Diabetes Mellitus

Diabetes mellitus is a disease caused by deficiency or diminished effectiveness of endogenous insulin. It is characterised by hyperglycaemia, deranged metabolism and sequelae predominantly affecting the vasculature. The main types of diabetes mellitus are:

- Type 1 diabetes mellitus: results from the body's failure to produce sufficient insulin.
- Type 2 diabetes mellitus: results from resistance to the insulin, often initially with normal or increased levels of circulating insulin.
- Gestational diabetes: pregnant women who have never had diabetes before but who have high blood glucose levels during pregnancy are said to have gestational diabetes. Gestational diabetes affects about 4% of all pregnant women. It may precede development of type 2 (or rarely type 1) diabetes.
- Maturity-onset diabetes of the young (MODY) includes several forms of diabetes with monogenetic defects of beta-cell function (impaired insulin secretion), usually manifesting as mild hyperglycaemia at a young age and usually inherited in an autosomal-dominant manner.
- Secondary diabetes: accounts for only 1-2% of patients with diabetes mellitus. Causes include:
  - Pancreatic disease: cystic fibrosis, chronic pancreatitis, pancreatectomy, carcinoma of the pancreas.
  - Endocrine: Cushing's syndrome, acromegaly, thyrotoxicosis, phaeochromocytoma, glucagonoma.
  - Drug-induced: thiazide diuretics, corticosteroids, atypical antipsychotics, antiretroviral protease inhibitors.
  - Congenital lipodystrophy.
  - Acanthosis nigricans.
  - Genetic:
    - Wolfram's syndrome (which is also referred to as DIDMOAD: diabetes insipidus, diabetes mellitus, optic atrophy and deafness).
    - Friedreich's ataxia.
    - Dystrophia myotonica.
    - Haemochromatosis.
    - Glycogen storage diseases.

Some patients with type 2 diabetes require insulin, so the old terms of insulin-dependent diabetes mellitus (IDDM) for type 1 diabetes and non-insulin-dependent diabetes mellitus (NIDDM) for type 2 diabetes are inappropriate. Type 2 diabetes is increasingly diagnosed in children and adolescents and so the old term maturity-onset diabetes for type 2 diabetes is also inappropriate.

Editor’s Note

March 2018 - Dr Hayley Willacy recommends the recent Lancet paper proposing a new classification model for adult-onset diabetes. Researchers from Sweden and Finland say the model can identify individuals with increased risk of complications at diagnosis.

- Cluster 1: SAID (severe autoimmune diabetes) - type 1 diabetes and latent autoimmune diabetes in adults (LADA).
- Cluster 2: SSDD (severe insulin-deficient diabetes) - high HbA1C, impaired insulin secretion and moderate insulin resistance.
- Cluster 3: SIRD (severe insulin-resistant diabetes) - obesity and severe insulin resistance.
- Cluster 4: MOD (mild obesity-related diabetes) - obesity without insulin resistance.
- Cluster 5: MARD (mild age-related diabetes) - similar to cluster 4 but comprising older adults and only modest metabolic disarrangement.

Individuals in cluster 3 (most resistant to insulin) have a significantly higher risk of diabetic kidney disease than individuals in clusters 4 and 5 who had been prescribed similar diabetes treatment. Cluster 2 (insulin deficient) have the highest risk of retinopathy.

Type 1 diabetes mellitus

The development of type 1 diabetes mellitus is based on a combination of a genetic predisposition and an autoimmune process that results in gradual destruction of the beta cells of the pancreas, leading to absolute insulin deficiency. There is usually a pre-diabetic phase where autoimmune has already developed but with no clinically apparent insulin dependency. Insulin autoantibodies can be detected in genetically predisposed individuals as early as 6-12 months of age.

Possible triggers for the process may include viruses, dietary factors, environmental toxins, and emotional or physical stress. Early cessation of breast-feeding has also been linked to increased risk of developing type 1 diabetes, but the association is unproven and controversial.

