# What is diabetes?

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## Abstract

Diabetes mellitus represents a set of autoimmune, metabolic and genetic disorders that share one major characteristic – hyperglycaemia. The recommended way of measuring plasma glucose and the threshold used to define what is normal or abnormal have gone through several iterations over the past few decades. These recommendations, and the current definitions of diabetes mellitus and intermediate states of hyperglycaemia, are reviewed here. Differences in approach between the USA and other parts of the world are highlighted.

**Keywords** Classification; glycated haemoglobin; impaired fasting glucose; impaired glucose tolerance; MRCP; type 1 diabetes mellitus; type 2 diabetes mellitus

## What is diabetes?

Diabetes mellitus is not a single disorder and its definition depends on one's perspective. From a medical perspective, it represents a series of metabolic conditions associated with hyperglycaemia and caused by partial or total insulin insufficiency. Exposure to chronic hyperglycaemia can result in microvascular complications in the retina, kidney or peripheral nerves. Although these are characteristic of diabetes, they cannot be used to define the disorder because they take too long to manifest. The so-called macrovascular complications of diabetes (myocardial infarction, stroke, peripheral arterial disease) occur more commonly as these are frequently present in the pre-diabetic state. It has been suggested that diabetes should be defined as 'premature atherosclerosis with associated hyperglycaemia', thereby emphasizing the clinical problems to which most patients succumb.

A definition of diabetes from a societal perspective includes the burden that the disease places on economies, in terms of both its costly treatment and associated premature morbidity and mortality.

From the individual patient's perspective, diabetes is a lifelong condition requiring daily attention to diet, lifestyle and self-monitoring of blood glucose, with frequent administration of medication. It can be associated with varying degrees of anxiety, depression and multiple visits to healthcare providers.

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## Key points

- Diabetes mellitus represents a series of metabolic conditions sharing the major characteristic of hyperglycaemia
- Exposure to chronic hyperglycaemia increases the risk of microvascular complications and long-term macrovascular disease
- Depending on the clinical scenario, plasma glucose or $HbA_{1c}$ can be used to establish the diagnosis of diabetes mellitus
- The intermediate zones between normal and overt diabetes are termed 'pre-diabetes' and are strong indicators of future diabetes development

## How is diabetes classified?

There are four major categories of diabetes mellitus: type 1 diabetes, type 2 diabetes, other specific types of diabetes and gestational diabetes (Table 1).

**Type 1 diabetes:** pancreatic β-cells are destroyed, usually by autoimmune inflammatory mechanisms. Serum autoimmune markers include islet cell autoantibodies and autoantibodies to glutamic acid decarboxylase (GAD); insulin, tyrosine phosphatases IA-2 and IA-2β, and zinc transporter ZnT8. This destructive process typically leads to absolute insulin deficiency with undetectable levels of plasma C-peptide, but the rate of progression can be variable.[1]

**Type 2 diabetes:** this is a complex metabolic disorder associated with β-cell dysfunction and varying degrees of insulin resistance. Insulin resistance is also found in other metabolic conditions, including hypertension, obesity and polycystic ovary syndrome, and these can coexist in individuals with type 2 diabetes.

**Gestational diabetes:** this is defined as carbohydrate intolerance with an onset or first recognition during pregnancy, excluding women who probably have overt pre-gestational diabetes. It is a common medical complication of pregnancy and is associated with an increase in adverse outcomes. Although the condition typically resolves after delivery, affected women should be assessed for persistent diabetes postpartum and advised that they are at increased risk of type 2 diabetes in later life.

**Less common types of diabetes mellitus:** less common forms for which the underlying defect or disease process can be identified are listed in Table 1. Although the genetic basis of type 2 diabetes is not well understood, several other types have been genetically characterized. The most common of these is maturity-onset diabetes of the young (MODY), a familial form of diabetes inherited in an autosomal dominant manner and associated with mutations in certain β-cell or hepatic genes (e.g. glucokinase, HNF homeobox A (HNF-1α)).

Other well-characterized forms of diabetes (often termed 'secondary diabetes') include diabetes associated with pancreatic

## Classification of diabetes mellitus

**Type 1 diabetes**
- Immune-mediated
- Idiopathic

**Type 2 diabetes**

**Other specific types**

*Genetic defects in β-cell function*
- HNF-4α (MODY 1)
- Glucokinase (MODY 2)
- HNF-1α (MODY 3)
- IPF-1 (MODY 4)
- HNF-1β (MODY 5)
- NeuroD1 or BETA 2 (MODY 6)
- Mitochondrial DNA
- Others

*Genetic defects in insulin action*
- Type A insulin resistance
- Donohue syndrome (leprechaunism)
- Rabson–Mendenhall syndrome
- Lipodystrophic diabetes
- Others

*Diseases of the exocrine pancreas*
- Pancreatitis
- Trauma/pancreatectomy
- Neoplasia
- Cystic fibrosis
- Haemochromatosis
- Fibrocalculous pancreatic diabetes
- Others

