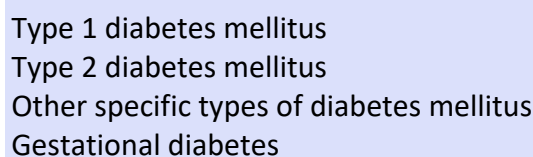


1. PATHOPHYSIOLOGY OF DIABETES MELLITUS

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Diabetes mellitus is heterogeneous group of disorders, connected by raised plasma glucose concentration and disturbance of glucose metabolism. Glucose is under-utilised with resulting hyperglycaemia. It is necessary to say that, in most cases, the real aetiology is still clouded. The World Health Organisation (WHO) has prepared a number of classification schemes of diabetes mellitus; nowadays the following is mostly accepted (Figure 1).



Type 1 diabetes mellitus
Type 2 diabetes mellitus
Other specific types of diabetes mellitus
Gestational diabetes

Figure 1. Classification scheme of diabetes mellitus

1.1. Basic concept of glucose metabolism

Glucose is the primary source of energy for the human body. Absorbed from the intestine it is metabolised by

- energy production (by conversion to water and carbon dioxide)
- conversion to amino acids and proteins or keto-acids
- storage as glycogen

Metabolism of glucose is regulated by complex orchestration of hormones activities. Dietary sugars are broken down into various carbohydrates. The most important is glucose, metabolised in nearly all body cells. Glucose enters the cell by facilitated diffusion (glucose transport proteins). This facilitated transport is stimulated very rapidly and effectively by an insulin signal (glucose transport into muscle and adipose cells is increased up to twenty fold). After glucose is transported into the cytoplasm, insulin then directs the disposition of it - conversion of glucose to glycogen, to pyruvate and lactate, and to fatty acids. Diabetes was initially diagnosed by the use of oral glucose tolerance test (oGTT) and the criteria were changed many times by WHO and ADA. The former term like IDDM - insulin-dependent diabetes mellitus, NIDDM - non-insulin dependent DM, juvenile-onset DM or adult-onset DM were abolished.

1.2. Type 1 diabetes mellitus

The terms insulin-dependent diabetes or juvenile-onset diabetes previously encompassed this type of diabetes. Type 1 diabetes results from an autoimmune destruction of the β -cells of the pancreas. There are several markers of this autoimmune destruction, detectable in

body fluids and tissues:

- islet cell autoantibodies (ICAs)
- autoantibodies to insulin (IAAs)
- autoantibodies to glutamic acid decarboxylase (GAD65)
- autoantibodies to the tyrosine phosphatases IA-2 and IA-2 β .

Despite increased knowledge, we are still far from understanding the aetiology of Type 1 DM. There are no doubts that genetic factors are strongly implicated as several genetic factors have been identified. On the other hand the concordance rate in twin studies is under 50% supporting the very important role of environmental factors, amongst which viral infections have to be counted. Type 1 diabetes mellitus results from a cellular-mediated autoimmune destruction of the insulin-secreting cells of pancreatic β -cells. The autoimmune process begins many years before clinical detection and presentation. The destruction must be very heavy as 10-20% of the volume of β -cells is sufficient to cover clinical symptoms. The rate of β -cell destruction is quite variable, being rapid in some individuals (mainly infants and children) and usually slow in adults.

1.2.1. Genetic factors

Type 1 diabetes mellitus is strongly genetically linked with HLA on chromosome 6 and 60% of the genetic susceptibility to Type 1 diabetes is conferred by the HLA system. Recent studies have indicated that HLA-DR3-DQ2, HLA-DR4, and DQ8 are the most important; HLA-DQ6 is negatively associated. Several approaches to identify other susceptibility genes have been taken. Currently there are more than 15 candidate loci identified, most important are on chromosome 2 and 11. It is speculated that these HLA molecules provide antigen presentations that generate T-helper cells that initiate an immune response to specific islet cells autoantigens. This immune response includes the formation of specific T cells, which can kill the insulin-producing cells in the islet of Langerhans, and leads to the formation of autoantibodies.

1.2.2. Antibodies

The most practical markers of β -cell autoimmunity are circulating antibodies that can be detected in the body fluids many years before the disease detection by raised plasma glucose concentration.

Islet cell antibodies (ICA) are focused against the antigen present in the cytoplasm of the endocrine cells in pancreatic islets. The reaction can result in the cell destruction. The usual way to detect ICA is immunofluorescence microscopy and can be found in 70-80% of those with newly diagnosed Type 1 diabetes mellitus. Later on the frequency of ICA presence declines to less than 5% 10 years after the diagnosis.

Insulin autoantibodies (IAA) are present also in other autoimmune diseases; at onset of type 1 diabetes the frequency is about 50% in children. They are less common in adults. The common presence of ICA and IAA significantly increase the risk of the development of type 1 diabetes mellitus.

