Experimental diabetes mellitus

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seminars and practicals from pathophysiology

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Definition of DM

- DM is a group of metabolic disorders characterized by hyperglycemia as a reason of impaired effect of insulin

- chronic hyperglycemia leads to organ damage (retina, kidney, nerves)

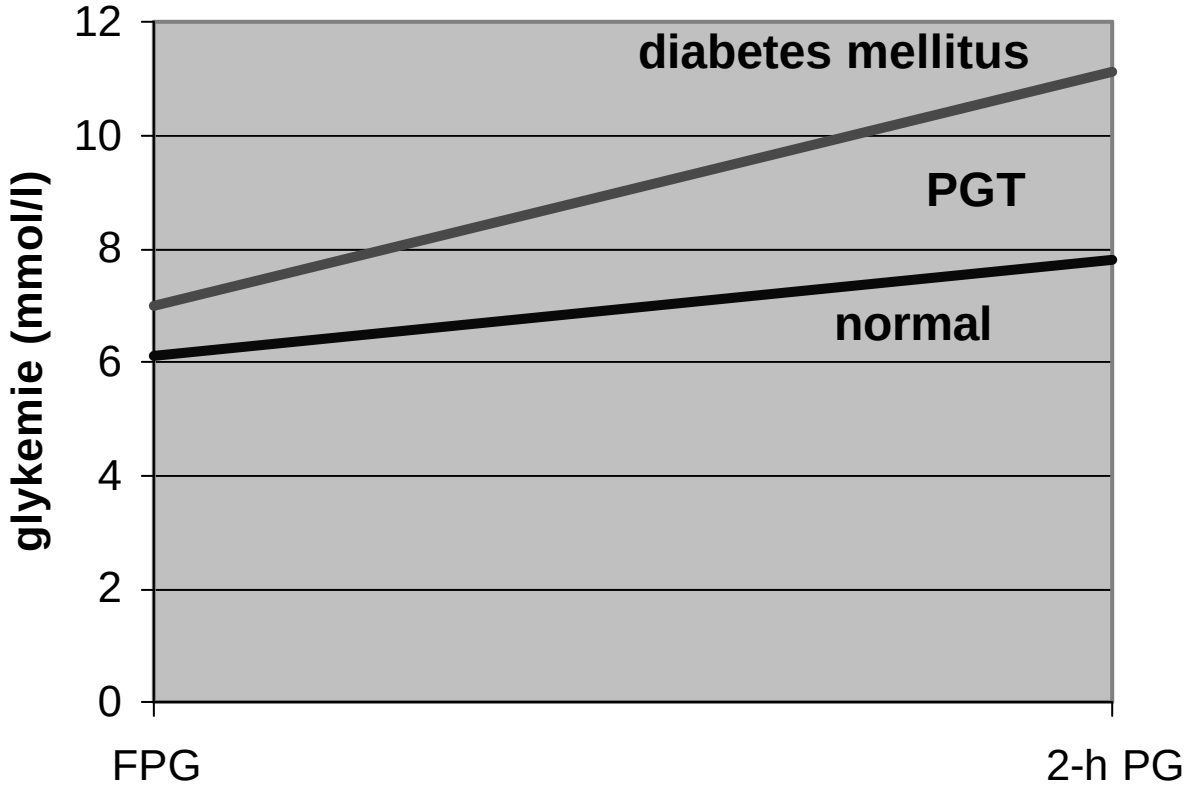
Diagnosis of DM

- clasical symptoms of diabetes + random plasma glycemia ≥11.1 mmol/l
  - any time of the day
  - symptoms incede polyuria, polydipsia and rapid loose of weight
- FPG ≥7.0 mmol/l
  - fasting means at least 8 h from the last meal
- 2-h PG ≥11.1 mmol/l during GTT

