Diabetes mellitus DM.

Definition

Diabetes mellitus comprises a heterogeneous group of metabolic diseases that are characterized by chronic hyperglycemia and disturbances in carbohydrate, lipid, and protein metabolism resulting from defects in insulin secretion, insulin action, or both.

Diabetes, the sixth leading cause of death by disease in the United States, and it is the leading cause of end-stage renal disease(***ESRD***), new cases of ***blindness***, and non-traumatic ***lower limb amputations*** in the United States.

Classification

The classification of diabetes includes four clinical classes:

- **Type 1 diabetes** (*5% to 10% of people with diabetes*) results from β-cell destruction, usually leading to absolute insulin deficiency.
- **Type 2 diabetes** *(90% to 95% of people with diabetes)* results from a progressive insulin secretory defect on the background of insulin resistance.
- **Other specific types of diabetes** due to other causes(*1% to 2% of patients with diabetes*), e.g., ***Genetic defects in β-cell function, genetic defects in insulin action, diseases of the exocrine pancreas*** e.g. (pancreatitis, pancreatectomy, neoplastic disease, cystic fibrosis, haemochromatosis, fibrocalculouspancreatopathy).
  Drug or chemical induced. (e.g. corticosteroids, thiazide diuretics, phenytoin). ***Endocrinopathies*** (e.g. growth hormone-acromegaly; Glucocorticoids-Cushing's syndrome; glucagon-glucagonoma; catecholamines-phaeochromocytoma; thyroid hormones-thyrotoxicosis). ***Infections***. (e.g. congenital rubella, mumps, Coxsackie virus B).
- **Gestational diabetes mellitus** (GDM) (diabetes diagnosed during pregnancy that is not clearly overt diabetes).

Distinguishing between T1DM and T2DM is not always a simple process. T2DM is diagnosed in children as young as 6 years and may account for as many as 25% to 33% of all new cases of diabetes diagnosed in adolescents 9 to 19years of age, often associated with an increase in weight and parallel decrease in physical activity.

These adolescents may even present in DKA before they ultimately achieve control of their disease with diet and oral antihyperglycemic agents.

T1DM can also occur in elderly patients. This condition has been described as latent autoimmune diabetes of adulthood[LADA] (also known as late-onset autoimmune diabetes, or type 1.5DM) and may account for many insulin-requiring patients previously misclassified as T2DM.

Type 1 diabetes

Is a disease resulting from absolute insulin deficiency, usually caused by autoimmune destruction of pancreatic islet cells.
The initial clinical presentation may be ketoacidosis with an acute illness, or a more gradual presentation with symptoms of hyperglycemia. Other autoimmune disorders may also be present such as Addison's disease, thyroiditis, and pernicious anemia.

Pathogenesis

Generally, T1DM is an autoimmune disease in which some environmental insult (microbial, chemical, or dietary) triggers an autoimmune reaction in a genetically susceptible individual.
HLA-DR3 or HLA-DR4 is present in 90% to 95% of patients with T1DM compared with 45% to 50% in the general population.
destruction of the B- cells of the islets of Langerhans is associated with several autoantibodies to islet cell constituents.
Hyperglycemia accompanied by the classical symptoms of diabetes occurs only when 70-90% of β cells have been destroyed.
At this time, the critical mass of remaining cells (10% to 20%) is unable to sustain compensatory insulin secretion at a level sufficient to maintain normal blood glucose values.
Genetic factors account for about ***one-third*** of the susceptibility to type 1 diabetes, the inheritance of which is ***polygenic***.

The typical patient with type 1 diabetes:

- Is often diagnosed as a child or young adult (although it can occur at any age).
- Is lean (i.e., BMI less than 25 kg/m2).
- Displays normal insulin sensitivity, i.e., insulin requirements do not exceed 0.7 units of insulin/kilogram body weight/24 hours.
- Displays evidence of anti-beta cell autoimmunity (i.e., anti-GAD, anti-IA-2, and/or anti-insulin antibodies).
- Is more "ketosis prone" than individuals with type 2 diabetes.

Risk of developing type 1 diabetes in an individual who has a first-degree relative with type 1 diabetes

Relative with type 1 diabetes	***% overall risk***
Identical twin	35
Non-identical twin	20
HLA-identical sibling	16
Non-HLA-identical sibling	3
Father	9
Mother	3
Both parents	Up to 30

Type 2 diabetes

Is a disease resulting from a relative, rather than an absolute, insulin deficiency with an underlying insulin resistance.

Type 2 diabetes is associated with obesity particularly visceral or central (as evidenced by the hip-waist ratio), is very common in type 2 DM (≥80% of patients are obese). Type 2 diabetes is also associated with age, and physical inactivity. Patients with type 2 diabetes are not prone to ketoacidosis, frequently do not require insulin, and may be asymptomatic, despite being hyperglycemic for many years.