- Approximately 15% of those with diabetes have type 1 diabetes - usually juvenile-onset, but it may occur at any age. It may be associated with other autoimmune diseases. It is characterised by insulin deficiency.
There is 30-50% concordance in identical twins and a positive family history in 10% of people with type 1 diabetes. Screening for the diagnosis of diabetes in first-degree relatives of patients with type 1 is therefore reasonable, keeping in mind that the absolute risk is quite low.

- Associated with HLA DR3 and DR4 and islet cell antibodies around the time of diagnosis.
- Patients always need insulin treatment and are prone to ketoacidosis.
- The most at-risk population for type 1 diabetes is Caucasian of northern European ancestry. Incidence is high in Scandinavian people.

**Type 2 diabetes mellitus**

- Approximately 85% of those with diabetes; they are usually older at presentation (usually >30 years of age) but it is increasingly diagnosed in children and adolescents.
- Type 2 diabetes is associated with excess body weight and physical inactivity.
- All racial groups are affected but there is increased prevalence in people of South Asian, African, African-Caribbean, Polynesian, Middle-Eastern and American-Indian ancestry.
- It is caused by impaired insulin secretion and insulin resistance and has a gradual onset.
- Those with type 2 diabetes may eventually need insulin treatment.

**Epidemiology**

The increasing prevalence of diabetes worldwide has led to a situation where approximately 360 million people had diabetes in 2011, of whom more than 95% would have had type 2 diabetes. This number is estimated to increase to 552 million by 2030 and it is thought that about half of those will be unaware of their diagnosis.\[6\]

**Risk factors for type 2 diabetes\[7\]**

- Obesity, especially central (truncal) obesity.
- Lack of physical activity.
- Ethnicity: people of South Asian, African, African-Caribbean, Polynesian, Middle-Eastern and American-Indian descent are at greater risk of type 2 diabetes, compared with the white population.
- History of gestational diabetes.
- Impaired glucose tolerance.
- Impaired fasting glucose.
- Drug therapy - e.g., combined use of a thiazide diuretic with a beta-blocker.
- Low-fibre, high-glycaemic index diet.
- Metabolic syndrome.
- Polycystic ovary syndrome.
- Family history (2.4-fold increased risk for type 2 diabetes).
- Adults who had low birth weight for gestational age.
- Statins have been associated with a small, but statistically significant risk of new-onset diabetes. Patients with risk factors for developing diabetes mellitus may be at higher risk. This risk is likely outweighed by the benefits of reducing cardiovascular risk.\[8\]

**Presentation**

- Patients with all types of diabetes may present with polyuria, polydipsia, lethargy, boils, pruritus vulvae or with frequent, recurrent or prolonged infections.
- Patients with type 1 diabetes may also present with weight loss, dehydration, ketonuria and hyperventilation. Presentation of type 1 diabetes tends to be acute with a short duration of symptoms.
- Presentation in patients with type 2 diabetes tends to be subacute with a longer duration of symptoms.
- Patients with diabetes may present with acute or chronic complications, as outlined in the section ‘Complications’, below.

**Diagnosis**

- Diabetes may be diagnosed on the basis of one abnormal plasma glucose (random ≥11.1 mmol/L or fasting ≥7 mmol/L) in the presence of diabetic symptoms such as thirst, increased urination, recurrent infections, weight loss, drowsiness and coma.
- In asymptomatic people with an abnormal random plasma glucose, two fasting venous plasma glucose samples in the abnormal range (≥7 mmol/L) are recommended for diagnosis.
- Two-hour venous plasma glucose concentration ≥11.1 mmol/L two hours after 75 g anhydrous glucose in an oral glucose tolerance test (OGTT).
- The World Health Organization (WHO) now recommends that glycated haemoglobin (HbA1c) can be used as a diagnostic test for diabetes. An HbA1c of 48 mmol/mol (6.5%) is recommended as the cut-off point for diagnosing diabetes. A value less than 48 mmol/mol does not exclude diabetes diagnosed using glucose tests.\[9\] See also the separate Glycated Haemoglobin (HbA1c) article.