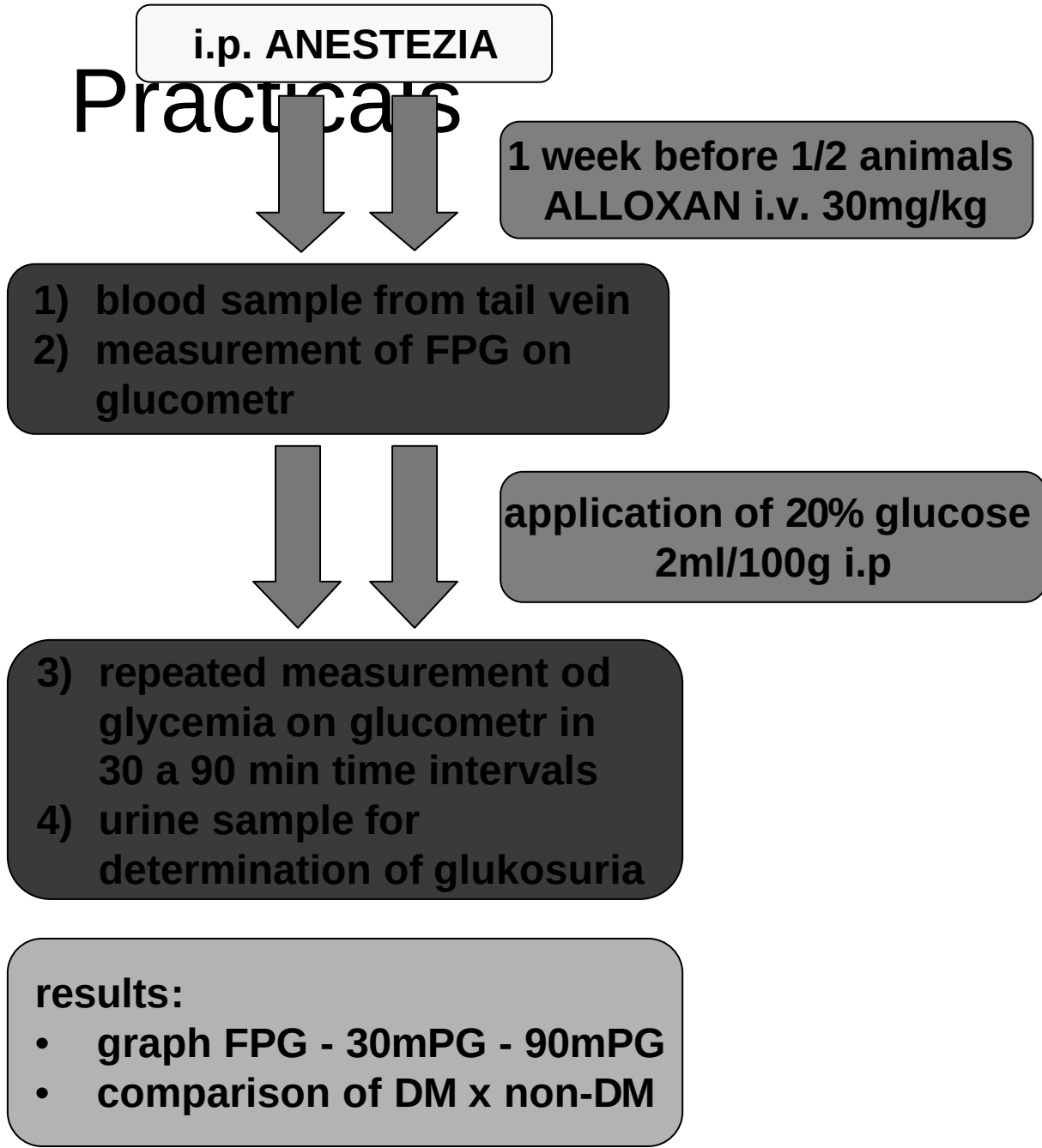
Interpretation of glycemia

- FPG:
  - <6.1 mmol/l = normal glycemia
  - 6.1-7.0 mmol/l = IGT (impaired glucose tolerance)
  - ≥7.0 mmol/l = diabetes
- oGTT – 2h PG:
  - <7.8 mmol/l = normal glucose tolerance
  - 7.8 – 11.1 mmol/l = IGT

