DIABETUS MELLITUS: ETIOLOGY, PATHOGENESIS, CLASSIFICATION, DIAGNOSTIC CRITERIA

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Epidemiology

- About 2 to 4% of the world population is affected with DM
- The disease is more common:
  - in persons after age 45
  - in obese individuals
  - in certain ethnic groups
  - in those with a positive family history of DM
- In patients with type 1 DM, complications from end stage renal disease are major cause of death, whereas patients with type 2 diabetes are more likely to have macrovascular diseases leading to myocardial infarction and stroke as main causes of the death
Diabetes mellitus (DM) -

is endocrine – metabolic disease, which develops due to absolute or relative insulin insufficiency and characterized by chronic hyperglycemia, changes of different systems and organs of patient
The term **DM**

- refers to the excretion of large quantities of sweet urine. Diabetes is an old word (from Greece “diabaino”) for siphon and means “dieresis”, mellitus (from Latina “mell”) means honey or “sweet” taste of a urine.
• The clinical syndrome known as DM comprises a wide variety of symptoms, physical findings and laboratory abnormalities, in which multiple etiologic factors are involved, the pathophysiology is partly understood and treatment is unsatisfactory.

• The hallmark of DM is hyperglycemia.
### Hormones of pancreatic gland

<table>
<thead>
<tr>
<th>Type of cells</th>
<th>Quantity of cells (%)</th>
<th>Secreted hormone</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>20 – 25</td>
<td>glucagon</td>
</tr>
<tr>
<td>B</td>
<td>75 – 80</td>
<td>insulin</td>
</tr>
<tr>
<td>Δ</td>
<td>5 – 15</td>
<td>somatostatin</td>
</tr>
<tr>
<td>G</td>
<td>-</td>
<td>gastrin</td>
</tr>
<tr>
<td>PP</td>
<td>5 - 10</td>
<td>pancreatic polypeptide</td>
</tr>
</tbody>
</table>
Insulin

- Molecular weight of this peptic substance is 6000.
- It consists of 51 aminoacidic parts from 16 different aminoacids
Insulin

- The most important biologic stimulator of insulin secretion is *glucose*
The action of insulin

- Insulin is an anabolic hormone (promotes the synthesis of carbohydrates, proteins, lipids and nucleic acids). The most important target organs for insulin action are:
  - the liver, muscles and adipocytes.
  - The brain (nervous tissue), retina, lens and blood cells are unresponsive to insulin.
  - It has no direct influence on kidney also
The effects of insulin on carbohydrate metabolism

- stimulation of glucose transport across muscle and adipose cell membranes;
- regulation of hepatic glycogen synthesis;
- inhibition of glucose formation – from glycogen (glycogenolysis) and – from amino-acid precursors (glyconeogenesis).
- The result of these actions is a reduction in blood glucose concentration.
Protein metabolism:

- the transfer of amino acids across plasma membranes;
- stimulation of protein synthesis;
- inhibition of proteolysis.
Lipid metabolism:

- Incorporation of fatty acids from circulating triglyceride into adipose triglyceride;
- Stimulation of lipid synthesis;
- Inhibition of lipolysis.
Nucleic acids metabolism:

- stimulation of nucleic acid synthesis by stimulating the formation of adenosine triphosphate (ATP), DNA and RNF.

Other effects:

- stimulation of the intracellular flow of potassium, phosphate and magnesium in the heart;

- inhibition of inotropic and chronoropic action (unrelated to hypoglycemia).
Insulin insufficiency

• **Absolute**
  1. Genetic disorders
  2. Autoimmune damaging of β-cells
  3. Damaged caused by viruses such as mumps, or Coxsackie B4
  4. Toxic influence on β-cells
  5. Diseases of pancreatic gland

• **Relative**
  - β-cells
  - Insulin transport
  - Receptors (tissue insensitivity)
Etiologic classification of DM (1999)

I. Type 1 of DM (destruction of β-cells which mostly leads to absolute insulin insufficiency):
   - autoimmune;
   - idiopathic.

II. Type 2 of DM (resistance to insulin and relative insulin insufficiency or defect of insulin secretion with or without resistance to insulin).

III. Other specific types:
   - genetic defects of β-cells function;
   - genetic defects of insulin action;
   - pancreatic diseases (chronic pancreatitis; trauma, pancreatectomy; tumor of pancreatic gland; fibrocalculosis; hemochromatosis);
   - endocrine disease (acromegaly, thyrotoxicosis, Cushing’s syndrome);
   - drug exposures;
   - infections and others.