Type 2 diabetes is a more complex condition than type 1 diabetes because there is a combination of resistance to the actions of insulin in liver and muscle together with impaired pancreatic β-cell function leading to 'relative' insulin deficiency. Insulin resistance appears to come first, and leads to elevated insulin secretion in order to maintain normal blood glucose levels. IGT, characterized by elevations in postprandial glucose, then develops. A further decline in insulin secretion and an increase in hepatic glucose production lead to overt diabetes with fasting hyperglycemia. Ultimately, beta cell failure ensues. Although both insulin resistance and impaired insulin secretion contribute to the pathogenesis of type 2 DM, the relative contribution of each varies from individual to individual.

However, in susceptible individuals the pancreatic β cells are unable to sustain the increased demand for insulin and a slowly progressive insulin deficiency develops.

Genetic factors are important in type 2 diabetes, as shown by marked differences in susceptibility in different ethnic groups and by studies in monozygotic twins where concordance rate for type 2 diabetes approach 100%.

Type 2 diabetes is associated ***with overeating***, especially when combined with ***obesity*** and ***underactivity***.

The risk of developing type 2 diabetes increases ***tenfold*** in people with a body mass index (BMI) > 30 kg/m2.

However, although the majority of patients with type 2 diabetes are obese, only a minority of obese people develop diabetes.

Type 2 diabetes is more common in the middle-aged and elderly.

The typical patient with type 2 diabetes:

 Is more likely to be diagnosed as an adult.
 Is overweight or obese (i.e., BMI >25 kg/m2, and often far exceeding that BMI).
 Is more likely to have a family history of diabetes (>90% of those with type 2 diabetes will have a first degree relative with the disease).
 If treated with insulin, is more likely to require very large doses to control the blood glucose (e.g., >0.7 units/kg/day) due to insulin resistance. Such individuals frequently have characteristics associated with insulin resistance, including abdominal obesity, hypertension, lipid abnormalities, atherosclerosis, and hyperuricemia.
 Does not have evidence of anti-beta cell specific antibodies.
 Is much less likely to have a history of diabetic ketoacidosis (DKA), but may have a history of hyperosmolar coma.
 Is more likely to suffer other consequences of the "metabolic syndrome," e.g. hypertension, hyperlipidemia.

The 'insulin resistance syndrome';

Type 2 diabetes, or its antecedent ***impaired glucose tolerance***, is often associated with other disorders, *particularly central (visceral) obesity*, *hypertension and dyslipidemia* (characterized by elevated levels of small dense low-density lipoprotein (LDL) cholesterol and triglycerides, and a low level of high-density lipoprotein (HDL) cholesterol). It has been suggested that coexistence of this cluster of conditions, all of which predispose to cardiovascular disease, is a specific entity (***the 'insulin resistance syndrome' or 'metabolic syndrome')***, with insulin resistance being the primary defect and the presence of obesity being a powerful amplifier of the insulin resistance.

*Features of the insulin resistance (metabolic) syndrome**

- Hyperinsulinaemia.
- Type 2 diabetes or impaired glucose tolerance.
- Hypertension.
- Low HDL cholesterol; elevated triglycerides
- Central (visceral) obesity
- Microalbuminuria and Increased fibrinogen .
- Increased plasminogen activator inhibitor-1.
- Increased C-reactive protein (CRP).
- Elevated plasma uric acid.

Clinical features of DM

Symptoms of hyperglycaemia

- Thirst, dry mouth
- Polyuria
- Nocturia
- Tiredness, fatigue, lethargy
- Noticeable change in weight (usually weight loss)

- Blurring of vision
- Pruritus vulvae, balanitis (genital candidiasis)
- Nausea; headache,apathy.
- Hyperphagia; predilection for sweet foods
- Mood change, irritability, difficulty in concentrating.

Diagnosis of DM

ADA Diagnostic Criteria for Diabetes and Pre-Diabetes .

❖ ***Normal***

1. Fasting plasma glucose <100 mg/dl.
or
2. Oral glucose tolerance test (OGTT) 2-hr plasma glucose <140 mg/dl.

❖ ***Pre-Diabetes***

1. ***HbA1C*** range of 5.7–6.4%.
or
2. ***Impaired fasting glucose*** (IFG) = fasting plasma glucose of 100–125 mg/dl.
or
3. ***Impaired glucose tolerance*** (IGT) = OGTT 2-hr plasma glucose of 140–199 mg/dl.