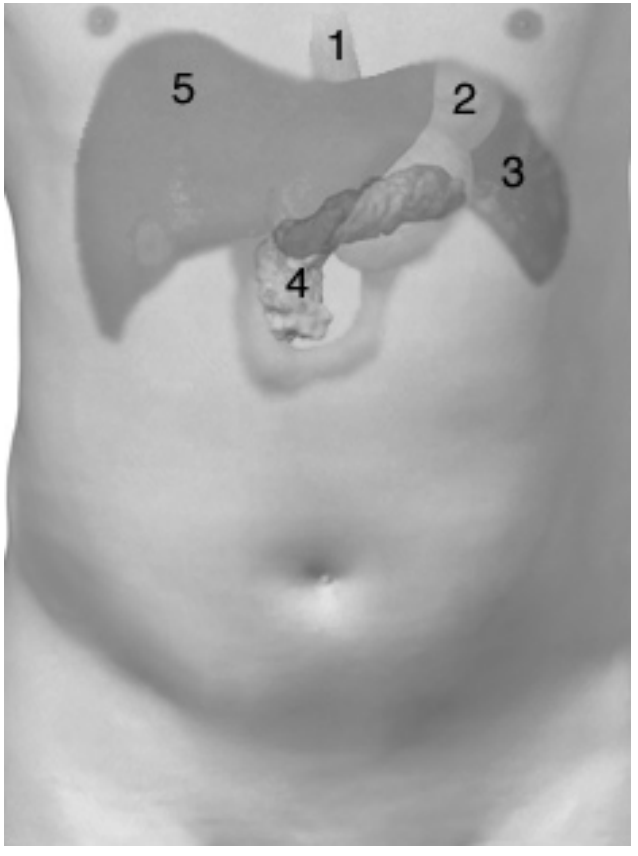
Oral glucose tolerance test



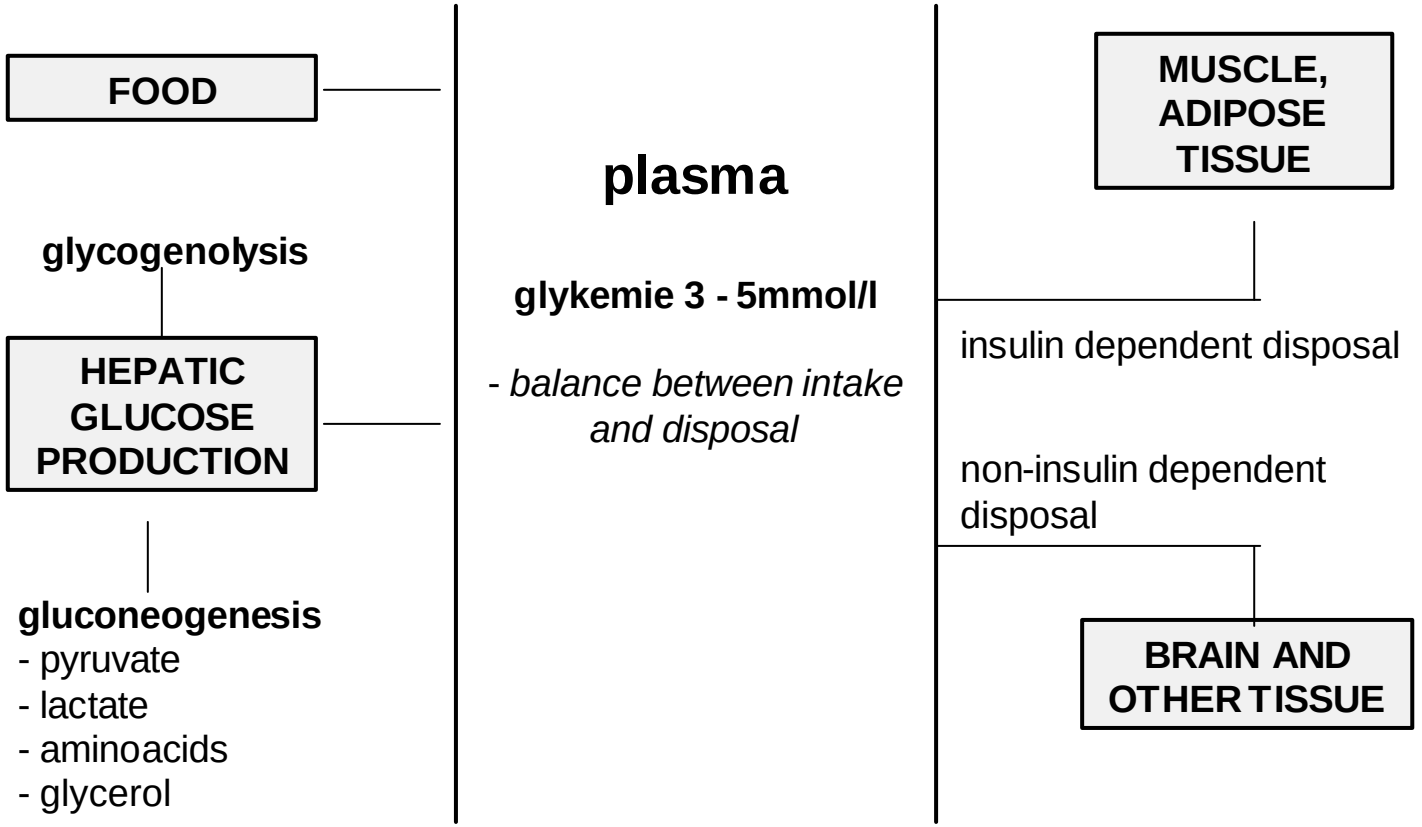
Practicals


i.p. ANESTEZIA
1 week before 1/2 animals
ALLOXAN i.v. 30mg/kg
1) blood sample from tail vein
2) measurement of FPG on glucometr
application of 20% glucose
2ml/100g i.p
3) repeated measurement od glycemia on glucometr in 30 a 90 min time intervals
4) urine sample for determination of glukosuria
results:
• graph FPG - 30mPG - 90mPG
• comparison of DM x non-DM

