



Diabetes Mellitus

Pretest: What are the signs of diabetes?

Diabetes mellitus

Diabetes mellitus refers to the group of diseases that lead to **high blood glucose** levels, due to defects in either **insulin secretion** or **insulin action** in the body.

Diabetes develops due to a diminished production of insulin (**type 1**) or a resistance to its effects (**type 2**), including **gestational diabetes**. This can lead to hyperglycemia, which is largely responsible for the acute **signs of diabetes**, namely:

1. Excessive urine production (polyuria)
2. Thirst and increased fluid intake (polydipsia)
3. Blurred vision
4. weight loss (in type 1)
5. Lethargy
6. Changes in energy metabolism.

Types of diabetes mellitus:

1- Genetic defects of b-cell function

A. Maturity-onset diabetes of the young (MODY):

MODY 1: mutation of the hepatocyte nuclear factor (HNF4A) gene,

MODY 2: mutation of the glucokinase gene,

MODY 3: mutation of the HNF1A gene.

Some cases are thought to be point mutations in mitochondrial deoxyribonucleic acid (DNA) associated with diabetes mellitus and deafness and are usually autosomal dominant.

B. Type A insulin resistance (insulin receptor defect).

2- defects of insulin action receptor (insulin resistance (type 2))

3- Insulin deficiency due to pancreatic disease

- Chronic pancreatitis.
- Pancreatectomy.

4- Drugs

- Interferon-a.
- Glucocorticoids.

5- Infections

- Septicemia.
- Congenital rubella.



Diabetes Mellitus

- Cytomegalovirus. Rare forms of autoimmune-mediated diabetes
- Anti-insulin receptor antibodies.

6- Genetic syndromes associated with diabetes

- Down's syndrome.
- Turner's syndrome.
- Klinefelter's syndrome.

7- Gestational diabetes mellitus

Resembles **type 2 diabetes**, but is transient, occurring in about 2–5% of pregnancies. While it is fully treatable, about 20–50% of affected women develop type 2 diabetes later in life.

Diabetes mellitus is characterized by recurrent or persistent hyperglycemia, and is **diagnosed** by demonstrating any one of the following:

- ✚ **Fasting plasma glucose** level at or above 126 mg/dl (7.0 mmol/l).
- ✚ **Plasma glucose at or above 200 mg/dl** (11.1 mmol/l), 2 hours after a 75 g oral glucose load in a glucose tolerance test.

symptoms of hyperglycemia and casual plasma glucose at or above 200 mg/dl (11.1 mmol/l).

Type 1 Diabetes:

- The cause of type 1 diabetes is not fully understood. An autoimmune attack (to the β -cells of the pancreas) may be triggered by reaction to an infection, for example by one of the viruses of the Coxsackie virus family or German measles, although the evidence is inconclusive.
- Individuals may display genetically; an observed inherited tendency to develop type 1 diabetes has been traced to particular human leukocyte antigen (HLA) genotypes (the major histocompatibility complex (MHC) in humans is known as the HLA system). Environmental factors can also strongly influence expression of type 1 diabetes.
- Type 1 diabetes is a polygenic disease (different genes contribute to its expression); it can be dominant, recessive or intermediate. The gene IDDM1, located in the MHC class II region on chromosome 6, is believed to be responsible for the histocompatibility disorder characteristic of type 1 diabetes. Insulin-producing pancreas cells (β - cells) display improper antigens to T-cells, which lead to the production of antibodies that attack those β -cells. Other associated genes are located on chromosomes 11 and 18. Pancreatic β -cells in the islets of Langerhans are destroyed or damaged sufficiently to effectively abolish endogenous insulin



Diabetes Mellitus

production. This an etiology distinguishes type 1 origin from type 2; that is, whether the patient is insulin resistant (type 2) or insulin deficient without insulin resistance (type 1).

