Increasing Insulin Secretion That Maintains Normal Glucose Tolerance^a



^aAdapted from Kahn et al.⁹ Abbreviation: IGT = impaired glucose tolerance.

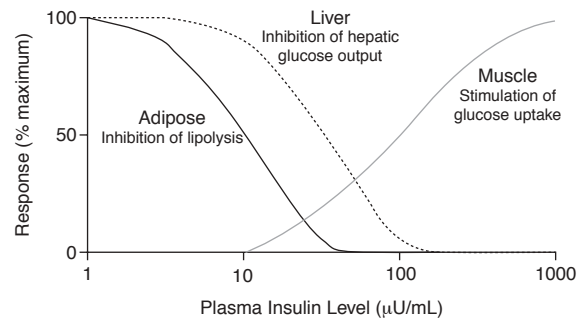
most common form of type 1 diabetes is an autoimmune disease in which the beta cells are selectively destroyed. It can be detected by the identification of anti-islet and GAD₆₅ antibodies. A small number of patients have been described who have a non-autoimmune loss of beta cell function. Type 2 diabetes is a heterogeneous genetic disorder, which can have varying degrees of insulin resistance and beta cell insulin secretory deficiency. It comprises approximately 85% of individuals with diabetes mellitus, but maybe as high as 95% to 98% in non-Caucasian populations. The development of the clinical disease is highly correlated with the appearance of central obesity and decreased physical activity. The “Other” category of diabetes mellitus includes all of the less common forms for which we know the specific gene abnormality or specific etiologic agent (see Table 3). Gestational diabetes is diabetes mellitus that develops during pregnancy. It usually occurs in the third trimester, is associated with the normal development of insulin resistance in the third trimester, and most often disappears postpartum only to reappear several years later as permanent diabetes.

PATHOGENESIS OF DIABETES

Two pathophysiologic processes can lead to the development of diabetes mellitus. The first and most important is a deficiency of insulin secretion.⁶ The second is an impairment of insulin action (insulin resistance), which should normally lead to a compensatory increase in insulin secretion (hyperinsulinemia).⁷ Insulin resistance can occur from genetic abnormalities or environmental factors or a combination of both.

Hyperglycemia occurs when insulin secretion is inadequate for the insulin requirements of the insulin-sensitive tissues.⁸ Figure 3 illustrates this relationship. For an individual's glucose tolerance to remain normal, insulin secretion must increase if insulin sensitivity decreases.⁹ If

Figure 4. The Different Concentration-Effect Relationships of Insulin Action in the 3 Major Insulin-Sensitive Tissues^a



^aThe most insulin is required to regulate muscle glucose uptake and metabolism and the least is required to regulate adipose tissue lipolysis.

insulin secretion falls below the fifth percentile for normally glucose-tolerant individuals for the specific level of insulin resistance, the individual will develop hyperglycemia. In individuals with normal insulin sensitivity, diabetes will occur only if there is a severe absolute deficiency of insulin (type 1 diabetes). In contrast, when insulin resistance is present, diabetes can occur even though there is moderate, though physiologically insufficient, insulin secretion.

Insulin is responsible for regulating glucose, lipid, and protein metabolism. The major tissues involved in the regulation of intermediary metabolism by insulin are skeletal muscle, liver, and adipose tissue. The effect of insulin on each of these 3 tissues follows a different dose-response curve (Figure 4), which accounts for different clinical presentations when in vivo insulin deficiency increases from moderate to marked to severe. Muscle glucose uptake requires high concentrations of insulin such as those that occur postprandially (Figure 4). Regulation of hepatic glucose production occurs in the range of fasting to slightly higher plasma insulin levels. The suppression of lipolysis in adipose tissue requires very low concentrations of insulin as shown in Figure 4. The clinical consequence of these different dose-response relationships is that the earliest abnormality of insulin insufficiency is postprandial hyperglycemia due to impaired postprandial muscle glucose uptake. Increasing insulin insufficiency then causes fasting hyperglycemia due to impaired suppression of hepatic glucose production. Severe insulin insufficiency results in excessive lipolysis, exaggerated ketone body production from beta oxidation of the free fatty acids by the liver, and the development of diabetic ketoacidosis.

Type 2 diabetes is a polygenic disorder in which individuals inherit a cluster of genes that confer a susceptibility to develop diabetes.² The development of type 2 diabetes requires an interaction between the genetic

Figure 5. The Interaction of Genetic and Environmental Factors in the Pathogenesis of Type 2 Diabetes

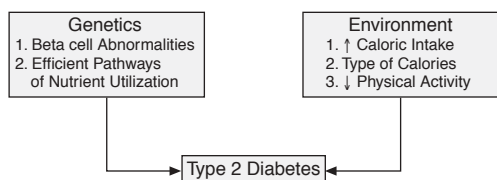
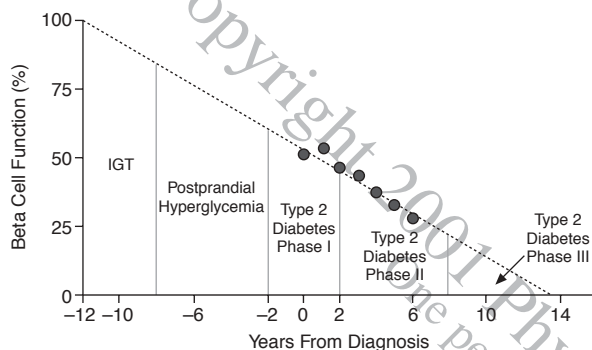