*Endocrinopathies*
- Cushing's syndrome
- Acromegaly
- Glucagonoma
- Phaeochromocytoma
- Somatostatinoma
- Aldosteronoma
- Hyperthyroidism
- Others

*Drug- or chemical-induced*
- Pentamidine
- Nicotinic acid
- Glucocorticoids
- Thyroid hormone
- Diazoxide
- β-Adrenoceptor agonists
- Thiazides
- Clozapine
- Protease inhibitors
- Second-generation antipsychotic drugs
- Immune checkpoint inhibitors

*Infections*
- Congenital rubella
- Cytomegalovirus
- Others

*Uncommon forms of immune-mediated diabetes*
- 'Stiff man' syndrome
- Anti-insulin receptor antibodies
- Others

*Other genetic syndromes sometimes associated with diabetes*
- Down's syndrome
- Klinefelter's syndrome
- Turner's syndrome
- Wolfram's syndrome
- Friedreich's ataxia
- Huntington's chorea
- Laurence–Moon–Biedl syndrome
- Myotonic dystrophy
- Porphyria
- Prader–Willi syndrome
- Others

*Gestational diabetes mellitus*

MODY, maturity-onset diabetes of the young. Adapted from Diabetes Care. 2009; 32(Suppl 1): S62–S67.

**Table 1**

disease (e.g. haemochromatosis-related diabetes), corticosteroid (or other) hormone excesses or certain drugs (e.g. protease inhibitors in human immunodeficiency virus infection, atypical antipsychotics in schizophrenia, immune checkpoint inhibitors in cancer treatment) (see article on What is type 2 diabetes? on pages 10–15 of this issue).

## How is diabetes diagnosed?

Table 2 outlines the criteria for the diagnosis of diabetes, which can be made in any one of the following scenarios:

- random plasma glucose concentration ≥11.1 mmol/litre in the presence of classical symptoms of hyperglycaemia,

## Diagnostic thresholds for diabetes mellitus and lesser degrees of impaired glucose regulation

| Category | Fasting plasma glucose | 2-hour plasma glucose | $HbA_{1c}$ |
|---|---|---|---|
| Normal[a,b] | <6.1 mmol/litre (<110 mg/dl) | <7.8 mmol/litre (<140 mg/dl) | <39 mmol/mol (<5.7%) or <42 mmol/mol |
| IFG | 6.1–6.9 mmol/litre (110–125 mg/dl) | – | _ |
| IGT | – | 7.8–11.0 mmol/litre (140–199 mg/dl) | _ |
| Diabetes | ≥7.0 mmol/litre (≥126 mg/dl) | ≥11.1 mmol/litre (≥200 mg/dl) | ≥48 mmol/mol (≥6.5%) |

IGT or IFG should be diagnosed only when diabetes is not diagnosed based on the corresponding fasting or 2-hour result.

[a] In 2003 the Expert Committee of the ADA published a report recommending that the FPG value used to diagnose IFG be reduced from 6.1 to 5.6 mmol/litre. This recommendation has not yet been endorsed by the WHO.

[b] The ADA recommends a range of 39–47 mmol/mol (5.7–6.4%) as identifying individuals with pre-diabetes. A number of other groups including the National Institute for Health and Care Excellence (NICE) in the UK recommend a pre-diabetes range of 42–47 mmol/mol (6.0–6.4%). The use of $HbA_{1c}$ for the diagnosis of pre-diabetes has not been endorsed by the WHO.

**Table 2**

including polydipsia, polyuria and weight loss (the latter usually a marker of insulin deficiency)
- fasting plasma glucose (FPG) ≥7.0 mmol/litre (fasting defined as no caloric intake for at least 8 hours)
- plasma glucose ≥11.1 mmol/litre 2 hours after a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water (i.e. the oral glucose tolerance test (OGTT))
- glycated haemoglobin ($HbA_{1c}$) ≥48 mmol/mol (≥6.5%).

It should be noted that, in the absence of symptoms, diagnosis should not be based on a single glucose determination but requires confirmatory testing. The above diagnostic criteria based on plasma glucose concentration were initially established by an expert committee of the American Diabetes Association (ADA) in 1997,[2] and later ratified by the World Health Organization (WHO). The diagnostic cut-off points of 7.0 mmol/litre (fasting) and 11.1 mmol/litre (OGTT 2-hour value) are based on the concentrations at which retinopathy begins to appear in a population.

The use of $HbA_{1c}$ as a diagnostic tool for diabetes was recommended by an International Expert Committee in July 2009.[3] $HbA_{1c}$ provides an integrated measure of prevailing plasma glucose over a 2–3-month period. Although it is the mainstay of monitoring glycaemic control among individuals with established diabetes, it had not previously been used to diagnose the condition. This is mainly because assays used to measure $HbA_{1c}$ were not standardized around the world. Standardization of assays has now been achieved in the USA, with all assays reporting results aligned with the $HbA_{1c}$ assay used in the DCCT (Diabetes Control and Complications Trial). In other parts of the world, the International Federation of Clinical Chemistry recommendation that the reporting of $HbA_{1c}$ results be changed to a more robust clinical chemistry standard (expressed in mmol/mol), and not a DCCT-aligned result (expressed in %), has been implemented.