IV. Gestation diabetes.
Stages of DM development

- I. Prediabetes (risk factors or predispose factors).
- II. Impaired glucose tolerance (latent DM).
- III. Clinical manifestation of DM.
Prediabetes (risk factors or predispose factors)

- obesity;
- positive family history of DM;
- persons which were born with weight more than 4,0 kg;
- women who had children with weight more than 4,0 kg; abortions and dead child in anamnesis;
- persons with: atherosclerosis, hypertension; auto-immune diseases; furunculosis; rubella, mumps, Coxsackie virus, infectious hepatitis, cytomegalovirus, infection mononucleosis;
- endocrine disorders
## Glucose tolerance test (GTT)

<table>
<thead>
<tr>
<th></th>
<th>Fasting serum glucose, mmol/l</th>
<th>2 hours after glucose loading, mmol/l</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Capillary blood</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health</td>
<td>3,3 – 5,5</td>
<td>&lt;7,8</td>
</tr>
<tr>
<td>Impaired glucose tolerance</td>
<td>5,6 – 6,1</td>
<td>7,8 – 11,1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>≥ 6,1</td>
<td>≥ 11,1</td>
</tr>
<tr>
<td>Impaired fast glucose tolerance</td>
<td>5,6 – 6,1</td>
<td>&lt; 7,8</td>
</tr>
</tbody>
</table>
# Degrees of severity of DM

<table>
<thead>
<tr>
<th></th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fast serum glucose, mmol/l</td>
<td>&lt; 8</td>
<td>8 - 14</td>
<td>&gt; 14</td>
</tr>
<tr>
<td>Glucosuria, gr./l</td>
<td>&lt; 20(&lt; 2 %)</td>
<td>20 – 40</td>
<td>&gt; 40 (4 %)</td>
</tr>
<tr>
<td>Compensation can be achieved by</td>
<td>diet</td>
<td>oral hypoglycemic agents or insulin</td>
<td>oral hypoglycemic agents or insulin</td>
</tr>
<tr>
<td>Chronic and acute complications</td>
<td>only functional stages</td>
<td>not last stages ketosis can occur</td>
<td>last stages of chronic complications are present, ketosis is common</td>
</tr>
</tbody>
</table>
Stages of compensation

• **Criteria of compensative stage.**

1. Patient hasn’t new complains.
2. Fast serum glucose level is normal.
3. Glucose in urine is absent.
4. Glucose level fluctuation is under 4.4-5.5 mmol/l during the day.
5. HbA1c is 6.0 – 7.0 for the 1 type of DM,
   6.0-6.5 for the 2 type of DM
6. Comatose and precomatose status are absent.
Criteria of decompensative stage:

• 1. Postprandial glycemia is >9,0 mmol/l.
• 2. HbA1c is higher then 7,5 for the 1 type of DM, 7,0 for the 2 type of DM
• 3. Comatose or precomatose status are present.
Duration of DM

1. Stabile
- glucose level fluctuation is under 4.4-5.5 mmol/l during the day
- comatose or precomatose status are absent.

2. Labile
- glucose level fluctuation is over 4.4-5.5 mmol/l during the day
- or comatose and precomatose status are present.
Type I, or insulin-dependent diabetes mellitus (IDDM)

- is characterized by pancreatic islet beta cell destruction and absolute insulinopenia.
- This individuals are ketosis prone under basal conditions. The onset of the disease is generally in youth, but it can occur at any age. Patients have dependence on daily insulin administration for survival.
Pathogenesis of type I DM includes the following:

I. Current formulation of the **genetic predisposition**, conferred by diabetogenic genes on the short arm of chromosome 6, either as part of it or in close proximity to the major histocompatibility complex (MMHC) region (more than 95% of type I diabetes individuals are HLA DR3, DR4 or DR3/DR4; on the other hand, HLA DR2 confers protection against the development of type I DM);

II. **Putative environmental triggers** (possibly **viral infections** (Coxsackie B, rubella) or **chemical toxins** (nitrosourea compounds)) that in genetically susceptible individuals might play a role in initiating the disease process.