GAD is a 64-kD enzyme required for the production of g-aminobutyric acid (GABA). Anti-GAD antibodies are present up to 10 years before the clinical onset of type 1 diabetes and its sensitivity for diagnostic purposes is very high. On the other hand specificity is lower as GADA frequency in general population is about 3%.

Insulinoma associated 2 autoantibodies (IA-2A) are focused against the protein tyrosine phosphatase, the family of signal and transducing enzymes. These are present in more than 60% of newly diagnosed persons with type 1 diabetes mellitus.

1.2.3. Environment

There are no doubts that environmental factors are involved in the initiation of diabetes. Viruses (rubella, coxsackie virus B and mumps), chemicals and, sometimes, even cow's milk are the most common factors.

1.3. Type 2 diabetes mellitus

Type 2 diabetes mellitus was formerly known as non-insulin-dependent diabetes mellitus (NIDDM), type II, or adult-onset diabetes. It is much more common than type 1 diabetes and comprises approximately 90% of all individuals with diabetes. The patients are usually older at the onset of disease, mostly present only minimal symptoms. Insulin concentrations are mostly increased but they can be normal or decreased. Obesity is quite common and weight reduction ameliorates the hyperglycaemia. The disease usually develops after 40 years of age. Oral hypoglycaemic drugs and dietary manipulation represent the biggest role in therapy; insulin is sometimes required to correct hyperglycaemia. The groups of disorders, of which two are most common, represent the new knowledge type 2 diabetes mellitus.

The first one is a decreased ability of insulin to act on peripheral tissues. Usually we call it "insulin resistance". Insulin resistance is defined as a decreased biological response to normal concentrations of circulating insulin and represents the primary underlying pathological process. The second is the dysfunction of pancreatic β -cells, represented by the inability to produce sufficient amount of insulin to overcome insulin resistance in the peripheral tissues. Later on the insulin production can be insufficient to compensate the insulin resistance due to β -cells dysfunction. The common result is the relative deficiency of insulin. Long discussion was held about the primary reason - insulin resistance or derangement of insulin production. Data support the concept that insulin resistance is the primary defect, preceding the derangement of insulin secretion. Insulin resistance usually precedes the clinical signs by as much as 20 years. The basis of insulin resistance and insulin secretion defect results from a combination of environmental and genetic factors.

1.3.1. Genetic factors

The contribution of genetic factors to the development of type 2 diabetes mellitus is widely accepted. Twin studies and family penetrance strongly support a genetic basis, but up to now there is no clear resolution. There are several genes associated with type 2 diabetes affecting insulin secretion and action as well as regulate body weight. Type 2 diabetes mellitus remains a "geneticist's nightmare".

1.3.2. Environmental factors

Body weight and exercise are the most important. The links between obesity and type 2 diabetes are complex: although 60-80% of those with type 2 diabetes are obese, diabetes develops in fewer than 15% of obese individuals. The clinical signs and therapy requirement usually go down with weight reduction and body exercise.

1.4. Insulin resistance

Insulin resistance was described first. It is difficult to measure directly in clinical practice and indirect assessments are used - higher fasting insulin concentration or the insulin response to the glucose load. The broad clinical spectrum of insulin resistance exists, with normo- or hyper-glycaemia. Even in patients with normoglycaemia, marked elevation of endogenous insulin concentration is found in plasma.

1.5. Gestational diabetes mellitus

Gestational diabetes mellitus is usually asymptomatic and not life threatening to the mother. The condition is associated with an increased incidence of neonatal morbidity, neonatal hypoglycaemia, macrosomia and jaundice. Even normal pregnancies are associated with increasing insulin resistance, mostly in the second and third trimesters. Euglycaemia is maintained by increasing insulin secretion. In those women who are not able to increase the secretion of insulin, gestational diabetes develops.

The pathophysiology of gestational diabetes mellitus is not well known and includes family history of diabetes mellitus, obesity, complications in previous pregnancy(ies) and advanced maternal age. It is essential to detect pre-existing diabetes mellitus which has a much worse prognosis for the fetus.

1.6. Other specific types of diabetes mellitus

Other specific types of diabetes mellitus are heterogeneous. The following are the biggest groups:

- genetic defects of β -cell function
- genetic defects in insulin action
- diseases of the exocrine pancreas
- other endocrinopathies
- drug- or chemical-induced diabetes mellitus
- infection-induced diabetes mellitus
- rare forms of immune-mediated diabetes
- other genetic syndromes sometimes associated with diabetes

The aetiology and pathophysiology are very different, mostly complicated or connected to insulin secretion and action derangement, as well as signal transduction inside the cells disarrangement.

Recommended literature:

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