Langerhans islets

Paul Langerhans (1847-1888)
described islets in 1869

Beiträge zur mikroskopischen Anatomie
der Bauchspeicheldrüse

Cell types in the islets

A, alpha	glukagon	20%
B, beta	**insulin**	**70%**
D, delta	somatostatin	5-9%
PP, pankreatic polypeptide		1-2%

D1	VIP
EC	serotonin

and other

Diabetes mellitus - classification

primary

- Type 1 (IDDM)
- Type 2 (NIDDM)
- monogenic types MODY x DM of newborns

gestational

secondary

- infectious causes
  - congenital rubella (German measles)
  - CMV
- **endocrinopathies** (adrenals - cortex, hypophysis)
- **corticosteroid therapy**
- other genetic diseases (Down syndrome)

- **chronic fibrotizing pancreatitis**
- **pancreatic resection**
- pancreatic neoplasms
- hemochromatosis

DM type 2

clinical begins > 30 y
obesity
insulin in blood - normal or increased
antibodies against L islets absent
ketoacidosis unusual

genetics 100% identical twins
HLA does not play a role

patogenesis
insulin resistency
relative defficiency of insulin

L islets insulitis absent
late:
atrophy ±, amyloidosis
β cell depletion - mild

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DM type 1

clinical begins < 20 let
body weight normal
insulin in blood - low / absent
antibodies against L islets present
ketoacidosis common

genetics 50% identical twins
HLA-D system involved

patogenesis
autoimmune
defficiency of insulin

L islets insulitis
atrophy + fibrossis
β cell depletion absolute

DM monogenic types, examples

MODY – maturity onset diabetes of the young
- autosomal dominant

- begins up to 25 years (70%)
- functional disorder of β cells / body weight normal
  antibodies absent, no insulin resistency

MODY 1 HNF-4 alfa gene / chromosome 20 – **secretoric disorder**

MODY 2 gene coding for glukokinase / chromosome 7
decreased response of β-cells to the glucose level

MODY 3 HNF-1 alfa gene / chromosome 12q (exon 5) – **secretoric disturbance**

MODY 4 insulin promoter factor-1

MODY5 HNF-1 beta

MODY6 NeuroD1

mitochondrial DNA – point mutations (DM + deafness)

Frequency of DM in CZ

I. type	II. type	secondary	DM together
57 945	786 586	13 479	858 010
6,7%	92%		

Frequency of DM in Europe

Estimation in 2015 – 56 millions
by 2035 expected growtih by10 millions

At present – prevalence – 8,5%

DM = a disease of the 21st century

type 1 DM - pathogenesis

reduction of B cells → severe insulin defficiency
develops in childhood, manifests at puberty

<u>genetic predisposition</u>

racial groups (whites)
family clustering, inheritance unclear
first-order relatives 5% (25x – 50x increased risk)
identical twins

IDDM1 gene

HLA complex
DR3, DR4,
DQ heterodimer B1 (point mutation), DQ B1*04, DQA1

IDDM2 gene

gene coding for insulin - polymorphism

autoimmunity
environmental factors

type 1 DM - pathogenesis

Autoimmunity

- lymphocytic insulitis (T8, T4)
- expression of class II HLA on β cells
  - induced locally through cytokines
- autoantibodies (appear early)
  - glutamic acid decarboxylase (GAD)
- other autoimmune disorders

type 1 DM - pathogenesis

Autoimmunity

- lymphocytic insulitis (T8, T4)
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Environmental factors

- virus coxsackie B
- measles, mumps, rubella, IM
- seasonal trends
- geographic distribution (Finland 40x vs.Japan)
- cow milk antigens (bovine serum album x HLA)

- intestinal microbiome

type 2 DM - pathogenesis

impaired insulin secretion + reduced tissue sensitivity

genetically programmed failure of the β-cells to compensate for peripheral insulin resistance
(no reduction of B cells)

Genetic predisposition

- family clustering, inheritance unclear
  - first-order relatives
  - identical twins 90%
- no link with HLA
- no autoimmunity

type 2 DM - pathogenesis

Impaired insulin secretion

delayed

insufficient

Reduced tissue response

insulin resistance (obesity, pregnancy)

↓ synthesis of GLUTs

insulin insufficient

hyperglycemia

stimulation of β–cells

obesity

type 2 DM - pathogenesis

A. obesity and insulin resistency

1. non-esterified fatty acids (NEFAs)
2. adipokine production by adipous tissue
3. inflammatory factors - secretion by adipocytes

