CHAPTER 1
Classification of diabetes mellitus and other categories of glucose intolerance

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Key points
- The classification and diagnosis of diabetes is based on etiology and not on pharmacologic treatment.
- Diagnoses of diabetes are made using fasting plasma glucose, 2-hour postchallenge of glucose or HbA1c.
- Differentiation between type 1 and type 2 diabetes is usually straightforward but can be difficult among obese children and adults.
- Precise diagnoses of certain monogenic diabetes using genetic testing can be useful as the outcomes can influence treatment decisions.
- A range of commonly used drugs such as statins and glucocorticoid steroids can lead to the development of diabetes.

Historical perspective and current classifications

Previous classifications
In 1965, an Expert Committee on Diabetes Mellitus published the first World Health Organization (WHO) report on diabetes classification [1]. The report includes one of the first attempts at international consensus on a classification. They decided to classify diabetes: “… based on the age of recognized onset, which seemed to be the only reliable means of classification for universal use.”

The report also recognized certain specific types of diabetes including brittle, insulin-resistant, gestational, pancreatic, endocrine, and iatrogenic diabetes. Since then, several pathogenic mechanisms have been described and long-term studies have shown different courses and outcomes of different types of diabetes.

A revised classification of glucose intolerance, was formulated by the National Diabetes Data Group (NDDG) [2]. This was amended and adopted in the second report of the WHO Expert Committee in 1980 [3] and in a modified form in 1985. The 1980 Expert Committee proposed two major classes of diabetes mellitus and named them insulin-dependent diabetes mellitus (IDDM) or type 1, and non-insulin-dependent diabetes mellitus (NIDDM) or type 2 [3]. In the 1985 Study Group Report, the terms type 1 and type 2 were omitted, but the classes IDDM and NIDDM were retained and a new class of malnutrition-related diabetes mellitus (MRDM) was introduced [4]. The 1985 WHO classification was essentially based on clinical descriptions, with a specific focus on the pharmacologic management of patients (i.e., insulin-dependent, non-insulin-dependent, gestational). The question as to whether certain clinical forms

Introduction

A critical requirement for orderly epidemiologic, genetic and clinical research, and indeed for the management of diabetes mellitus and other forms of glucose intolerance is an appropriate classification system. Furthermore, a hallmark in the process of understanding the etiology of a disease and studying its natural history is the ability to identify and differentiate its various forms and place them into a rational etiopathologic framework. While there have been a number of sets of nomenclature and diagnostic criteria proposed for diabetes, no systematic categorization existed until the mid 1960s [1]. Now diabetes mellitus is recognized as being a syndrome, a collection of disorders that have hyperglycemia and glucose intolerance as their hallmark, due either to insulin deficiency or to impaired effectiveness of insulin’s action, or to a combination of these.
of diabetes (such as the so-called “tropical diabetes”) had been given adequate priority to correct hierarchic order that was raised many years before probably led to the introduction of MRDM, although more precise epidemiologic data and a better assessment were needed, and called for.

Both the 1980 and 1985 reports included other types of diabetes and impaired glucose tolerance (IGT) as well as gestational diabetes mellitus (GDM). The 1985 classification was widely accepted and used internationally, and represented a compromise between clinical and etiological classifications. Furthermore, it permitted classification of individual patients in a clinically useful manner even when the specific etiology was unknown. The 2011 American Diabetes Association (ADA) [5] classifications or staging of diabetes still include clinical descriptive criteria but a complementary classification according to etiology is recommended by both organizations.

In 1999, the WHO incorporated an approach developed by Kuzuya and Matsuda [6], which clearly separated the criteria related to etiology from those related to the degree of deficiency of insulin or insulin action, and defined each patient on the basis of these two sets of criteria (Figure 1.1). It is now well established that diabetes may progress through several clinical stages during its natural history, quite independent of its etiology. The clinical staging reflects this and, indeed, individuals may move from one stage to another stage in both directions (Figure 1.1). Even if there is no information concerning the underlying etiology, persons with diabetes or those who are developing the disease can be categorized by stage according to clinical characteristics.

**Current classification**

The current classification allows for various degrees of hyperglycemia in individuals irrespective of the disease process. These are glycemic stages ranging from normoglycemia (normal glucose tolerance) to hyperglycemia where insulin is required for survival. All individuals with the disease can be categorized according to clinical stage [7]. The stage of glycemia may change over time depending on the extent of the underlying disease processes. As shown in Figure 1.1, the disease process may be present but may not have progressed far enough to cause hyperglycemia. The etiological classification is possible as the defect or process which may lead to diabetes may be identified at any stage in the development of diabetes, even at the stage of normoglycemia. As an example, the presence of islet cell antibodies (ICA) and/or antibodies to glutamic acid decarboxylase (anti-GAD) [8] in a normoglycemic individual indicates the autoimmune process, which underlies type 1 diabetes, is present, although the individual may or may not ultimately develop diabetes [7,9]. For type 2 diabetes, there are few useful highly specific indicators, though the presence of risk factors such as obesity indicates the likelihood of developing type 2 diabetes. Hopefully, future research will reveal some specific markers of the type 2 diabetes disease process.

<table>
<thead>
<tr>
<th>Stages</th>
<th>Normoglycemia</th>
<th>Hyperglycemia</th>
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<tbody>
<tr>
<td>Types</td>
<td>Normal glucose tolerance</td>
<td>IGT and/or IFG</td>
</tr>
<tr>
<td>Type 1</td>
<td>• Autoimmune</td>
<td>• Predom. insulin resistance</td>
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<td></td>
<td>• Idiopathic</td>
<td>• Predom. insulin secretory defects</td>
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<tr>
<td>Type 2</td>
<td>• Predom. insulin resistance</td>
<td>Other specific types</td>
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<td>Other specific types</td>
<td>• Genetic defects of β-cell function</td>
<td>• Genetic defects of insulin action</td>
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<td>• Genetic defects of insulin action</td>
<td>• Diseases of exocrine pancreas</td>
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<td>• Diseases of exocrine pancreas</td>
<td>• Endocrinopathies</td>
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<td>• Endocrinopathies</td>
<td>• Drug or chemical induced</td>
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<td>• Drug or chemical induced</td>
<td>• Others</td>
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<tr>
<td>Gestational hyperglycemia</td>
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</table>

*Figure 1.1* Disorders of glycemia: etiologic types and clinical stages. Source: World Health Organization 1999 [7]. Reproduced with permission of the WHO.
The same disease process can cause various degrees of impaired glucose metabolism such as impaired fasting glycemia (IFG) and impaired glucose tolerance (IGT) without fulfilling the criteria for the diagnosis of diabetes [7]. Weight reduction, exercise and/or oral hypoglycemic therapy can achieve satisfactory glycemic control in some persons with type 2 diabetes. These persons, therefore, do not require insulin initially but may do so much later in their course as β-cell function deteriorates. Some persons require insulin for adequate glycemic control at an earlier stage in type 2 diabetes but could survive without it. By definition these persons have some residual insulin secretion. Patients with extensive β-cell destruction (minimal residual insulin secretion) do require insulin for survival and this is the hallmark of type 1 diabetes [7,9].