III. **An immune mechanism gone awry**, either initiation of immune destruction or loss of tolerance, **IV. leading to slow, progressive loss of pancreatic islet β-cells** (50%) and **V. eventual clinical onset of type I diabetes**. **VI. Total destruction of β-cells**
Type II, or noninsulin-dependent diabetes mellitus (NIDDM)

- Type 2 is the most common form of diabetes, accounting for 95 – 90 % of the diabetic population. Most investigators agree that genetic factors underlie Type 2 DM, but it is probably not caused by defects at a single gene locus.
  - Obesity,
  - diet,
  - physical activity,
  - intrauterine environment,
  - stress
are among the most important **environmental factors** which play a role in the development of the disease.
Pathogenetic and clinical difference of type I and type II DM

<table>
<thead>
<tr>
<th>N</th>
<th>Signs</th>
<th>Type 1</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Age</td>
<td>Young (under 35)</td>
<td>Old, middle</td>
</tr>
<tr>
<td>2</td>
<td>Beginning of disease</td>
<td>Acute</td>
<td>Gradual</td>
</tr>
<tr>
<td>3</td>
<td>Duration</td>
<td>Labile</td>
<td>Stable</td>
</tr>
<tr>
<td>4</td>
<td>Ketosis, ketoacidosis</td>
<td>Often develops</td>
<td>Rarely develops</td>
</tr>
<tr>
<td>5</td>
<td>Body weight</td>
<td>Decreased or normal</td>
<td>Obesity in 80-90 % of patients</td>
</tr>
</tbody>
</table>
Pathogenetic and clinical difference of type I and type II DM

<table>
<thead>
<tr>
<th>N</th>
<th>Signs</th>
<th>Type 1</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Treatment</td>
<td>Insulin, diet</td>
<td>Diet, drugs, insulin</td>
</tr>
<tr>
<td>7</td>
<td>Degrees of severity</td>
<td>Middle, hard</td>
<td>Mild, middle, hard</td>
</tr>
<tr>
<td>8</td>
<td>Season of disease beginning</td>
<td>Frequently autumn-winter period</td>
<td>Absent</td>
</tr>
<tr>
<td>9</td>
<td>Connection with HBA-system</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>10</td>
<td>Level of insulin and C-peptide</td>
<td>Decreased or absent</td>
<td>Frequently normal level</td>
</tr>
</tbody>
</table>
Pathogenetic and clinical difference of type I and type II DM

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<th>N</th>
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<th>Type 1</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>11.</td>
<td>Antibodies to β-cells</td>
<td>Present in 80-90 % of patients on first week, month</td>
<td>Absent</td>
</tr>
<tr>
<td>12.</td>
<td>Late complications</td>
<td>Microangiopathies</td>
<td>Macroangiopathies</td>
</tr>
<tr>
<td>13.</td>
<td>Mortality</td>
<td>Less than 10%</td>
<td>More than 20%</td>
</tr>
<tr>
<td>14.</td>
<td>Spreading</td>
<td>10-20%</td>
<td>80-90%</td>
</tr>
</tbody>
</table>
### Pathophysiology of DM

<table>
<thead>
<tr>
<th>Insulin lack</th>
<th>Defective polymorphonuclear function → infection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hyperglycemia → glucosurea → polyurea → dehydration</td>
</tr>
<tr>
<td></td>
<td>↓</td>
</tr>
<tr>
<td></td>
<td>Hyperosmolality</td>
</tr>
<tr>
<td></td>
<td>Proteolysis → weight loss → muscle wasting → polyphagia</td>
</tr>
<tr>
<td></td>
<td>Lipolysis → free fatty acid release → ketosis → acidosis</td>
</tr>
</tbody>
</table>
Clinical presentation

The classic manifestation of type 1 DM include:

- **polyurea** (when the level of the blood glucose is more than 9 mmol/l, glucosurea arises).
- **polydipsia** (as more water is excreted, the body requires more water intake);
- **polyphagia** (as a result of lack of energy);
- **loss of weight** (energy (calories) is lost as glucose in the urine. Loss of water itself also contributes to weight loss. Increased proteolysis with mobilization of aminoacids leads to progression of protein catabolism and loss of weight, mostly in muscle mass);
- **fatigue and weakness** (probably occur as a result of decreased glucose utilization and electrolyte abnormalities);
- **acidosis** (develops due to increased lipolysis which cause the release of free fatty acids, which are metabolized to ketones by the liver)
Presenting signs and symptoms of type 2 DM include:

- polyurea,
- polydipsia,
- polyphagia;

but they are not prominent

The majority of patients (80 – 85 %) are obese, but it can also occur in thin persons.
Classification of chronic (long-term) complications of DM.

I. Diabetic angiopathy:
   1. Microangiopathy:
      1) nephropathy;
      2) retinopathy;
      3) angiopathy of lower extremities.
   2. Macroangiopathy:
      1) heart (ischemic heart disease);
      2) brain
      3) angiopathy of lower extremities.

