**Diabetes mellitus**

**Definition of diabetes mellitus (DM)**
- DM is a group of metabolic disorders characterized by hyperglycemia resulting from a lack of insulin effect
  - due to either defect in insulin secretion or insulin action
- **chronic hyperglycemia** leads to long-term cell, tissue & organ damage = **diabetic complications**
  - retina
  - kidney
  - nerves

**Diagnosis of DM**
- diabetes
  - **classical symptoms** + **random plasma glycemia** ≥11.1 mmol/l (venous plasma)
    - random = any time of the day
    - symptoms include polyuria and polydipsia
  - FPG (fasting plasma glucose) ≥7.0 mmol/l
    - fasting means at least 8 h from the last meal
  - **2-h PG (postprandial glucose)** ≥11.1 mmol/l during oGTT
    - oGTT: according to the WHO consists of FPG examination followed by a standard load of 75g of glucose (diluted in water) and examination of glycemia in 60th and 120th minute
- impaired glucose tolerance (IGT)
  - excluded <7.8 mmol/l
  - 2-h PG ≥7.8 - <11.1 mmol/l during oGTT
- impaired fasting glucose (IFG)
  - diabetes excluded by FPG ≤5.6 mmol/l
  - FPG ≥5.6 – <7 mmol/l

**Interpretation of glycemia**

<table>
<thead>
<tr>
<th>glycemia (mmol/l)</th>
<th>diabetes</th>
<th>IGT</th>
<th>IFG</th>
<th>normal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>11.1</td>
<td>11.1</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>7.0</td>
<td>7.8</td>
<td>7.8</td>
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<td></td>
<td></td>
<td>5.6</td>
<td></td>
<td></td>
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</tbody>
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<tr>
<th>FPG</th>
<th>60 min</th>
<th>120 min</th>
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<td>7.8</td>
<td>5.6</td>
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</table>
Regulation of glycemia

- **Humoral**
  - **Principal**
    - insulin
    - glucagon
  - **Auxiliary**
    - glucocorticoids
    - adrenalin
    - growth hormone

- **Neural**
  - sympathetic
    - hyperglycemia
  - parasympathetic
    - hypoglycemia

Main contra-regulation: insulin/glucagon

The way glucose enters the cell???

- Exocytosis from B-cells of islets of Langerhans into portal circulation
  - 50% degraded during first pass through liver
  - parallel cleavage of the C-peptide
- Total daily production in healthy subject ~20-40 U
  - 1/2 **basal** (postabsortive) secretion
    - pulsatile (5 - 15 min intervals)
  - 1/2 **stimulated** (postprandial)
    - early phase (ready insulin)
      - Glc/KATP-dependent
    - late phase (synthesis de novo)
      - other secretagogues

*Stimulation of secretion*
- < < glucose
- < < amino acids
- < GIT hormones (incretins)
- FFA
  - variable stimulation (length of chain & (un)saturation)!!
  - since insulin is acting also as peripheral "satiety" signal, reaching the satiety is delayed after fatty meal
Insulin synthesis

C peptide
- activity
  - certain beneficial vascular effects (nitric oxide)
- mainly diagnostic use
  - equimolar to insulin
  - unlike insulin, C-peptide is not degraded from portal blood in liver
  - the systemic concentration reflects endogenous insulin production

Coupling: glycemia – insulin secretion

Summary: coupling of glycemia → biphasic insulin secretion

Insulin Secretion is Biphasic

Phase 1
- Insulin Exposure
- Mobilization (aqueous phase)
- 1st phase
- High glucose levels
- 1st phase
- 2nd phase
- Membrane insulin and hormone release
- Glucose metabolism