Pathophysiology of diabetes mellitus



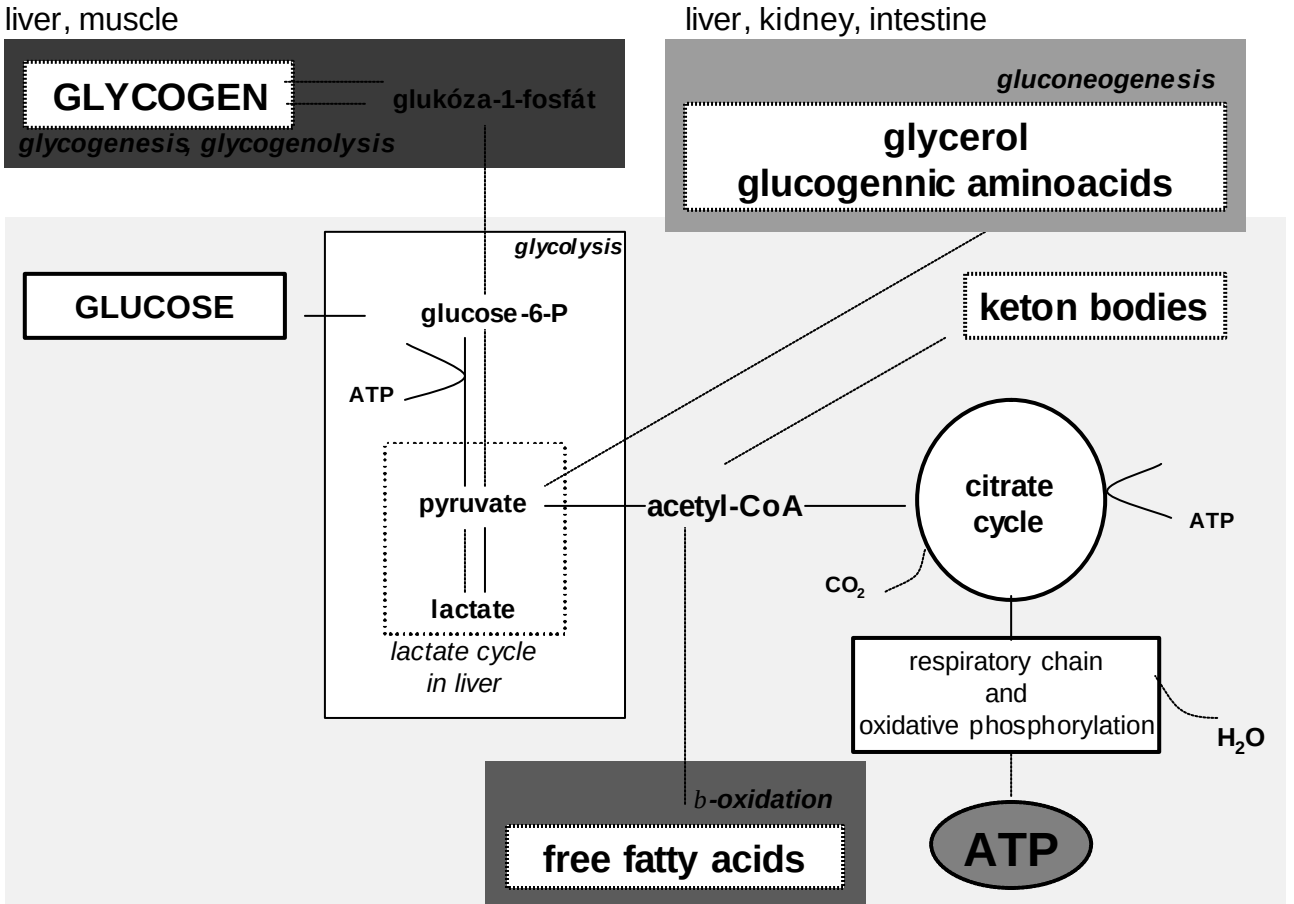
Regulation of glycemia



Regulation of glycemia

- humoral
  - principal
    - insulin
    - glucagon
  - modulatory
    - glucocorticoids