II. Diabetic neuropathy:
    1) central (encephalopathy);
    2) peripheral;
    3) visceral (dysfunction of inner organs).
• The long-term degenerative changes in the blood, vessels, the heart, the kidneys, the nervous system, and the eyes as responsible for the most of the morbidity and mortality of DM.
Skin

- The skin is dry and itch
- Infections of the skin by *bacteria and fungi*, candidiasis of the external female genitalia, hyperkeratosis, nail disorders are common in the patients with DM but nothing is specific with regard to their development.
• The most common skin lesion is *diabetic dermopathy* (it is characterized by brown, atrophic, well-demarcated areas in the pretibial region which resemble sears), besides patients sometimes have *xanthoma diabeticorum*, which is usually located on the buttocks, elbows and knees, look like eruptions (but is not really diabeticorum since it occurs in the patients with lipoprotein abnormalities, particularly hyperchylomicronemia, whether or not patient has DM)
Subcutaneous adipose tissue

• The abdomen type of obesity is common in patients with type II DM.
• Sometimes generalized subcutaneous adipose tissue atrophy can be observed in diabetics.
Bones and joints

- Osteoporosis and osteoarthropaphy can be find in patients with DM also.
- *Diabetic chairopathy* (decreasing of the movements of joints)
**Gastrointestinal tract**

- Paradontosis, gastritis with decreased secretion ability, gastroduodenitis, hepatosis are common in patients with DM.

- **Visceral dysfunction gastrointestinal tract:**
  
  **esophageal neuropathy** (disturbances of peristalsis in the body of the esophagus.)

  **diabetic gastroparesis** (irregular food absorption and is characterized by nausea, vomiting, early satiety, bloating and abdomen pain.);

  **diabetic enteropathy** (diarrhea (mostly at night time, postural diarrhea), constipation, malabsorption and fecal incontinence)
Cardiovascular system (CVS).

- **Diabetic autonomic cardiopathy:**
  - orthostatic hypotension (is characterized by dizziness, vertigo, faintness, and syncope upon assumption of the upright posture and is caused by failure of peripheral arteriolar constriction.);
  - tachicardia (but it does not occur in response to hypotension because of sympathetic involvement).

- **Dismetabolic cardiomyopathy**
  (IHD, rhythm disturbances)
Ischemic heart disease

1. Cardiovascular changes tend to occur earlier in patients with DM when compared with individuals of the same age.

2. Frequency of myocardial infarction (MI) and mortality is higher in diabetics than that in nondiabetics of the same age.

3. The prognosis is even worse if ketoacidosis, or other complications of DM are present.

4. Diabetic patients have more complications of MI (arrhythmias, cardiogenic shock and others) than nondiabetic ones.

5. Often can observe atypical forms (without pain).

Respiratory system

- Mucomycosis of the nasopharynx, sinusitis, bronchitis, pneumonia (prolonged duration, slow recurrence), tuberculosis are more common in patients with diabetes than in nondiabetics.
Kidneys and urinary tract.

- **Inflammation processes** (10 – 30 %): pyelitis, pyelonephritis, cystitis
- **Diabetic cystopathy** or neurogenic vesicle dysfunction (enlargement of the volume of the cyst bladder, insidious onset and progression of bladder paralysis with urinary retention, decreasing of quantity of urinations)
- **Diabetic nephropathy**

**Sexual disorders:**
- retrograde ejaculation (which is caused by dysfunction of the pelvic autonomic nervous system);
- impotence, and sometimes decreased libido;
Diabetic nephropathy (by Mogensen)

I. Hyperfunction of kidneys
- increased renal blood circulation;
- increased glomerular filtration rate (GFR) (> 140 ml/min);
- hypertrophy of kidneys;
- normoalbuminuria (<30 mg/day).

II. Stage of initial changes of kidney structure.
- mesangial changes due to accumulation of immunoglobulins (IgG, IgM), complement and other nonimmunologic proteins (lipoproteins, fibrin);
- high GFR;
- normoalbuminuria

III. Initial nephropathy.
- microalbuminuria (30 to 300 mg/day);
- high or normal GFR;
- periods of blood hypertension
IV. Nephropathy or nephrotic stage.
- persistent proteinurea (>500 mg/day);
- normal or decreased GFR;
- persistent blood hypertension.