The classification by etiological type (Table 1.1) results from improved understanding of the causes of diabetes, although this is still far from complete, particularly for type 1 diabetes.

The terms “insulin-dependent diabetes mellitus,” “non-insulin-dependent diabetes mellitus” and their acronyms “IDDM” and “NIDDM” have been removed from classifications. These terms were very confusing and frequently resulted in misclassification, as patients were classified on the basis of their treatment, and indeed their age, rather than on pathogenesis. In the current classification, the terms “type 1” and “type 2” are retained (using Arabic rather than Roman numerals) [7].

Type 1 includes those cases attributable to an autoimmune process (although the basic precipitating cause of this process is still unknown), as well as those with β-cell destruction for which neither an etiology nor a pathogenesis is known (idiopathic). Those forms of β-cell destruction or failure to which specific causes can be assigned (e.g., cystic fibrosis, mitochondrial defects) are not included in this type of diabetes. These issues are discussed in greater detail later.

Type 2 includes the common major form of diabetes which results from defect(s) in insulin secretion and/or from insulin resistance, and often a combination of both. Malnutrition-related diabetes (MRDM) is no longer part of the WHO classification [7]. Of its two subtypes, protein-deficient pancreatic diabetes (PDPD or PDDM) needs more studies for a better definition. The other former subtype of MRDM, fibrocalculous pancreatic diabetes (FCPD), is now classified as a disease of the exocrine pancreas labeled “fibrocalculous pancreatopathy”, which may lead to diabetes.

Impaired glucose tolerance (IGT) and impaired fasting glycemia (IFG) are classified as stages of impaired glucose regulation, since they can be observed in any hyperglycemic disorder.

Gestational diabetes is a state of glucose intolerance first recognized during pregnancy which usually resolves after delivery but is associated with later increased long-term risk of type 2 diabetes. It encompasses the groups formerly classified as gestational impaired glucose tolerance (GIGT) and gestational diabetes mellitus (GDM) [7].

### Table 1.1  Etiologic classification of disorders of glycemia* [7]

**Type 1 (β-cell destruction, usually leading to absolute insulin deficiency)**
- Autoimmune
- Idiopathic

**Type 2 (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with or without insulin resistance)**

**Other specific types** (see Table 1.3)
- Genetic defects of β-cell function
- Genetic defects in insulin action
- Diseases of the exocrine pancreas
- Endocrinopathies
- Drug- or chemical-induced infections
- Uncommon forms of immune-mediated diabetes
- Other genetic syndromes sometimes associated with diabetes

**Gestational diabetes**

*As additional subtypes are discovered it is anticipated that they will be reclassified within their own specific category.

**Includes the former categories of gestational impaired glucose tolerance and gestational diabetes.

Source: World Health Organization 1999 [7]. Reproduced with permission of the WHO.

### Diabetes Types

#### Type 1 process

Type 1 indicates the processes of β-cell destruction that may ultimately lead to diabetes in which insulin is required for survival in order to prevent the development of ketoacidosis, coma, and death. This category comprises:

- **Immune-mediated diabetes mellitus:** This is the classical form of type 1 diabetes, which can occur at any age, and results from a cell-mediated autoimmune destruction of the pancreatic β cells. The type 1 process is characterized by the presence of ICA, anti-GAD, islet antigen 2 (IA2) or insulin autoantibodies which identify the autoimmune process associated with β-cell destruction [9]. Other autoimmune disorders such as Grave’s disease, Hashimoto’s thyroiditis and Addison’s disease may be associated with type 1 diabetes mellitus [9].

  The rate of β-cell destruction is quite variable, typically being rapid in children and slower in adults. Typically, type 1 diabetes requires insulin therapy from the time of presentation in both adults and children, but a slowly progressive form, latent autoimmune diabetes in adults (LADA), is well described [8]. Blood glucose in LADA can initially be controlled by lifestyle change and oral hypoglycemic agents, and may therefore masquerade as type 2 diabetes. However, in comparison to the typical patient with type 2 diabetes, LADA patients are leaner and...
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progress much more rapidly to requiring insulin. Importantly, markers of autoimmunity (most commonly anti-GAD antibodies) are present, and therefore LADA falls within type 1 autoimmune diabetes.

- **Idiopathic:** There are some forms of type 1 diabetes which have no known etiology, and no evidence of autoimmunity. Some of these patients have permanent insulinopenia and are prone to ketoacidosis [10]. This form is more common among individuals of African and Asian origin [11].

**Type 2 process**

Type 2 diabetes is the commonest form of diabetes and is characterized by disorders of insulin resistance and insulin secretion, either of which may be the predominant feature. Both are usually present at the time when diabetes is clinically manifest. Insulin levels may be normal or even elevated at the time when diabetes is diagnosed. However, in the setting of insulin resistance, these levels are inadequate to maintain normoglycemia. This relative insulin deficiency is what differentiates diabetic insulin-resistant individuals from normoglycemic insulin-resistant individuals. Indeed, it is noteworthy that, to date, the majority of the genes that have been associated with type 2 diabetes are related to insulin secretion, and not to insulin resistance [12].