❖ ***Diabetes***

1. ***HbA1C >6.5%.*** The test should be performed in a laboratory using a method that is certified by the National Glycohemoglobin Standardization Program (NGSP) and standardized to the Diabetes Control and Complications trial (DCCT) assay.
or
2. ***Fasting plasma glucose >126 mg/dl.*** Fasting is defined as no caloric intake for at least eight hours.
or
3. ***2-h plasma glucose >200 mg/dl during an oral glucose tolerance test.*** The test should be performed using a glucose load containing the equivalent of 75-g anhydrous glucose dissolved in water.
or
4. ***Symptoms of diabetes and a casual(random) plasma glucose >200 mg/dl.*** "Casual"or random is defined as any time of day, without regard to the time since the last meal. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.

****To definitively make the diagnosis of diabetes, these criteria should be confirmed on another day using any of the three tests.****

In some people, an abnormal blood glucose result is observed under conditions which impose a burden on the pancreatic β cells, e.g. during pregnancy, infection, myocardial infarction or other severe stress, or during treatment with diabetogenic drugs such as corticosteroids.

This 'stress hyperglycaemia' usually disappears after the acute illness has resolved. However, blood glucose should be remeasured and an OGTT will often show persistence of impaired glucose tolerance.

The diagnostic criteria for diabetes in pregnancy are more stringent than those recommended for non-pregnant subjects.

Pregnant women with abnormal glucose tolerance should be referred urgently to a specialist unit for full evaluation.
When a diagnosis of diabetes is confirmed, other investigations should include plasma urea, creatinine and electrolytes, lipids, liver and thyroid function tests, and urine testing for ketones, protein or microalbuminuria.

SCREENING;

Widespread use of the FPG or the HbA1c as a screening test for type 2 DM is recommended because (1) a large number of individuals who meet the current criteria for DM are asymptomatic and unaware that they have the disorder, (2) epidemiologic studies suggest that type 2 DM may be present for up to a decade before diagnosis, (3) some individuals with type 2 DM have one or more diabetes-specific complications at the time of their diagnosis, (4) treatment of type 2 DM may favorably alter the natural history of DM, diagnosis of prediabetes should spur efforts for diabetes prevention. The ADA recommends screening all individuals >45 years every 3 years and screening individuals at an earlier age if they are overweight (BMI >25 kg/m2 or ethnically relevant definition for overweight) and have one additional risk factor for diabetes.

Risk Factors for Type 2 Diabetes Mellitus;

1-Family history of diabetes (i.e., parent or sibling with type 2 diabetes)
2-Obesity (BMI ≥25 kg/m2 or ethnically relevant definition for overweight)
3-Physical inactivity
4-Race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
5-Previously identified with IFG, IGT, or an hemoglobin A1c of 5.7‑6.4%
6-History of GDM or delivery of baby >4 kg (9 lb)
7-Hypertension (blood pressure ≥140/90 mmHg)
8-HDL cholesterol level <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.82 mmol/L)
9-Polycystic ovary syndrome or acanthosis nigricans
10-History of cardiovascular disease.

Clinical assessment of diabetic patient;

The classical symptoms of thirst, polyuria, nocturia and rapid weight loss are prominent in type 1 diabetes, but are often absent in patients with type 2 diabetes, many of whom are asymptomatic or have non-specific complaints such as chronic fatigue and malaise. Uncontrolled diabetes is associated with an increased susceptibility to infection and patients may present with skin

sepsis (boils) or genital candidiasis, and complain of pruritus vulvae or balanitis. A history of pancreatic disease, particularly in patients with a history of alcohol excess, makes insulin deficiency more likely, although such patients may develop incidental classical type 2 diabetes.

While the distinction between type 1 and type 2 diabetes is usually obvious, overlap occurs particularly in age at onset, duration of symptoms and family history. A few young people have a form of diabetes designated 'maturity-onset diabetes of the young' (MODY-Diabetes develops during adolescence/early adulthood and can be managed with diet and tablets for many years; they usually have a remarkably strong family history of early-onset diabetes).

Classical type 2 diabetes is developing increasingly in obese sedentary young people, including children. Some middle-aged and elderly people present with typical autoimmune type 1 diabetes. Some patients with type 2 diabetes have advanced pancreatic β-cell failure at the time of presentation and require treatment with insulin. For these reasons, the definitive diagnosis of the type of diabetes may sometimes be unclear until the natural history or responsiveness to different therapies becomes apparent with time.

The physical signs in patients with type 2 diabetes at diagnosis depend on the mode of presentation.

In Western populations more than 80% are overweight, and the obesity is often central (truncal or abdominal). Obesity is much less evident in Asians. Hypertension is present in at least 50% of patients with type 2 diabetes. Although dyslipidaemia is also common, skin lesions such as xanthelasma and eruptive xanthomas are rare.

An increasing number of patients now present with non-alcoholic fatty liver disease, usually identified by their elevated blood transaminase values, but they may also have non-tender hepatomegaly.