V. Chronic renal failure or uremia.
- decreased GFR;
- blood hypertension;
- increased serum creatinine
- signs of intoxication.
**Eyes**

- Ceratities, retinatis, chorioretinatis, cataracts, glaucoma
- **Diabetic retinopathy**
  - Evidence of retinopathy, rarely present at diagnosis in type I DM, is present in up to 20% of type II DM patients at diagnosis. About 85% of all diabetics eventually develop some degree of retinopathy
  - The initial retinal changes (seen on the ophthalmoscopic examination) does not significantly alter vision, but it can lead to processes that cause blindness
Diabetic retinopathy
(is classified according to the changes seen at background during ophthalmoscopic examination)

I stage.  Background retinopathy

II stage.  Maculopathy or preproliferative retinopathy

III stage.  Proliferative retinopathy
Diabetic retinopathy

I stage. *Background retinopathy* is usually the earliest sign and consists of retinal microaneurysms, hard and soft exudates.
Diabetic retinopathy

II stage. *Maculopathy or preproliferative retinopathy* is characterized by macular edema and/or hemorrhages.

III stage. The hallmark of *proliferative retinopathy* is neovascularization, i.e., growth of new vessels in areas of hypoperfusion. Adhesion of the vessels to the vitreous leads to retinal detachment, vitreous hemorrhage and others. The prognosis is extremely poor. 5 years after recognition of this complication 50% of the patients are blind.
Diabetic angiopathy of lower extremities.

Atherosclerosis of large vessels (macroangiopathy) leads to intermittent claudication, cold extremities and other symptoms which can be also find while arteriols and capillaries are affected (microangiopathy).
Classification of lower extremities’ angiopathy.

I. Nonclinic stage. (Changes could be find only during instrumental examination.)

II. Functional stage. (It is characterized by cold extremities, numbness, tingling, pain during physical examination.)

III. Organic stage. (It is characterized by trophyc changes: dry skin, hypo- or atrophy of muscles, ulcers, gangrene.)
Neuropathic arthropathy (Charcot’s joints)

- is characterized by painless swelling of the feet without edema or signs of infection. The foot becomes shorter and wider, eversion, external rotation, and flattening of the longitudinal arch. This arthropathy is associated with sensory involvement, particularly impairment of afferent pain proprioceptive impulses.
Peripheral neuropathy
Diabetic foot

Appearance of diabetic foot is caused by a combination of vascular insufficiency, neuropathy, and infection.

Diabetic foot is divided on:

- ischemic;
- neuropathy;
- mixed.
<table>
<thead>
<tr>
<th>Sign</th>
<th>Ischemic</th>
<th>Neuropatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature of the skin</td>
<td>Decreased</td>
<td>normal</td>
</tr>
<tr>
<td>Color of the skin</td>
<td>pallor or cyanotic</td>
<td>normal or pink</td>
</tr>
<tr>
<td>Pulsation on peripheral vessels</td>
<td>decreased or absent</td>
<td>normal</td>
</tr>
<tr>
<td>Edema</td>
<td>Absent</td>
<td>can be</td>
</tr>
<tr>
<td>Sensibility</td>
<td>partly decreased or normal</td>
<td>decreased or absent</td>
</tr>
<tr>
<td>Ulcers</td>
<td>peripheral (distant)</td>
<td>under the pressure</td>
</tr>
<tr>
<td>Gangrene</td>
<td>Dry</td>
<td>moist</td>
</tr>
</tbody>
</table>
The diagnosis of DM include:

1. **Clinical manifestations** of DM.
2. **Laboratory findings.**
   - fasting serum glucose (if the value is over 6,1 mmol/l (120 mg/dl) on two or more separate days, the patient probably has DM);
   - the glucose tolerance test (GTT)
   - glycohemoglobin >6,5 % (this test is an indicator of blood sugar control during the previous 2-to-3-month period);
   - islet cell antibody levels will be positive prior to any insulin administration in 60 – 80 % of patients with type I DM;
   - C-peptide (it is not affected by antibodies to exogenous insulin and is used to distinguish type I and II DM if there is still a need after clinical determination);
   - glucose level in urine;
   - acetonurea;
   - blood lipids and others.
3. **Instrumental investigations** usually are used to diagnose chronic complications of DM.
• Conditions for performing an oral GTT have been standardized:
  • no special dietary preparation is required for an oral GTT unless the patient has been ingesting <150 gm/day of carbohydrate. Then give 150 – 200 gm carbohydrate daily for 3 days prior to test;
  • unrestricted physical activity should proceed the test;
  • test is performed in the morning, following overnight fast of 10 to 16 hours;
  • subjects should remain seated, without prior coffee or smoking;
  • blood for glucose determination is obtained from an antecubital vein before glucose ingestion and every 30 minutes far 2 hours after ingestion;
  • the amount of glucose given is 75 g for adults (100 g pregnant women, and 1.75 g/kg of ideal body weight for children). Patient have to drink glucose dissolved in 250 ml of water;