At least initially, and often throughout their lifetime, these individuals do not need insulin treatment to survive [13]. Type 2 diabetes is frequently asymptomatic and undiagnosed for many years because the hyperglycemia is often not severe enough to provoke noticeable symptoms [14]. Nevertheless, such patients are at increased risk of developing macrovascular and microvascular complications. Type 2 diabetes is a very heterogeneous disorder and there are certainly many different causes of this form of diabetes. However, it is likely that the number of patients placed in this category will decrease in the future as identification of specific pathogenic processes and genetic defects permit better differentiation and a more definitive classification. Although the specific etiologies of type 2 diabetes are not known, autoimmune destruction of the pancreas does not occur and patients do not have any of the other specific causes of diabetes listed in Table 1.2.

Most patients with the type 2 process of diabetes are overweight or obese, and obesity itself causes insulin resistance. Many of those not obese by traditional criteria, for example body mass index, may have an increased percentage of body fat distributed predominantly in the abdominal region [13]. Ketoacidosis seldom occurs in type 2 diabetes and when seen, it usually arises in association with the stress of another illness such as infection. Ketosis-prone atypical diabetes, also referred to as ketosis-prone type 2 diabetes is characterized by presentation with severe hyperglycemia and ketoacidosis requiring immediate insulin therapy [15]. More than 50% of these individuals will revert to an insulin-free near-normoglycemia.

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### Table 1.2 Other specific types of diabetes [7]

<table>
<thead>
<tr>
<th>Genetic defects of β-cell function</th>
<th>Genetic defects in insulin action</th>
<th>Diseases of the exocrine pancreas</th>
<th>Endocrinopathies</th>
<th>Drug- or chemical-induced</th>
<th>Infections</th>
<th>Uncommon forms of immune-mediated diabetes</th>
<th>Other genetic syndromes</th>
</tr>
</thead>
<tbody>
<tr>
<td>HNF1A MODY</td>
<td>INSR Type A insulin resistance</td>
<td>Fibrolaculosis pancreaticopathy</td>
<td>Cushing syndrome</td>
<td>Congenital rubella</td>
<td></td>
<td>Insulin autoimmune syndrome (antibodies to insulin)</td>
<td>Other genetic syndromes (see Table 1.4)</td>
</tr>
<tr>
<td>HNF4A MODY</td>
<td>INSR Leprechaunism</td>
<td>Pancreatitis</td>
<td>Aldosteronoma</td>
<td>Cytomegalovirus</td>
<td></td>
<td>Anti–insulin receptor antibodies</td>
<td></td>
</tr>
<tr>
<td>HNF1B MODY</td>
<td>INSR Rabson–Mendenhall syndrome</td>
<td>Trauma / pancreatectomy</td>
<td>Acromegaly</td>
<td>Others</td>
<td></td>
<td>“Stiff man” syndrome</td>
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<tr>
<td>GCK MODY</td>
<td>LMNA FPLD</td>
<td>Pheochromocytoma</td>
<td>Cystic fibrosis</td>
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<td>Others</td>
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<tr>
<td>MORA 3243 MIDD</td>
<td>PRARG FPLD</td>
<td>Glucagonoma</td>
<td>Hemochromatosis</td>
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<tr>
<td>KCNJ11 PNDM</td>
<td>AGPAT2 CGL</td>
<td>Hyperthyroidism</td>
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<tr>
<td>KCNJ11 DEND</td>
<td>BSC1 CGL</td>
<td>Somatostatinoma</td>
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<td>6q24 TNDM</td>
<td>IF2AK3 Wolcott–Rallison syndrome</td>
<td>Lipoatrophic diabetes</td>
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<tr>
<td>ABC18 TNDM</td>
<td>WFS1 Wolfram syndrome</td>
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<td>WFS1 Wolfram syndrome</td>
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**Notes:** Nomenclature: the gene name is followed by the clinical syndrome with the gene number designated using the HUGO convention.

- MODY: maturity onset diabetes of the young
- MIDD: maternally inherited diabetes and deafness
- PNDM: permanent neonatal diabetes mellitus
- DEND: development delay epilepsy
- TNDM: transient neonatal diabetes mellitus

Source: World Health Organization 1999 [7]. Reproduced with permission of the WHO.
within weeks or months with multiorgan insulin resistance not dissimilar to type 2 diabetes [16]. This condition is commonly found in sub-Saharan Africa and African migrants and is referred to as “Flatbush diabetes”[17].

The risk of developing type 2 diabetes increases with age, obesity, and lack of physical activity. It occurs more frequently in women with prior GDM, in those with hypertension or dyslipidemia, and its frequency varies between different ethnic subgroups [7]. Type 2 diabetes is often associated with strong familial, likely genetic, predisposition but the genetics of type 2 diabetes are quite complex and not clearly defined [18]. Some patients who present a clinical picture consistent with type 2 diabetes have been shown to have antibodies similar to those found in type 1 diabetes.

Although diagnosis in most patients with type 2 diabetes is made in adult years, the disease is now increasingly seen in adolescents and even children, especially in a background of high obesity prevalence. At presentation, ketosis or even ketoacidosis, may occur in this younger age group and insulin is often required in the initial management. However, once the acute metabolic disturbance is rectified, insulin can often be withdrawn, and glycemic control achieved with lifestyle measures and oral pharmacotherapy.

Other specific types

The other specific types of diabetes are less common and can be broadly classed as genetic, exocrine pancreatic, endocrine, and drug-induced causes [7]. A more comprehensive breakdown is provided in Table 1.2 and the more common types are discussed briefly later.

Classification of genetic disorders

With ongoing advances in the study of molecular genetics, there has been considerable progress in the identification of specific subtypes of diabetes of genetic origin. Through this work, it has been shown that the clinical subgroups are heterogeneous and there has been recognition of several novel, genetic-based syndromes associated with diabetes. The progress in our ability to examine genes to arrive at a diabetes diagnosis has improved treatment for these patients [19] and thus genetic diagnosis has become a key part of clinical management in many countries.