**Assessment and monitoring**

- Assessment: see the separate Assessment of the Patient with Established Diabetes article.
- Monitoring: see the separate Glycated Haemoglobin (HbA1c) and Self-Monitoring in Diabetes Mellitus articles.
Management

The management plan for a person with diabetes includes.[7]

- Diabetes education: structured education and self-management (at diagnosis and regularly reviewed and reinforced) to promote awareness.
- Diet and lifestyle: healthy diet, weight loss if the person is overweight, smoking cessation, regular physical exercise.
- Maximising glucose control while minimising adverse effects of treatment, such as hypoglycaemia.
- Reduction of other risk factors for complications of diabetes, including the early detection and management of hypertension, drug treatment to modify lipid levels and consideration of antiplatelet therapy with aspirin.
- Monitoring and early intervention for complications of diabetes, including cardiovascular disease, eye problems, kidney problems and neuropathy.

A global assessment of an individual's cardiovascular risk is essential. See the separate Cardiovascular Risk Assessment article.

See the separate articles:

- Management of Type 1 Diabetes.
- Management of Type 2 Diabetes.
- The Patient with Newly-diagnosed Diabetes.
- Diabetes Diet and Exercise.
- Diabetes Education and Self-management Programmes.
- Antihyperglycaemic Agents used for Type 2 Diabetes.
- Insulin Regimens.
- Precautions with Patients with Diabetes Undergoing Surgery.
- Diabetes and Intercurrent Illness.
- Diabetes in Pregnancy.
- Gestational Diabetes.

Acute complications

- See Diabetic Ketoacidosis and Hyperosmolar Hyperglycaemic State.
- See Emergency Management of Hypoglycaemia.

Chronic complications

- Cardiovascular disease: see coronary heart disease (Stable Angina, Acute Coronary Syndrome), Cerebrovascular Events and Peripheral Arterial Disease.
- See Diabetic Nephropathy.
- See Diabetic Retinopathy and Diabetic Eye Problems.
- See Diabetic Neuropathy, Autonomic Neuropathy and Neuropathic Pain and its Management.
- See Diabetic Foot, Leg Ulcers and Painful Foot.
- Frequent, recurrent and persistent infections.

Prognosis

Type 1 diabetes[10]

- Many people with type 1 diabetes have good health but there is an increased risk of severe sight impairment, end-stage kidney disease, cardiovascular disease and, in some cases, early death.
- Controlling blood glucose, lipids, blood pressure and weight are important prognostic factors.

Type 2 diabetes[7]

- 75% of people with type 2 diabetes will die of heart disease and 15% of stroke.
- The mortality rate from cardiovascular disease is up to five times higher in people with diabetes than in people without diabetes.
- For every 1% increase in HbA1c level, the risk of death from a diabetes-related cause increases by 21%.

Prevention

Type 1: despite a great deal of ongoing research, there are currently no interventions before diagnosis that have shown any benefit.[11]

There is now an emerging interest as to whether vaccination can be applied in autoimmune and inflammatory conditions. Vaccination may have a future role in the prevention of type 1 diabetes. [13]

Type 2: see the separate Prevention of Type 2 Diabetes article.
Further reading & references

1. Maturity-onset Diabetes of The Young; Online Mendelian Inheritance in Man (OMIM)
2. Wolfram Syndrome 1, WFS1; Online Mendelian Inheritance in Man (OMIM)
6. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD; European Heart Journal (2013)
7. Diabetes - type 2; NICE CKS, October 2015 (UK access only)
9. Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus; World Health Organization, 2011
10. Diabetes - type 1; NICE CKS, December 2014 (UK access only)

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