    - adrenalin
    - growth hormon
- neural
  - sympaticus
    - hyperglycemia
  - parasympaticus
    - hypoglycemia

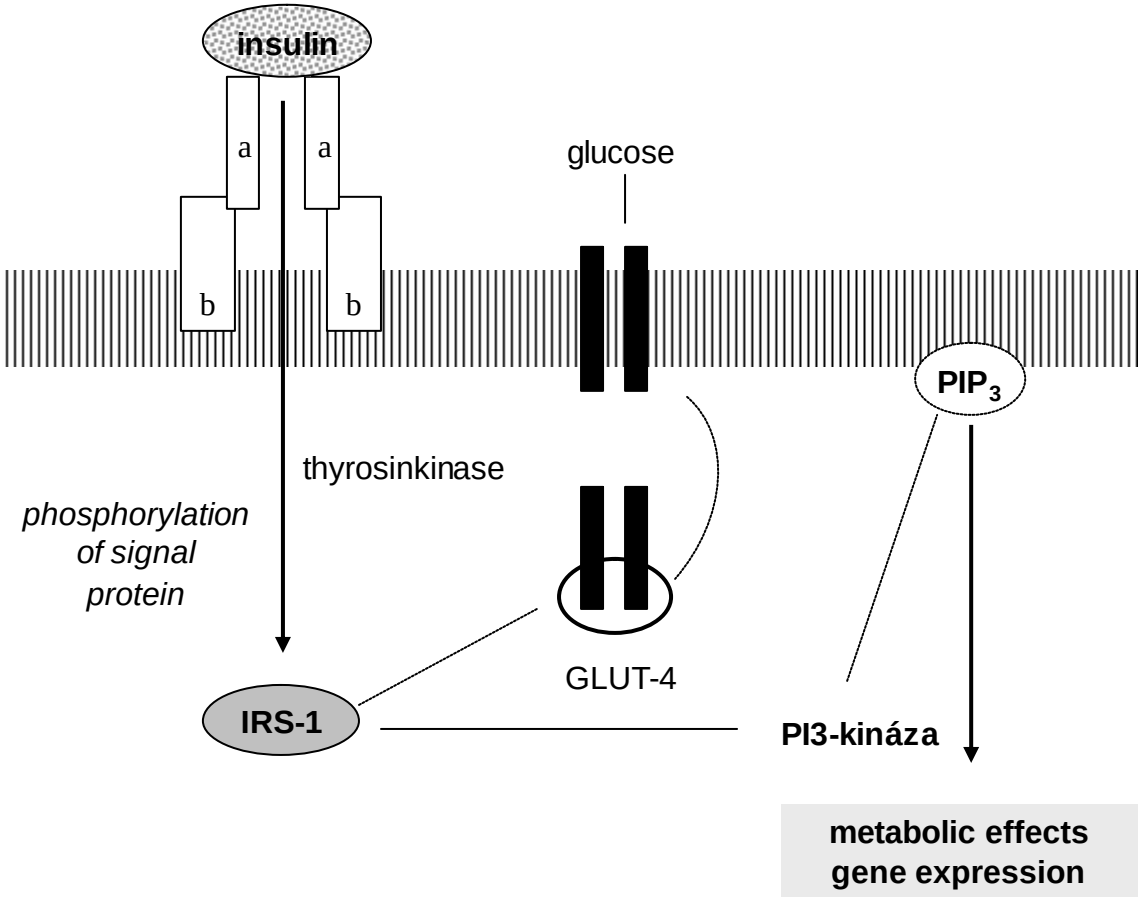
Mutual interchange of substrates in intermediate metabolism