Genetic defects of β-cell function

The diabetic state may be associated with monogenic defects in β-cell function. These forms are characterized by onset of mild hyperglycemia during childhood or early adulthood, and include maturity-onset diabetes of the young (MODY), permanent neonatal diabetes (PNDM), transient neonatal diabetes (TNDM), and many other insulin-deficient syndromes with a myriad of other clinical features [7]. The most well characterized of these is MODY. MODY is inherited in an autosomal dominant pattern and typically presents before the age of 25 years. While the condition results from β-cell dysfunction, it is not always insulin dependent. Molecular genetic testing can define a diagnosis in 1–2% of all diabetic patients with monogenic diabetes. Advances in this field have led to the identification of the genes associated with many clinically identified subgroups of diabetes and explained clinical heterogeneity in conditions defined by age of diagnosis, for example neonatal diabetes and MODY. Molecular genetic tests are now available to help define the diagnosis, and importantly alter prognosis and optimize treatment of children, young adults and their families with diabetes.

Several mutations associated with MODY have been identified to date, of which the most common genetic subtypes are: GCK MODY, HNF1A MODY, HNF4A MODY, and IPF1 MODY [19]. These are listed in Table 1.2. Among these subtypes, the HNF1A MODY subtype is the most common and results in a progressive and marked hyperglycemia with a high risk of microvascular and macrovascular complications [20], but these patients respond well to sulfonylureas [21]. Subtype HNF4A is similar to HNF1A but patients have marked macrosomia and transient neonatal hypoglycemia [22]. The other subtype, GCK MODY, is a milder form of diabetes, characterized by a mild fasting hyperglycemia that is generally lifelong with little deterioration with age and does not require treatment [23,24].

In children less than 6 months of age, diabetes is more likely to be monogenic than autoimmune type 1 diabetes [25]. However, in approximately 50% of these infants, the diabetes is transient (TNDM) [24]. Further to the specific genetic types mentioned here, there are also many subtypes of neonatal diabetes which present as a result of multisystem clinical syndromes [26]. For example, Wolfram syndrome, also referred to as DIDMOAD, is inherited by autosomal recessive trait, is a monogenic multisystem syndrome, and is characterized by marked β-cell dysfunction [27].

Point mutations in mitochondrial DNA have been found to be associated with diabetes and sensori-neural deafness [28] and lead to a condition known as maternally inherited diabetes and deafness (MIDD). Genetic abnormalities that result in the inability to convert proinsulin to insulin have been identified in a few families. Usually such traits are inherited in an autosomal dominant pattern [29] and the resultant carbohydrate intolerance is mild.

Genetic defects in insulin action

Genetic defects in insulin action are rare, and the associated metabolic abnormalities may range from hyperinsulinemia and modest hyperglycemia to severe symptomatic diabetes resulting in death [30]. Acanthosis nigricans may be present in some of these individuals. This syndrome was termed type A insulin resistance in the past. In such patients, diabetes only occurs when there is no β-cell response to the insulin resistance.
Two pediatric syndromes that have mutations in the insulin receptor gene with subsequent alterations in insulin receptor function and extreme insulin resistance are called leprechaunism and the Rabson–Mendenhall syndrome [31]. A heterogeneous group of disorders of lipid storage characterized by lipodystrophy, in which insulin resistance is a common feature, has also been described [32].

**Diseases of the exocrine pancreas**

Pancreatitis, trauma, infection, pancreatic carcinoma, and pancreatectomy are some of the acquired processes of the pancreas that can cause diabetes. Any process that diffusely injures the pancreas may cause diabetes [33]. With the exception of cancer, damage to the pancreas must be extensive for diabetes to occur. However, adenocarcinomas that involve only a small portion of the pancreas have been associated with diabetes. This implies a mechanism other than a simple reduction in β-cell mass [34].

Hemochromatosis will also damage β cells and impair insulin secretion [35]. Fibrocalculous pancreatitis may be accompanied by abdominal pain radiating to the back and pancreatic calcification on X-ray and ductal dilatation. Pancreatic fibrosis and calcified stones in the exocrine ducts are found at autopsy [36].

**Endocrinopathies**

Insulin action can be antagonized by several hormones (e.g. growth hormone, cortisol, glucagon, epinephrine). Diseases associated with excess secretion of these hormones can cause diabetes (e.g. acromegaly, Cushing syndrome, glucagonoma and pheochromocytoma) [7]. These forms of hyperglycemia resolve when the hormone excess is removed. Somatostatinoma and aldosteronoma-induced hypokalemia, can cause diabetes at least in part by inhibiting insulin secretion [37]. Hyperglycemia generally resolves following successful removal of the tumor.

**Drug-or chemical-induced diabetes**

Insulin secretion may be impaired by many drugs. They may not, by themselves, cause diabetes but may precipitate diabetes in persons with insulin resistance [38]. Pancreatic β-cell destruction may occur with the use of certain toxins such as Vacor (a rat poison) [39], pentamidine [40], and some immunosuppressive drugs. Among these β-cell toxic agents, the most commonly used are the immunosuppressive agents of which the calcineurin inhibitors (e.g. tacrolimus and cyclosporin) are the main culprits. While the main action of calcineurin inhibitors in inducing diabetes is by reducing insulin secretion by pancreatic β cells, these drugs may also increase insulin resistance [41]. There is good evidence to suggest that there is greater potential of tacrolimus to induce diabetes compared with cyclosporine [42]. Diabetes induced by these drugs may be permanent due to β-cell destruction, or may only occur while the drug is being taken, with recovery between treatment cycles [42].

Studies involving other immunosuppressive agents such as mycophenolate mofetil and sirolimus are few and results are inconsistent. Clinical studies have shown that daclizumab seems to have a neutral effect [43]. Patients receiving interferon alpha have been reported to develop diabetes associated with islet cell autoantibodies and, in certain instances, severe insulin deficiency [44].

There are also many drugs and hormones that can impair insulin action. The list shown in Table 1.3 is not all-inclusive, but reflects the more commonly recognized drug-, hormone-, or toxin-induced forms of diabetes and hyperglycemia. Among these, there are several commonly used diabetes-inducing drugs that deserve special mention. These include the HMG CoA reductase agents (statins), glucocorticoid steroids, anti-HIV agents and antipsychotic drugs.