In 2010, the ADA officially recommended $HbA_{1c}$ testing for the diagnosis of diabetes, and in 2011 the WHO endorsed this recommendation.[4,5] This endorsement was made on the understanding that stringent quality assurance tests are in place, assays are standardized and no conditions are present that preclude accurate measurement of the $HbA_{1c}$.

The most common factors affecting $HbA_{1c}$ are haemoglobinopathies, certain anaemias and disorders associated with accelerated red cell turnover, such as malaria. Other situations in which $HbA_{1c}$ is not appropriate for diagnosis include those in which diabetes may have been present for <2 months. This can be suggested by the presence of symptoms for <2 months, prescription within the past 2 months of diabetogenic medication (e.g. corticosteroids) or a context of acute pancreatic damage or pregnancy. In these clinical scenarios, plasma glucose criteria should be used for diagnosis.

The ADA recommends that, when feasible, and in the absence of symptoms, the same test be repeated for confirmation. However, if a patient has discordant results on two different tests, the test that has produced a result above the diagnostic cut-off point should be repeated, and the diagnosis made on the basis of the outcome.[4]

Finally, clinicians should be aware that using $HbA_{1c}$ versus an OGTT result to diagnose diabetes (or pre-diabetes, see below) identifies different patient cohorts. For example, multiple studies have confirmed that, compared with FPG and $HbA_{1c}$ cut-off points, the 2-hour glucose value diagnoses more individuals with diabetes.[1] Further investigation is required to clarify the benefits of identifying and treating more patients versus the potential risks, including overmedicalization of those with milder glucose disturbance.

## What is pre-diabetes?

The intermediate zones between normal and overt diabetes are termed 'impaired fasting glucose' (IFG) and 'impaired glucose tolerance' (IGT) (Table 2). These states of milder hyperglycaemia are not clinical disorders, although the term 'pre-diabetes' has been used to describe them. They are important because they are strong risk indicators of the future development of overt diabetes. In addition, the increased cardiovascular risk associated with overt diabetes appears to extend into the range of pre-diabetes.

According to the WHO, the upper limit of the normal range for FPG is 6.1 mmol/litre, and for the 2-hour glucose during an OGTT 7.8 mmol/litre. The ADA recommends an alternative upper limit of FPG (and thereby lower limit of IFG; see below) of 5.6 mmol/litre. Although widely used in the USA, this revised cut-off point has not been endorsed by the WHO. In terms of $HbA_{1c}$, the ADA recommends a range of 39–47 mmol/mol (5.7–6.4%) as identifying individuals with pre-diabetes.[1] A number of additional guidelines including National Institute for Health and Care Excellence (NICE) guidelines in the UK recommend a range of 42–47 mmol/mol (6.0–6.4%). The WHO advises that there is currently insufficient evidence to make formal recommendations on the interpretation of $HbA_{1c}$ values <6.5%.[5] ◆


**KEY REFERENCES**

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# TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

### Question 1

A 44-year-old man underwent a routine annual medical examination. He was asymptomatic. He had a history of hypertension. His brother and father had been diagnosed with type 2 diabetes in their 40s.

On clinical examination, the man had a body mass index of 28 $kg/m^2$.

**Investigations**

- Fasting plasma glucose 6.8 mmol/litre (3.0–6.0)
- $HbA_{1c}$ 50 mmol/mol (20–42); 6.7% (4.0–6.0)

**What is the most appropriate next step in his management?**

A. Repeat the $HbA_{1c}$ measurement
B. Commence metformin
C. Complete an oral glucose tolerance test
D. Check fasting glucose and insulin levels
E. Request genetic testing for maturity-onset diabetes of the young

### Question 2

A 32-year-old woman presented 8 weeks' postpartum. She had been found to have gestational diabetes in the late second trimester of this, her first pregnancy. Her $HbA_{1c}$ at 12 weeks' gestation had been 35 mmol/mol (20–42) 5.4% (4.0–6.0); She had required insulin to manage hyperglycemia after the diagnosis of gestational diabetes, but this had been discontinued after delivery.

**What is the most appropriate next step?**

A. Commence metformin
B. Check the $HbA_{1c}$ concentration
C. Advise daily capillary glucose monitoring
D. Complete an oral glucose tolerance test
E. Test for autoimmune markers of type 1 diabetes

### Question 3

A 74-year-old man presented with a 5-day history of fatigue and a dry mouth. He had been drinking approximately 4 litres of fluid per day for the previous week and had polyuria. Ten days previously, he had been found to have giant cell arteritis and had been advised to take prednisolone 60 mg daily.

**Investigation**

- Plasma glucose concentration 1 hour after lunch was 18 mmol/litre (3.0–6.0)

**What is the most appropriate next step in the diagnostic pathway?**

A. Repeat the plasma glucose measurement
B. Check the $HbA_{1c}$ concentration
C. Check the fasting plasma glucose the next morning
D. No further testing is necessary
E. Complete an oral glucose tolerance test