Insulin

- gene in 11th chromozome
- preproinzulin $\rightarrow$ proinzulin $\rightarrow$ inzulin + C-peptide
- exocytosis into portal circulation
  - 50% degraded during first pass through liver
- total daily production 20 - 40 U
  - 1/2 basal secretion, 1/2 stimulated
- basal secretion pulsatile
  - 5 - 15 min intervals
- stimulated – glucose, aminoacids, FFA, GIT hormons

Intracellular cascade of insulin receptor



Two kinds of tissue from the point of view of insulin action:

- insulin-sensitive
  - muscle, adipose tissue, liver
  - facilitated diffusion by GLUT 4
  - integration into cytoplasmic membrane regulated by insulin
- inzulin-nonsensitive
  - others
  - facilitated diffusion by GLUT 1, 2, 3 a 5
  -
  - transport of glucose depend solely on concentration gradient

Diabetes mellitus

- heterogenous syndrome characterized by hyperglycemia due to deficiency of insulin action (as a result of complete depletion or peripheral resistance)

- prevalence of DM in general population 5%, over the age of 65 20%

Causes of insulin deficiency

- absolute
  - destruction of β cells in the Langerhan´s islands
- relative
  - isnulin
    - abnormal product of β cells
    - abnormal molecule of insulin (mutation)
    - defective conversion of preproinsulí to insulin
    - circulating antibodies against insulir or receptor
  - insulin resistance in peripheral tissue
    - receptor defect

Classification of DM

I. DIABETES MELLITUS
Diabetes mellitus of type 1 (T1DM)
Diabetes mellitus of type 2 (T2DM)
Gestational diabetes mellitus
Other specific types 1) genetic defects of ß cell function (MODY) 2) genetic abnormalities of insulin receptor 3) exocrine pancreas disorders 4) endocrinopathies 5) iatrogenic 6) rare genetic syndromes 7) others
II. IMPAIRED GLUCOSE TOLERANCE (IGT)
- with obesity - without obesity

Symptoms of DM

- chronic
  - polyuria
  - polydipsia
  - weight loss
  - impairement of visus
  - cutaneous infections
- acute
  - hyperglycemic coma
    - ketoacidotic
    - non-ketoticidotic

DM of type 1 (IDDM)

- selective destruction of β cells of LO in genetically predisposed individuals
  - MHC-II (loci DR3, DR4 a DQ β)
- autoimunity mediated by T-lymphocytes (antibodies against β cells (ICA, GAD) as well)
  - started by infection (virus)
  - manifestation typically in childhood

DM of type 2 (NIDDM)

- imbalance between secretion and affect of insulin
- genetic predisposition – polygenic
  - insulin resistance
  - impairement of secretion
- clinically manifested T2DM has concomitant insulin resistance and impairment of secretion
  - due to epigenetic factors

Insulin resistance

- state, when physiologic amount of insulin does not cause adequate response
  - unsupresed hepatic gluconeogenesis leads to fasting hyperglycemia
  - ineffective insulin-dependent glucose disposal in muscles leads to postprandial hypeglycemia
- compensatory hyperinsulinism
- further worsening by down-regulation of insulin receptors

Main characteristics of T1DM and T2DM

	T1DM	T2DM
onset	childhood	adults
genetic disposition	yes (oligogenic)	yes (polygenic)
clinical manifestation	often acute	slow or none
autoimunity	yes	no
insulin resistance	no	yes
depends on insulin	yes	no
obesity	no	yes

Complications of DM

- retinopathy
- nephropathy
- peripheral neuropathy
- diabetic foot (ulcerations, amputations and Charcot´s joint)
- atherosclerosis (CAD)
- hypertension
- abnormalities of lipoprotein metabolism
- periodontitis