**HMG CoA reductase agents**

HMG CoA reductase agents (statins) are commonly used drugs which have been purported to cause diabetes. Sattar et al. [45] reported that statin use compared to placebo increased risk of diabetes in a meta-analysis of 13 placebo-controlled trials. Another meta-analysis comparing intensive dose statin use with moderate statin therapy in five trials showed that the risk of developing diabetes was greater at higher statin doses [46]. The mechanism as to how statins cause diabetes is not known, but it has been suggested that these drugs may affect muscle and liver insulin sensitivity resulting in an increased diabetes risk [46]. It has also been suggested that the observed relationship between statins and diabetes is due to confounding as there is a tendency of individuals who take statins to have a high inherent risk of diabetes. Despite the increased risk of diabetes associated with statin use, a risk–benefit analysis has shown the beneficial nature of statins for cardiovascular disease (CVD), which outweighs the risk of diabetes associated with statin use [47].

**Antipsychotic agents**

There is accumulating evidence supporting an association of certain psychiatric conditions with type 2 diabetes which can be attributed to side-effects of treatment and a high baseline risk of diabetes in this patient group [48].

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**Table 1.3 Drug or chemical-induced diabetes**

<table>
<thead>
<tr>
<th>Drug or Chemical</th>
<th>Indication</th>
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<tbody>
<tr>
<td>Nicotinic acid</td>
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<td>Glucocorticoids</td>
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<td>Thyroid hormone</td>
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<td>Alpha-adrenergic agonists</td>
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<tr>
<td>Beta-adrenergic agonists</td>
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<td>Thiazides</td>
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<td>Dilantin</td>
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<td>Pentamidine</td>
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<td>Vacor</td>
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<td>Interferon-alpha therapy</td>
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<td>Statins</td>
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<td>L-asparagine</td>
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<tr>
<td>Antipsychotic drugs, e.g. clozapine,</td>
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<tr>
<td>Highly active antiviral therapy, e.g. protease inhibitors</td>
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<td>Others</td>
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can be induced by the use of atypical antipsychotics including clozapine, olanzapine, risperidone, quetiapine, ziprasidone, and aripiprazole. These drugs have a direct effect of raising blood glucose and also lead to weight gain, [48] which subsequently may increase blood glucose levels.

Clozapine and olanzapine have been associated with a higher risk of diabetes than other antipsychotic agents in several studies [48]. These drugs have been associated with new-onset diabetes, exacerbation of pre-existing diabetes, and presentations with complications such as ketoacidosis. The data on risperidone and quetiapine in the studies mentioned earlier show inconsistent findings [48].

Atypical antipsychotics may have an independent effect on insulin sensitivity. Studies comparing insulin sensitivity in patients taking clozapine, olanzapine, or risperidone showed that those in clozapine and olanzapine groups had significantly decreased insulin sensitivity compared to risperidone groups. While there is generally less long-term data on aripiprazole and ziprasidone, a comparison of olanzapine and aripiprazole use in schizophrenic patients showed an increase in glucose in the olanzapine group [48].

**Anti-HIV agents**

Diabetes is fourfold more common in HIV-infected men exposed to highly active antiretroviral therapy (HAART) than HIV-negative men. Although most of the diabetes observed in this group is type 2 there has been a recent report of autoimmune diabetes and the development of anti-GAD antibodies after immune system recovery post HAART therapy [49], which suggests that type 1 diabetes can also arise in this group from treatment.

HAART is based on the use of a class of drugs known as protease inhibitors (PIs) and include atazanavir, darunavir, saquinavir, and ritonavir. PIs have been shown to increase insulin resistance and reduce insulin secretion, by interfering with GLUT-4 mediated glucose transport. PIs interfere with cellular retinoic acid-binding protein type 1 which interacts with peroxisomal proliferator-activated gamma (PPARγ) receptor. Inhibition of PPARγ promotes adipocyte inflammation, release of free fatty acids and insulin resistance [49]. Hyperglycemia resolves in almost all patients when PIs are discontinued [49] and all PIs do not have the same metabolic effects, with some drugs having a worse adverse effect than others.

Apart from HAART, another class of anti-HIV drugs associated with diabetes are the nucleoside analogs (reverse transcriptase inhibitors) (NRTIs) [50] especially when used for long periods of time [51]. The risk of diabetes is highest with stavudine, but the risk is also significant with zidovudine and didanosine. Proposed mechanisms include insulin resistance, lipodystrophy, and mitochondrial dysfunction [51]. It is postulated that PIs confer acute metabolic risks, while NRTIs confer cumulative risks of diabetes in predisposed, exposed persons. The use of both classes of drugs may be additive for diabetes risk [51].

**Glucocorticoids**

Glucocorticoids are the most common cause of drug-induced diabetes. They are used in the treatment of many medical conditions but are mostly prescribed for their anti-inflammatory effects [52]. They act through multiple pathways at the cellular and molecular levels, suppressing the cascades that would otherwise result in inflammation and promoting pathways that produce anti-inflammatory protein [53]. The mechanism by which glucocorticoids cause diabetes is thought to be mainly via insulin resistance, but there is also some evidence of effects on insulin secretion [54].

The effect of glucocorticoids is mainly on nonfasting glucose rather than fasting glucose levels [52], but there is uncertainty as to whether this reflects a relationship with clock time (perhaps linked to dosing times), or to a predominant effect on postprandial blood glucose levels.

**Infections**

Certain viruses have been associated with β-cell destruction. Diabetes occurs in some patients with congenital rubella [55]. Coxsackie B, cytomegalovirus, and other viruses (e.g. adenovirus and mumps) have been implicated in inducing diabetes [56–58].

**Uncommon but specific forms of immune-mediated diabetes mellitus**

Diabetes may be associated with several immunologic diseases with a pathogenesis or etiology different from that which leads to the type 1 diabetes process. Postprandial hyperglycemia of a severity sufficient to fulfill the criteria for diabetes has been reported in rare individuals who spontaneously develop insulin autoantibodies. However, these individuals generally present with symptoms of hypoglycemia rather than hyperglycemia [59]. The “stiff man syndrome” is an autoimmune disorder of the central nervous system, characterized by stiffness of the axial muscles with painful spasms. Affected people usually have high titers of anti-GAD and approximately one third to one half will develop type 1 diabetes [60].

Anti-insulin receptor antibodies can cause diabetes by binding to the insulin receptor thereby reducing the binding of insulin to target tissues [61]. However, these antibodies can also act as an insulin agonist after binding to the receptor and can thereby cause hypoglycemia [62]. Anti-insulin receptor antibodies are occasionally found in patients with systemic lupus erythematosus and other autoimmune diseases [63].