Phase 2
Incretins – enteroinsular axis

- GIT hormones produced by endocrine cells of small intestine stimulating insulin secretion even **before elevation of blood glucose**
  - hypoglycemia – if the patient still conscious then better to give Glc per os
- "forward" regulatory mechanism – anticipation of increase of Glc
- 2 major incretin hormones
  - GIP (glucose-dependent insulino trophic peptide or gastric inhibitory peptide)
  - GLP-1 (glucagon-like peptide-1)
- treatment of T2DM (= delayed effect of Glc on Ins stimulation) by incretin analogues
  - GLP-1 analogue - exenatide (GLP-receptor agonist)
  - DPP-4 inhibitors (dipeptidyl peptidase 4 - proteolytic degradation of incretins) - gliptins
  - improvement of Glc-stimulated Ins secretion after meal
  - suppression of postprandial glucagon release
  - delayed gastric emptying
  - protection of β-cells from apoptosis

Insulin receptor signal cascade

- insulin receptor
  - tyrosinokinas type (2 α and 2 β subunits)
  - (1) cascade of phosphorylations (down-stream kinases)
    - balanced activation or inhibition of hormones
      - activation of anabolic pathways (i.e. glycogenogenesis, lipogenesis)
      - inhibition of catabolic pathways (e.g. lipolysis, glycogenolysis) and gluconeogenesis
  - (2) translocation of GLUT4

Classification of tissues according to insulin action:

- **insulin-sensitive**
  - muscle
  - adipose tissue
    - glucose uptake facilitated by GLUT4, which becomes integrated into cell membrane after insulin receptor activation
- **insulin-insensitive**
  - all others incl. muscle, adipose and liver
    - glucose uptake is realized by facilitated diffusion by GLUT1, 2, 3, 5, ...
    - permanently localized in the cell membrane
    - transport of glucose depends solely on concentration gradient
    - type and density of GLUTs

- liver
  - metabolic actions
Diabetes mellitus

- heterogeneous syndrome characterized by hyperglycemia due to deficiency of insulin action as a result of
  - absolute insulin deficiency
    - destruction of the β-cells of the islets of Langerhans
  - relative deficiency of insulin secretion and/or action
    - abnormal molecule of insulin (mutation of insulin gene)
    - defective conversion of preproinsulin to insulin
    - circulating antibodies against insulin or its receptor
    - secondary failure of β-cells of the islets of Langerhans
    - insulin resistance in peripheral tissues
      - receptor defect
      - post-receptor defect
- prevalence of DM in general population 5%, over the age of 65 already 25%

Prevalence (%) of diabetes (population 20-79 years)

<table>
<thead>
<tr>
<th>Year</th>
<th>Total Diabetes</th>
<th>Diabetics in Czech Rep.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>4.3 bil. (from a total of 7 bil.)</td>
<td>285 mil.</td>
</tr>
<tr>
<td>2030</td>
<td>5.6 bil. (from a total of 8.5 bil.)</td>
<td>1.2 mil.</td>
</tr>
</tbody>
</table>

Classification of DM

1. Diabetes mellitus type 1 (T1DM) ~5%
2. Diabetes mellitus type 2 (T2DM) ~90%
3. Other specific types:
   a. genetic defects of B-cell
      - monogenic DM (MODY1 - 6)
      - mutation of mitochondrial DNA
   b. genetic defects leading to insulin resistance
      - type A insulin resistance, leprechaunismus, Rabson-Mendenhall syndrome, lipoatrophic DM
   c. diseases of exocrine pancreas
      - pancreatitis, tumor, cystic fibrosis, hemochromatosis
   d. endokrinopathies
      - Cushing syndrome, acromegaly, pheochromocytoma, hyperthyreosis
   e. iatrogenic DM (i.e. drugs and toxins)
   f. other genetic syndromes associated with DM
      - Down, Klinefelter, Turner syndromes, ...
4. Gestational diabetes mellitus

T1DM (formerly IDDM)

- selective autoimmune destruction of β cells of islets in genetically predisposed individuals
- genetic susceptibility
  - chromosome 6 – MHC class III
    - DR3-DQ2 and DR4-DQ8
  - chromosome 11 – insulin gene
- cytotoxic autoimmunity mediated by T-lymphocytes
  - there are also antibodies against β cell structures (ICA, GAD, IAA), but they are rather markers of autoimmunity than causal agent
T1DM

