

Diabetes Mellitus

(Lecture 1)

Objectives

- 1. To define diabetes mellitus***
- 2. To give an account on the classification of diabetes.***
- 3. To give an account on the pathogenesis of T1D.***
- 4. To illustrate the pathophysiology of T1D.***
- 5. To give an account on the pathogenesis of T2D.***
- 6. To illustrate the pathophysiology of T2D***

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- 1. Definition of diabetes mellitus***
- 2. Classification of diabetes.***
- 3. Pathogenesis of T1D.***
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- 6. Pathophysiology of T2D.***

Definition

Diabetes mellitus (D.M) :

***Diabetes mellitus (D.M)* is a metabolic disorder of multiple aetiology characterized by chronic hyperglycemia associated with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both.**

Chronic hyperglycemia is associated with long-term damage and dysfunction of various organs, particularly the heart, kidneys, eyes, nerves and the vascular system.

Aetiological Classification

Type 1 diabetes

Usually affect thin younger people, mostly children

It is due to absolute insulin lack

There is slower onset form of T1D:

latent autoimmune diabetes (**LADA**),

occurs in adults

Type 2 diabetes

Usually affect over weight and obese adults

It is due to insulin resistance and gradual *B* – cell failure

Other specific types:

A. Genetic defects of β cell function

e.g. maturity-onset diabetes of the young (MODY)

B. Pancreatic disease:

e.g. Pancreatitis, Pancreatectomy, Neoplastic disease, Cystic fibrosis, Haemochromatosis)

C. Excessive production of Insulin Antagonists:

e.g. Acromegaly, Cushing's syndrome, Glucagonoma, Pheochromocytoma, Thyrotoxicosis

Other specific types (cont'd):

D. Drugs:

e.g. Corticosteroids, Thiazide diuretics, Phenytoin

E. Viral infections:

e.g. Congenital rubella, Mumps, Coxsackie B virus

F. Associated with genetic syndromes:

e.g. (Down's syndrome, Klinefelter's syndrome , Turner's syndrome, DIDMOAD, Friedrich's ataxia, Myotonic dystrophy

Gestational diabetes

Hyperglycaemia occurring for the first time during pregnancy

Unclassified diabetes

Diabetes that cannot be categorized into specific type at the time of diagnosis

Pathogenesis of T1D

T1D is a **T cell-mediated autoimmune disease** involving selective destruction of the insulin-secreting β cells in the pancreatic islets.

Genetic factors account for about one-third of the susceptibility to T1D, the inheritance of which is polygenic.

Pathogenesis of T1D

Over 40 different regions of the human genome show some linkage with T1D but most interest has focused on the human leucocyte antigen (HLA) region class II within the major histocompatibility complex on the short arm of chromosome 6.

The HLA loci *DR3*, *DR4*, *DQ8*, *DQ2* are associated with increased susceptibility to T1D

Environmental factors have an important role in promoting clinical expression of the disease.

Pathogenesis of T1D

1. Normal pancreatic islets.

Genetic susceptibility to immune dysfunction.

2. Environmental triggers and regulators leading to:

Insulinitis.

3. Loss of first phase insulin secretion.

Impaired glucose tolerance.

4. Beta-cell dysfunction.

Overt Diabetes.

Pathophysiology of T1D

A. No insulin (severe deficiency).

B. Increased counter regulatory hormones:

1. Unrestrained gluconeogenesis, lipolysis and ketogenesis.

2. Blocked peripheral glucose utilization.

C. Protein catabolism with muscle wasting and negative nitrogen balance.

D. Leads to ketoacidosis.

Pathogenesis of T2D

T2D is a more complex condition than T1D because there is a combination of:

1. *Insulin Resistance.*

with:

2. *Gradual beta – Cell Failure.*

Genetic predisposition

Genetic factors are important in type 2 diabetes, as shown that the concordance rate for T2D in monozygotic twins approach 100%.

Pathogenesis of T2D

1. *Insulin Resistance (IR)*

The primary cause of IR remains *unclear*.

A. *Intra-abdominal adipose tissue:*

Is metabolically active, and releases large quantities of FFAs which may induce IR because they compete with glucose as a fuel supply for oxidation in peripheral tissues such as muscle.

Pathogenesis of T2D

1. *Insulin Resistance (IR)*

B. Adipokines:

Adipose tissue releases a number of **adipokines**: including **Leptin**, **adiponectin** and **Resistin** acting on specific receptors to influence sensitivity to insulin in other tissues.

Pathogenesis of T2D

1. Insulin Resistance (IR)

C. Central obesity :

May have a particularly potent influence on insulin sensitivity in the liver, and thereby adversely affect gluconeogenesis and hepatic lipid metabolism.

Pathogenesis of T2D

1. Insulin Resistance (IR)

D. Physical activity state:

Is another important determinant of insulin sensitivity. Inactivity is associated with down-regulation of insulin-sensitive kinases and may promote accumulation of FFAs within skeletal muscle. Sedentary people are therefore more insulin-resistant than active people with the same degree of obesity.

Pathogenesis of T2D

2. *Pancreatic B-cell failure*

In the early stages of T2D, reduction in the total mass of pancreatic islet tissue is modest.

At the time of diagnosis, around 50-65 % of β -cell function has been lost and this declines progressively with time.

Pathogenesis of T2D

2. *Pancreatic B-cell failure*

Some pathological changes are typical of T2D, the most consistent of which is *deposition of amyloid*.

Elevated plasma glucose and FFAs exert toxic effects on pancreatic β cells to impair insulin secretion.

Pathophysiology of T2D

A. Insulin resistance:

- 1. *hepatic and peripheral.***
- 2. *Impaired postprandial glucose uptake especially in skeletal muscles.***

B. Increased glucagon:

Enhanced hepatic glucose output.

C. Ketoacidosis rarely develops.