**Other genetic syndromes associated with diabetes**

Many genetic syndromes are accompanied by an increased incidence of diabetes mellitus. These include the chromosomal abnormalities of Down syndrome, Klinefelter syndrome, and Turner syndrome. These and other similar disorders are listed in Table 1.4.
Diabetes is commonly observed in cystic fibrosis patients. While it shares features of type 1 and type 2 diabetes, cystic fibrosis-related diabetes (CFRD) is a distinct clinical entity. It is primarily caused by insulin insufficiency, although fluctuating levels of insulin resistance related to acute and chronic illness and medications such as bronchodilators and glucocorticoids also play a role [64]. Since blood glucose levels within the IGT range appear to have an adverse effect on lung function, it has been suggested that diagnostic criteria for CFRD should be lower than that for other forms of diabetes, but data are currently inadequate to make this change [64]. CFRD is not associated with atherosclerotic vascular disease, despite the fact that individuals with cystic fibrosis nowadays can have a lifespan well into the 50s and 60s.

There are several distinct clinically defined subgroups of diabetes where an etiology has not yet been defined. In recognition of this, during the most recent WHO consultation, it was recommended that a category of “unclassified” or “nonclassical phenotype” be available.

**Diabetes in children and youth**

Type 1 diabetes in children and youth is typically characterized by weight loss, polyuria, polydipsia, blurring of vision, very high plasma glucose concentrations, and ketonuria. The diagnosis is usually very clear with high random glucose values, and there is rarely a need to investigate with an oral glucose tolerance test (OGTT). Type 2 diabetes in children is associated with milder symptoms and is often associated with obesity. In these cases, diagnosis is made using any one of OGTT, fasting plasma glucose, or HbA1c, with preference for HbA1c as there is no requirement to fast. However, there is still debate as to the use of the latter in children [65].

Classification of diabetes in youth poses special problems. Although type 1 diabetes remains the most common form of diabetes in youth of European background, type 2 diabetes is increasingly common, especially among adults at particularly high risk of type 2 diabetes. With the increase in obesity over the last 20 years, there has been an increase in type 2 diabetes in children especially among ethnicities at high risk as well as an increase in the number of children with type 1 who are overweight. Type 2 diabetes may also be present in youth with ketosis or ketoacidosis, which serves only to compound the problem further. While a practical delineation between these may be the use of insulin, it can no longer be assumed that those on insulin are type 1. Other investigations which could provide insight include measurement of C-peptide, characteristic type 1 antibodies, for example anti-GAD antibodies, and the monitoring of endogenous insulin secretion over time [17].

There has also been an increase in the number of children and adolescents with a mixture of the two types of diabetes, that is, subjects who are obese and/or with signs of insulin resistance as well as being positive for markers of autoimmunity to β cells. These cases present a problem under the current classification as they present with an overlapping phenotype of both type 1 and type 2 diabetes and have been referred to as hybrid diabetes, double diabetes, or latent autoimmune diabetes in youth (LADY) [66]. In such children, presentation of double diabetes is similar to LADA in adults. However, unlike LADA, little is known about the prevalence of double diabetes or the prevalence and significance of autoimmune markers in children. In addition, whether autoimmune-positive youth with double diabetes progress more rapidly to insulin dependence than those with type 2 diabetes without is not known. This is particularly important as these children/youth could be at risk for complications associated with β-cell dysfunction, as well as macro- and microvascular complications of type 2 diabetes. It has been suggested that the current classification of diabetes should be revised to include this new phenotype [66].

Another challenge among young people is the possibility of misdiagnosis of monogenic diabetes as type 1 and type 2. As noted previously, monogenic diabetes results from the inheritance of mutation(s) in a single gene that regulates β-cell function or less commonly in genes related to insulin resistance.

The clinical characteristics of a child with monogenic diabetes compared to children and youth with type 1 and type 2 are shown in Table 1.5. Monogenic diabetes should be considered in a child initially diagnosed as type 1 who has been diagnosed at less than 6 months of age, has a family history of diabetes with a parent affected, evidence of endogenous insulin production outside the “honeymoon” phase of diabetes with detectable C-peptide, and the absence of pancreatic islet autoantibodies (measured at diagnosis) [67].

In children with an initial diagnoses of type 2, a diagnosis of monogenic diabetes should be considered in the following circumstances: when the child is not obese or other diabetic family members have weight in the normal range, and the child does not have acanthosis nigricans; when the child is from an ethnic group with a low prevalence of type 2 diabetes and when there is no evidence of insulin resistance with normal fasting C-peptide levels [24,68].

In scenarios when monogenic diabetes is misdiagnosed as type 1 or 2, the afore-mentioned criteria should be considered as a
Table 1.5 Clinical characteristics of type 1 diabetes, type 2 diabetes, and monogenic diabetes in children and adolescents [67]

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Type 1 Polygenic</th>
<th>Type 2 Polygenic</th>
<th>Monogenic Monogenic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetics</td>
<td>Polygenic</td>
<td>Polygenic</td>
<td>Monogenic</td>
</tr>
<tr>
<td>Age on onset</td>
<td>6 months and older</td>
<td>Usually pubertal (or later)</td>
<td>Often postpubertal except glucokinase and neonatal diabetes</td>
</tr>
<tr>
<td>Clinical presentation</td>
<td>Most often acute, rapid</td>
<td>Variable; from slow, mild (often insidious) to severe</td>
<td>Variable (may be incidental in glucokinase)</td>
</tr>
<tr>
<td>Autoimmunity</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Ketosis</td>
<td>Common</td>
<td>Uncommon</td>
<td>Common in neonatal diabetes, rare in other forms</td>
</tr>
<tr>
<td>Obesity</td>
<td>Population frequency</td>
<td>Increased frequency</td>
<td>Population frequency</td>
</tr>
<tr>
<td>Acanthosis nigricans</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Frequency (% of all diabetes in young people)</td>
<td>Usually &gt;90%</td>
<td>Most countries &lt;10%, Japan 60–80%</td>
<td>71–3%</td>
</tr>
<tr>
<td>Parents with diabetes</td>
<td>2–4%</td>
<td>80%</td>
<td>90%</td>
</tr>
</tbody>
</table>

whole rather than individually and are not absolute. DNA testing is now also available for diagnosis of monogenic diabetes.