Figure 6. Stages of Type 2 Diabetes^a



^aReprinted with permission from Lebovitz.¹³ Abbreviation: IGT = impaired glucose tolerance. The evolution of glucose intolerance from normal to type 2 diabetes is primarily due to progressive deterioration of beta cell insulin secretory function. The various stages of glucose intolerance are related to the degree of loss of beta cell function.

background and environmental factors (Figure 5). The environmental factors that bring out the clinical disease are nutritional and physical activity. Excess calorie intake, high fat ingestion, and decreased physical activity lead to obesity and insulin resistance.⁷ Insulin resistance in an individual with inadequate beta cell insulin secretory reserve leads to the development of hyperglycemia and type 2 diabetes. Insulin resistance occurs with the development of upper-body (central or visceral) obesity and not lower body or generalized obesity.^{10,11} The regulation of the different adipose tissue depots is genetically determined, and visceral adipose tissue has many characteristics that differ from subcutaneous adipose tissue and are responsible for the unique effect of this adipose tissue pool on insulin action.¹² The accumulation of relatively small amounts (2 to 3 kg [4.4 to 6.7 lb]) of visceral adipose tissue is sufficient to cause insulin resistance.

The natural history of type 2 diabetes starts with the development of insulin resistance in an individual with the genetic predisposition to develop diabetes. This may occur any time from childhood on. The initial response to insulin resistance is a compensatory hyperinsulinemia (see Figure 3) sufficient to overcome the insulin resistance and maintain normal glucose tolerance. After some period of time,

Table 4. Components of the Metabolic Syndrome^a

Insulin resistance
Hyperinsulinemia
Central obesity
Dyslipidemia (↑ triglycerides; ↓ high-density lipoprotein cholesterol)
Hypertension
Procoagulant state
Endothelial dysfunction
Hyperuricemia
Microalbuminuria

^aBased on Lebovitz.¹⁵

which varies from individual to individual, beta cell function begins to deteriorate because of genetically determined abnormalities (Figure 6), and as the compensatory hyperinsulinemia decreases, postprandial plasma glucose levels rise progressively. The individual progresses from normal glucose tolerance to impaired glucose tolerance to type 2 diabetes with primarily postprandial hyperglycemia. At the time of clinical diagnosis, when individuals have fasting hyperglycemia and symptoms of diabetes, beta cell function is reduced to about 50% of normal.¹⁴ With increasing duration of diabetes, beta cell function continues to deteriorate, and many patients become sufficiently insulin deficient that they need exogenous insulin as part of their treatment. Insulin resistance changes very little during the evolution from normal glucose tolerance to diabetes. Persistent marked hyperglycemia causes glucose toxicity, which itself makes the beta cell insufficiency worse and also increases insulin resistance by a modest amount.

In summary, insulin resistance places the beta cell under stress. A stressed beta cell that is genetically predisposed undergoes progressive loss of insulin secretory function and causes the development of type 2 diabetes. Untreated or poorly treated hyperglycemia leads to glucose toxicity, which worsens the hyperglycemia.

Insulin resistance itself is associated with a cluster of metabolic abnormalities independent of whether the individual develops type 2 diabetes or not. This metabolic cluster, which is listed in Table 4, is known as the “insulin resistance syndrome” or the “metabolic disease syndrome” and is associated with an increased risk for cardiovascular disease in general and coronary heart disease in particular.⁷

MECHANISMS BY WHICH DRUGS CAN CAUSE DIABETES MELLITUS

It is apparent from the discussion above that drugs can cause diabetes mellitus through 1 of 2 mechanisms. If a drug either destroys beta cells or impairs insulin secretion, it can cause diabetes in any healthy individual and more easily in those who have genetically abnormal beta cells. This mechanism could cause a diabetic phenotype such as type 1 diabetes or, in a less severe case, type 2 diabetes.

Table 5. Mechanisms by Which Drugs Can Cause Insulin Resistance

Increase appetite and calorie intake
 Change the distribution of body fat
 Decrease physical activity
 Decrease oxidative metabolism in tissues
 Interfere with the insulin action cascade
 Increase counterregulatory hormones
 Increase free fatty acid release from adipose tissue

Table 6. Monitoring Susceptible Patients Who Are Taking Atypical Antipsychotic Medications

1. Check body weight periodically
2. Obtain baseline fasting plasma glucose and lipid profile
3. Repeat the baseline measurements at 6 weeks and the fasting plasma glucose every 3 months thereafter
4. Rising or abnormal values of blood glucose or plasma lipids are indications for medical consultation and an oral glucose tolerance test
5. Weight gain should initiate meaningful dietary intervention
6. Be alert to the possibility of diabetic ketoacidosis

If a drug causes insulin resistance by inducing visceral obesity or by any other mechanism listed in Table 5, it would precipitate type 2 diabetes only in those who have genetically predisposed beta cells. It is possible that some of the atypical antipsychotic drugs can cause diabetes by a combination of both mechanisms.

In the event that drugs such as the atypical antipsychotics are known to increase the risk of individuals' developing diabetic ketoacidosis, type 2 diabetes, or hypertriglyceridemia with its risk of acute pancreatitis, a surveillance program such as that listed in Table 6 might be instituted. This would identify the potential for these complications early in treatment in order to institute appropriate preventative or treatment measures.

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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