- Type 1 diabetes, formerly known as ‘childhood’, ‘juvenile’ or ‘insulin-dependent’ diabetes, is not exclusively a childhood problem.
- Type 1 diabetes is treated with insulin replacement therapy, usually by insulin injection or insulin pump, along with attention to dietary management and careful monitoring of blood glucose levels.
- The most definitive laboratory test to distinguish type 1 from type 2 diabetes is the C-peptide assay, which is a measure of endogenous insulin production.
- With type 2 diabetes, proinsulin can be split into insulin and C-peptide; lack of C-peptide indicates type 1 diabetes. The presence of anti-islet antibodies or absence of insulin resistance (determined by a glucose tolerance test) is also suggestive of type 1. Homeostasis Model Assessment (HOMA) = $F1 * FG / 405$

Type 2 diabetes

- Type 2 diabetes (**non-insulin-dependent diabetes mellitus** (NIDDM) or **adult-onset diabetes**) is a metabolic disorder characterized of two processes: a slowly developing **resistance to insulin** signaling and a compensatory **increase in β -cell release of the hormone**. With time β -cells no longer produce enough insulin to maintain control of metabolism and type 2 diabetes results.
- While the underlying cause of insulin resistance is unknown, there is see correlation between **obesity, increased plasma lipids and resistance**. Insulin resistance is generally ‘post receptor’, meaning it is a problem with the cells that respond to insulin rather than a problem with production of insulin.
- Central obesity (fat concentrated around the waist in relation to abdominal organs, but not subcutaneous fat) is known to predispose individuals to insulin resistance.
- Abdominal fat is especially active hormonally, secreting a group of hormones called adipokines, which may possibly impair glucose tolerance. Obesity is found in approximately 55% of patients diagnosed with type 2 diabetes.
- There is also a strong inheritable genetic connection in type 2 diabetes. Having relatives (especially first degree) with this disorder substantially increases the risk of developing type 2 diabetes. Environmental exposures may contribute to recent increases in the rate of type 2 diabetes.



Diabetes Mellitus

A comparison and explanation of the common symptoms of types 1 and 2 diabetes

Symptom	Type 1 diabetes	Type 2 diabetes
Tiredness	Inefficient utilisation of fuels	Inefficient utilisation of fuels
Thirst/polyuria	High glucose (osmotic diuresis)	–
Very low insulin	Damage to insulin-producing β -cells	–
Raised insulin	–	Suggests insulin resistance – linked with obesity
Weight loss	Protein catabolism to provide amino acids for gluconeogenesis, and utilisation of fats for energy	–
Raised HbA1c	High – blood glucose constantly high	Moderate – blood glucose often higher than normal
Ketonuria	Increased metabolism of fats, raised acetyl CoA and increased ketogenesis	–

Glycation

- Many of the pathological effects of diabetes arise from the process of glycation.
- Glycation is the non-enzymatic and haphazard condensation of the aldehyde and ketone groups in sugars with amino groups in proteins, leading to their functional impairment (the enzyme-controlled addition of sugars to protein or lipid molecules is termed glycosylation).
- These may undergo further chemical reactions to produce ‘advanced glycation end products’, or (AGEs). Glycation damages collagen in blood vessel walls, leading to inflammation and atherosclerosis.
- This process is now considered to be a major contributor to diabetic pathology and has resulted in greater clinical emphasis on good glycaemic control.
- Clinical measurement of glycated haemoglobin (HbA1c) and serum albumin is used to assess the adequacy of blood sugar regulation in diabetic patients (see in table). Normal (non-diabetic) values of glycated haemoglobin are 4.0–6.5%; that is, approximately 6 red cells out of every 100 will have glucose attached.

Clinical HbA1c level

HbA1c (%)	Normal/abnormal	Average blood glucose (mM)
4–6.5	Normal (without diabetes)	3–8
6.5–7.5	Target range (with diabetes)	8–10
8–9.5	High	11–14
>9.5	Very high	>15