- autoimmunity has to be triggered by various factors
  - infection
    - viruses
      - rubella, measles, coxsackie B, CMV, EBV, enteroviruses, retro-viruses
    - mechanism is unclear
      - cytolytic (sequestration of antigens
      - formation of neoantigens
    - molecular mimicry or superantigens
  - environmental factors (according to the epidemiologic evidence)
    - diet – early exposition proteins of cow’s milk
    - bovine insulin
    - vitamin D – reason for northern-southern geographical gradient?
    - toxins (diet, water, bacteria)
    - gluten???
  - manifestation typically in childhood
  - absolute dependence on exogenous supplementation by insulin

Natural history of T1DM

T2DM (formerly NIDDM)

- insulin sensitivity is a continuous trait with distinct interindividual variability, it can be assessed by:
  - hyperinsulinemic euglycemic clamp
  - calculated indexes (based on relationship between glycemia and insulin during fasting or oGTT) – e.g., HOMA, QUICKI, ...
- main pathophysiologic feature of T2DM is an imbalance between insulin secretion and its effect
  - in the time of clinical manifestation there are both insulin resistance and impairment of insulin secretion
  - what is “chicken” and what is “egg”??
  - insulin resistance
    - genetic predisposition (polygenic) – thrifty phenotype
    - acquired factors
      - competition of Gls with NEFA!!! (diet)
      - effect of adipokines from adipose tissue (obesity)
      - ↓ mobilisation of GLUT4 in physical inactivity
      - down-regulation of ins. receptor due to hyperinsulinemia
  - impairment of secretion
    - inherited factors
      - fewer B-cells (~20-40%)
      - defect of 1. phase of Ins secretion (~80% reduction)
    - acquired factors
      - gluco- and lipotoxicity for B-cells
  - 90% of subjects are obese – metabolic syndrome!!!

Pathogenesis of T2DM
Natural history of T2DM

Insulin- and “sport”-dependent translocation of GLUT4

Main characteristics of T1DM and T2DM

Clinical presentation of DM

<table>
<thead>
<tr>
<th></th>
<th>T1DM</th>
<th>T2DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>onset</td>
<td>childhood</td>
<td>adults</td>
</tr>
<tr>
<td>genetic disposition</td>
<td>yes (oligogenic)</td>
<td>yes (polygenic)</td>
</tr>
<tr>
<td>clinical manifestation</td>
<td>often acute</td>
<td>mild or none</td>
</tr>
<tr>
<td>autoimmunity</td>
<td>yes</td>
<td>No</td>
</tr>
<tr>
<td>insulin resistance</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>dependence on insulin</td>
<td>yes</td>
<td>No</td>
</tr>
<tr>
<td>obesity</td>
<td>no</td>
<td>yes</td>
</tr>
</tbody>
</table>

- due to the increase of blood osmolality, osmotic diuresis and dehydratation
  - classical
    - polyuria, thirst, polydipsia
    - tiredness
  - others
    - temporary impairment of visus
    - recurrent infections
    - perio-/parodontitis

- extreme hyperglycemia
  - ketoacidotic coma
  - non-ketoticidotic hyperglycemic coma
  - lactic coma
Complications of DM

- microvascular
  - diabetic retinopathy
  - diabetic nephropathy
  - diabetic neuropathy
    - sensoric
    - motoric
    - autonomous

- macrovascular
  - accelerated atherosclerosis (CAD, peripheral and cerebrovascular vascular disease)

- combined
  - diabetic foot (ulcerations, amputations and Charcot’s joint)

- others
  - periodontitis
  - cataract
  - glaucoma

Pathogenesis of complications

(1) extracellular protein cross-linking
(2) modification of intracellular proteins (ubiquitin / proteasome)
(3) binding to receptors & activation of signaling pathways