B. β cell dysfuncion

type 2 DM - pathogenesis

A. obesity and insulin resistency

1. non-esterified fatty acids (NEFAs) – overproduction in circulation →
↑ amount of neutral triglycerids in muscles and liver in the obese
↑ NEFAs in cells → contribute to ↑ intermedial metabolites:

diacylglycerol (DAG) + ceramid („toxic" metabolites)
- they activate **serin/threonin kinases** –↑ **fosforylation**

- activate serin/threonin at insulin receptor (IR)
and IRS - *insulin receptor substrates*

⇒ **pathologic fosforylation of IR decreases the activity of IR**

B. β-cell dysfunction

type 2 DM - pathogenesis

A. obesity and insulin resistency

2. production of adipokines by the adipous tissue

- adipous tissue is an endocrine organ = adipokines
  - **hyperglykemic**
    resistin and **retinol** binding protein 4 (**RBP4**)
  - anti-hyperglykemic
    leptin a adiponektin
    - both increases sensitivity of IR boosting activation

adiponectin level ↓↓ in the obese ⇒ contributes to hyperglycemia

B. β-cell dysfunction

type 2 DM - pathogenesis

A. obesity and insulin resistency

3. production of inflammatory factors by adipocytes

- TNF, IL-6, protein 1 atracting macrophages

boosting a cell stress by activation of signal lines antagonizing insulin effect

a decrease of inflammatory factors → strenghten insulin sensitivity

B. β-cell dysfunction

type 2 DM - pathogenesis

B. β-buněk cell dysfunction

function

- may be normal
- increased
- impaired and decreased

- the greatest risk of type 2 DM – gene TCF7L2 at 10q (transcription faktor 7-like-2) – WNT pathway leads to decreased insulin secretion from β cells

- amyloid

Complictions of diabetes mellitus

acute

- ketoacidosis
- hypoglycemia

- hyperosmolar syndrome
- lactate acidosis

chronic

- specific
- non-specific
- diabetic foot syndrome
- infectious complications

Complictions of diabetes

acute metabolic complications

- **ketoacidosis** – esp. DM 1
  lack of insulin → lipolysis → MK ↑ in blood → level ↑ production of ketosubstances (acetoacetate, 3-hydroxybutyrate)
  → metabolic acidosis + dehydration + hypokalemia
  + stres (→ hyperglycemia), infection
  may end up in death

- **hypoglycemia** (may end up in **coma**) – *esp. patients with type 1 DM*
  activation of sympathetic nerve system
  CNS
  untreated leads to death

- **hyperosmolarity syndrome** – *esp. patients with 2nd type of DM*
  insulin production preserved, no ketoacidosis present
  dehydration, hyperosmolarity + hyperglycemia
  untreated may end up in death

- **lactate acidosis** – *diabetics with the 2nd type of DM*
  develops with therapy of p.o. antidiabetic drugs (PAD) - metformine (biguanide)
  untreated often ends up in death

Complictions of diabetes

chronic

- **specific** – result of hyperglycemia
  - diabetic mikroangiopathy
    - retinopathy
    - neuropathy
    - nephropathy

- **non-specific**
  - diabetic macroangiopathy
    - ICH heart
    - ICH CNS
    - ICH lower extremities

Specific complications of DM – non-enzymatic glykosylation of proteins

AGE → protein networking

functional disturbance of basement membranes

bind cholesterol and LDL

cataract

AGE → RAGE

endothelia + smooth muscle cells

↑ ROS by endothelia

↑ procoagulative activity

↑ production of extracellular substances

macrophages

↑ production of inflammatory cytokines (alarmins are major RAGE ligands)