**DIAGNOSTIC CRITERIA**

Diabetes is characterized by hyperglycemia, and thus diagnostic tests focus on establishing elevated blood glucose levels [69]. A casual blood glucose, fasting glucose or an OGTT of 75 grams may be performed. For children, the oral glucose load is proportional to body weight at 1.75 g per kg body weight. Recently, HbA1c has been added as an acceptable and reliable means of diagnosing diabetes (discussed later). The cutpoints for the diagnosis of diabetes are listed in Table 1.6.

In the absence of symptoms clearly attributable to diabetes, a diagnosis should not be based on a single measurement, but requires results within the diabetes range on two separate days.

The most notable change in diagnostic criteria in recent years is the recommendation by the ADA and WHO to use HbA1c for diagnosis of diabetes. A summary of the evolution of this decision is described in the following section.

**Diagnosis of diabetes using HbA1c**

HbA1c is a hemoglobin variant primarily composed of glycohemoglobin, which is formed by the nonenzymatic attachment of glucose to hemoglobin [70]. It was first identified in 1968 by Rabar, who noted it was associated with diabetes. By 1980, its clinical utility as a marker of glycemic control had been recognized. By the 1990s, supported by strong evidence from two studies, the Diabetes Control and Complications Trial [71] and the United Kingdom Prospective Diabetes Study [72], and the development of new high throughput methods and improved coefficients of variation (CV), HbA1c had become the cornerstone marker in the monitoring of diabetes. In more recent years, a US national glycohemoglobin standardization program has been established and the International Federation of Clinical Chemistry (IFCC) has taken the lead to ensure that HbA1c assays are standardized. In 2011, the units of reporting were also changed from percentage points to IFCC mmol/mol. After a period of dual reporting, HbA1c will be reported in mmol/mol in many countries.

With some improvement in the assay and standardization of HbA1c, together with evidence from key trials demonstrating the importance of intensive glycemic control (as reflected by HbA1c levels) in reducing the risk of microvascular complications of diabetes, the move from using glucose for diagnosis to HbA1c had begun to gather support. However, concerns over standardization of the HbA1c assays and over other factors that may affect HbA1c continued to dampen the enthusiasm for use of HbA1c for diagnosis. In the last 10 years, however, several developments have resulted in the incorporation of HbA1c into the diagnostic armamentarium. There has been significant improvement in the assays of HbA1c [73], analysis from eight different studies showed that HbA1c is as strongly related to the presence of diabetic retinopathy as are blood glucose levels [74], and HbA1c is strongly predictive of macrovascular outcomes and mortality [75,76].

The advantages of using HbA1c for diagnosis are clear. Firstly, HbA1c has far less day-to-day biological variation than fasting or 2-hour glucose [77]. Secondly, HbA1c is stable for one week at room temperature after collection while glucose is susceptible to glycolysis despite the use of fluoride oxalate to preserve the sample. Thirdly, unlike glucose measurement, there is no requirement for the patient to fast. Finally, glucose
levels are also susceptible to modification by short-term lifestyle intervention while HbA1c reflects glycemia over a period of 3 to 4 months.

The major disadvantage of HbA1c is that there are a number of nonglycemic conditions that interfere with the assay. In particular, alterations of red blood cell turnover (e.g., kidney failure, hematocrit deficiencies, hemolysis, acute blood loss, pregnancy, and erythropoietin therapy) may affect the relationship between HbA1c and recent glycemia. The other important disadvantage is the need for a laboratory to use an IFCC aligned assay and be part of a standardization program, which may not be possible in developing countries.

Cutpoints of HbA1c have been set using similar methods to those adopted for the setting of blood glucose criteria. Cross-sectional data from 47,364 individuals from 12 countries reported that the threshold for diabetes-specific retinopathy was 6.3% (45 mmol mol\(^{-1}\)), with an optimal decision limit of 6.5% [74]. This latter cutpoint has been adopted by the ADA and WHO as an appropriate cutpoint for diabetes.

Although support for the use of HbA1c for diagnosis of diabetes has increased over the years, several questions about its suitability remain. For example, what should be the appropriate HbA1c ranges for pre-diabetes or intermediate glycemia? The ADA suggested that 5.7–6.5% (39–48 mmol mol\(^{-1}\)) should be used [5] to indicate intermediate glycemia while the WHO [78] suggested that levels of HbA1c below 6.5% may indicate intermediate glycemia but were reluctant to indicate a precise lower cutpoint. An international expert committee suggested that those with HbA1c between 6.0–6.5% (42–48 mmol mol\(^{-1}\)) could be considered at high risk, and should be targeted for diabetes prevention activities [79].

A further concern about moving from glucose to HbA1c to diagnose diabetes is that we will observe a change in prevalence of diabetes, as an elevated HbA1c does not identify exactly the same individuals as does an elevated blood glucose. It should, however, be noted that a similar discrepancy in individuals identified also applies to diagnosis by fasting glucose compared to diagnosis by 2-hour plasma glucose in the OGTT.

In general, the use of HbA1c for diagnosis of diabetes results in a lower prevalence of diabetes with the magnitude of the difference between blood glucose-based prevalence and HbA1c-based prevalence varying widely between populations [80].

Diagnosis of diabetes using HbA1c is now recommended by both the ADA and WHO as detailed in Table 1.6. As discussed earlier, it is important to ensure that the HbA1c assay used meets stringent quality assurance test and is aligned with the IFCC standardization program. It is also important to ensure that there are no clinical conditions that preclude its accurate measurement.
Diagnosis of gestational diabetes mellitus

The diagnosis of gestational diabetes mellitus has been traditionally based on glucose tolerance levels measured between 24 and 28 weeks of gestation [7] using an OGTT. These guidelines have been modified due to the evidence from the Hyperglycemia and Adverse Pregnancy Outcome Study (HAPO) [81]. HAPO was a large, prospective, blinded, multinational study showing a strong and continuous relationship of maternal glycemia at 24–28 weeks with neonatal outcomes of increased birth weight and increased cord–blood serum C-peptide levels, and to increased cesarean section delivery rates in the mothers. Based on these data, new GDM guidelines [82] were proposed which have since been adopted internationally. Diagnostic criteria for gestational diabetes are shown in Table 1.7.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Diagnostic criteria for gestational diabetes mellitus [82]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting venous PG</td>
<td>≥5.1 mmol L⁻¹</td>
</tr>
<tr>
<td>1-h venous PG</td>
<td>≥10.0 mmol L⁻¹</td>
</tr>
<tr>
<td>2-h venous PG</td>
<td>≥8.5 mmol L⁻¹</td>
</tr>
</tbody>
</table>

One or more of these values must be abnormal for the diagnosis of GDM.