T lymfocytes

Complication of DM

Intracellular hyperglycemia

A ↑ **intracellular osmolarity** → influx of H_2O
↑ Na^+ / K^+ ATP activity

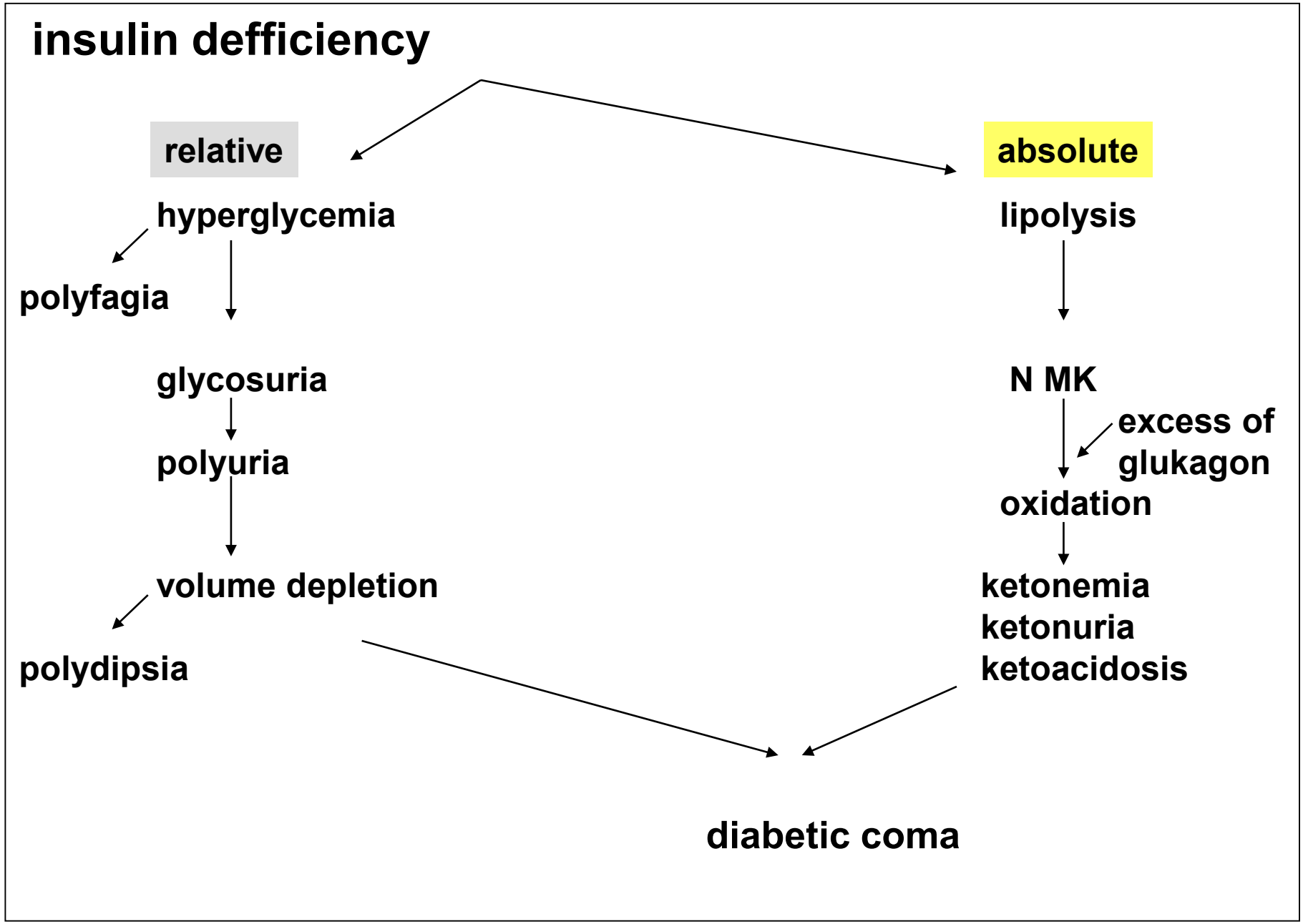
B **– *activation of polyolic pathway***
NADPH
glucose → <u>sorbitol</u> → fructose

↓ NADPH for regeneration of reduced glutathion → cell damage by ROS

C ↑ **production of diacylglycerol**
activation PKC → VEGF, TGF-beta ↑ molecules pf basement membranes

oxidative stress + nitrating stress

neuropathy (Schwann cells)
retinopathy (pericytes)
cataract


insulin defficiency
relative
absolute
hyperglycemia
lipolysis
polyfagia
glycosuria
N MK
excess of
glukagon
polyuria
oxidation
volume depletion
ketonemia
ketonuria
ketoacidosis
polydipsia
diabetic coma

Morfology of diabetes

a) Langerhans islets

b) vessels and organs

- diabetic microangiopathy
- arteriolosclerosis – hyaline
- atherosclerosis
- diabetic nefropathy
- retinopathy, cataract
- neuropathy
- diabetic foot

Clinical course variable

1st type DM

2nd type DM