OTHER GLUCOSE TOLERANCE CATEGORIES

Impaired glucose regulation (impaired glucose tolerance and impaired fasting glycemia)

Impaired glucose tolerance (IGT) and impaired fasting glycemia (IFG) are categorized as stages in the natural history of disordered carbohydrate metabolism. They occur in all individuals as they progress from normal to diabetes, but since the transition through these states is rapid in type 1 diabetes, they are rarely identified in such individuals. Therefore, nearly all of the literature dealing with IGT and IFG is concerned with issues relating to type 2 diabetes, such as risk of developing type 2 diabetes and CVD.

IFG and IGT represent a metabolic state intermediate between normal glucose homeostasis and diabetes. The pathophysiologic aspects of hyperglycemia of each category are somewhat different. IGT is associated with muscle and liver insulin resistance and thus IGT is often associated with the metabolic or insulin resistance syndrome [7], while IFG is usually related to insulin secretory deficits.

A meta-analysis suggested that there is a positive relationship between IFG/IGT and diabetes which varies across ethnicity and age [83]. This study showed that individuals with combined IGT and IFG had the highest risk of future diabetes. In terms of sensitivity and specificity for the subsequent development of diabetes, the sensitivity of IFG as originally defined at 6.1 mmol L⁻¹ (110 mg dL⁻¹) is less than that of IGT in most populations [84], but the specificity of IFG is greater [85]. IGT is more common than IFG using 6.1 mmol L⁻¹ (110 mg dL⁻¹) in most populations but it should be noted that the sensitivity and specificity of both IGT and IFG are entirely dependent on the cutoffpoints selected, and not on any inherent differences between FPG and 2hPG [86]. If IGT and IFG are defined such that they have similar prevalence to each other, then they have the same predictive values for subsequent diabetes [86]. Further, with the ADA cutpoint of IFG (5.6 mmol L⁻¹ or 100 mg dL⁻¹—see later), the sensitivity of IFG is similar to IGT, but the specificity falls.

Thus, neither the risk of developing diabetes nor the sensitivity and specificity for future diabetes seem to differ enough between IGT and IFG to suggest one category is more useful than the other. In reality, in most populations IGT is more prevalent than IFG (if IFG is defined as FPG of 6.1–6.9 mmol L⁻¹ (110–125 mg dL⁻¹)), and thus it identifies a greater proportion of those who will develop diabetes. Furthermore, although at the lower cutpoint of IFG of FPG 5.6–6.9 mmol L⁻¹ (100–125 mg dL⁻¹), the prevalence of IFG approaches that of IGT, the two groups remain limited in their overlap. Relying on only a FPG will not identify the same proportion of individuals at risk compared to undertaking an OGTT.

The relationship between IGT and IFG and CVD is well studied in meta-analyses. In a review of the evidence from 27 studies [87], IFG (at both cutpoints) and IGT were both associated with a significantly increased risk of approximately 20% of CVD.

Diagnosis of IGT and IFG categories has been traditionally made by measuring blood glucose levels, either in the fasting state (for IFG) or during an OGTT (for IGT) (see Table 1.6 for cutoffpoints). Since individuals with IFG may have diabetes, it is recommended that those who are found to have IFG should have an OGTT to exclude diabetes [7].

Whilst IGT has been part of the classification of glucose intolerance for many years, IFG was only added in 1997, with a lower cutpoint of 6.1 mmol L⁻¹ (110 mg dL⁻¹). However, in 2002, the ADA proposed a new cutpoint of IFG of 5.6 mmol L⁻¹ (100 mg dL⁻¹), as this maximized the sensitivity and specificity for predicting future diabetes [88]. On review of the same evidence, the WHO decided not to adopt this new cutpoint, as it significantly increased the number of people being labeled as abnormal, but without evidence that so doing would improve outcomes [69].

The purpose of defining other categories of glucose intolerance or prediabetes is to identify a group of the population at increased risk for the development of both diabetes and CVD, so that interventions (lifestyle and pharmacologic) can be applied to reduce these risks. IGT and IFG are considered risk factors for diabetes and CVD.

In summary, longitudinal data show that IFG and IGT are rather similar to each other in their ability to predict future diabetes and CVD. However, since the populations of
Normoglycemia

The notion underpinning setting a normal category of glucose is that people with values below the upper limit of normal are at no or only "normal" risk of developing diabetes or its micro- and macrovascular complications [5,7,84,89]. Since the risks of future development of diabetes and CVD are related to blood glucose across most of its spectrum, and well into any normal ranges that have been set, such notions of "normal" blood glucose should be interpreted very cautiously. The actual setting of the cutpoint indicating normoglycemia over the years has undergone considerable changes. The early classification in 1985 by US NDDG that was adopted by WHO had set diabetes at a fasting glucose of 7.8 mmol L\(^{-1}\) (140 mg dL\(^{-1}\)) and those under this threshold were labeled "normoglycemia". In 1997, upon the availability of new data, the ADA, with support from WHO reset the cutpoint of a "normal" fasting plasma glucose from 7.8 mmol L\(^{-1}\) (140 mg dL\(^{-1}\)) to 6.0 mmol L\(^{-1}\) (110 mg dL\(^{-1}\)) [5,7,89]. In 2002–2003, the ADA recommended that the cutpoint be 5.5 mmol L\(^{-1}\) (100 mg dL\(^{-1}\)) [88].

Summary

The classification of diabetes is an evolving process. As the research into diabetes is a continuing and dynamic process and epidemiologic and clinical studies are in progress, there may well be revision and refinement of the classification system. This is especially important given the recent recommendation to use HbA1c to diagnose diabetes and the caveats to its use. As more knowledge emerges about the etiology of cases currently positioned in the type 2 process category, modification and refinement may be necessary.

References


