TREATMENT OF DIABETES

JAN SVIHOVEC
Diabetes mellitus is not only a metabolic disease, it is primarily a disease of the cardiovascular system - cardiabetes.

In particular, this applies to diabetes with reduced tissue response to insulin – type II diabetes.
## Diabetes Mellitus

<table>
<thead>
<tr>
<th>Type I.</th>
<th>Type II.</th>
</tr>
</thead>
<tbody>
<tr>
<td>• destruction of pancreatic beta-cells with acute shortage insulin</td>
<td>• Insulin resistance,</td>
</tr>
<tr>
<td>• acute onset</td>
<td>• level of insulin normal or higher</td>
</tr>
<tr>
<td>• weight reduction, fatigue, polyuria</td>
<td>• slow onset</td>
</tr>
<tr>
<td>• more rare 7-8% diabetics</td>
<td>• frequent obesity</td>
</tr>
<tr>
<td>• children and individuals up to 35 years</td>
<td>• most frequent type (90%)</td>
</tr>
<tr>
<td></td>
<td>• diseases of the middle and higher age</td>
</tr>
</tbody>
</table>
TYP I (insulin-dependent DM)

- previously juvenilní diabetes
- absolute lack of insulin
- lesions of the pancreatic B-cells (usually autoimmune illness) → infiltration by T- leukocyte
- antibodies against islets tissue and insulin
TYP II (T2DM, non-insulin dependent DM)

- former old age diabetes
- the relative lack of insulin
- Inulin level can be normal, under-or higher than normal, target organs show a reduced sensitivity to insulin
- the decrease number of insulin receptors
- patients with T2DM often have overweight
INSULIN
ORIGINS OF INSULIN TREATMENT

Mering and Minkowski (1889) - diabetes as a result of pancreas extirpation

N. Paulescu (1921) – pancreas as a source of insulin

F. Banting a Ch. Best (1921) – insulin

1922 – the first clinical use of insulin
DM – Banting a Best

- 1921 - insulin discovery
- 1922 - 1. patient treated
- 1923 – first treatment in CR
1923 – Banting got Nobel Price
INSULIN

- human insulin – low molecular weight protein
- strong electronegativ (binding to proteins and to insulin surface cell membrane receptors)
- 2 peptid chains A (21 AMA) and B (30 AMA)
- preproinsulin → proinsulin → insulin and C-peptide (marker of the endogenous insulin secretion)
- glucose and lipids metabolic utilization
PREPROINSULIN

C-Peptide

Lys  Arg

Arg  Arg

Signal peptide

NH$_2$

C-peptid

+

INSULIN
Human insulin

A-chain

B-chain

21 AMA

30 AMA

monomers

dimers

hexamers

autoaggregation

In the solution
INSULIN RECEPTORS

- β-subunit – transmembrane protein with a tyrosinkinase activity
  
  INS binding to receptor α-subunit $\rightarrow$ conformation changes $\rightarrow$ activated tyrosinkinase $\rightarrow$ trigers cascade protein fosforylation (IRS – insulin receptor substrate proteins), second messengers

  $\rightarrow$ glucose transporters GLUT translocation to surface of membrane $\rightarrow$ fast glucose transport into cell by facilitated diffusion
Glucose entrance to $\beta$-cells

- Glucose transporter 2 (GLUT2)
- Glucokinase

Glucose metabolism

- ADP/ATP

Potassium channel ($K_{ATP}$) closed

Insuline secretion

- Role of glucose, $K^+$, and $Ca^{2+}$

Ca $Ca^{2+}$ channel open

Insuline secretion granula

$ADP/ATP$
INSULIN EFFECTS

- Main hormone regulating intermediate metabolism in the liver, muscle and fat tissue
- Stimulates anabolic and inhibits katabolic processes
- Facilitates glucose uptake, AMA and lipids
- Acute effect of insulin produces hypoglycemia
Insulin
GLUT4 activation in muscles and adipocytes

In insulin receptor

Inactivating the signal cascade

Intracellular GLUT4

Mobilization of GLUT4 to plasma membrane

Integration GLUT4 into membrane

Entry of glucose into cells via GLUT4

GLUT4 = glucose transporter 4
Insulin pharmacokinetics

- The speed of absorption depends on physico-chemical properties, dose and blood flow at injection site.
- No important binding to plasmatic proteins.

Insulin degradation

- Kidney (35 - 40 %), liver (60 %),
- Elimination half-life 7 - 10 minutes.
INSULIN SECRETION

/ 30-40 IU for 24 h

• Basal (cca 50 %)

  . Postprandial (stimulated)
    (cca 50 %)
INSULIN ANALOGS

A- chain

B-chain

Asp

Lys

Glu

Lys Pro

Gly

Arg Arg

human insulin
dimers a hexamers

aspart
limited autoaggregation monomers in solution

glulisin
limited autoaggregation monomers in solution

lispro
limited autoaggregation monomers in solution

glargine
Soluble low pH Precipitation in neutral. pH s.c.
Therapeutic problem control of fasting and postprandial hyperglycemia

uncontrolled diabetes (A1C ~6%)

fasting hyperglycemia

postprandial hyperglycemia

physiology

Insulin analog profiles

- aspart, glulisin, lispro 4–6 h
- regular 6–8 h
- lente 12–20 hod
- ultralente 18–24 hod
- glargin 24 hod

plasma insulin

hours

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
<table>
<thead>
<tr>
<th>product</th>
<th>onset</th>
<th>maximum</th>
<th>duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>aspart, glulisin, lispro</td>
<td>~15 min</td>
<td>1–2 h</td>
<td>4–6 h</td>
</tr>
<tr>
<td>human regular</td>
<td>30–60 min</td>
<td>2–4 h</td>
<td>6–8 h</td>
</tr>
<tr>
<td>human – lente</td>
<td>2–4 h</td>
<td>4–10 h</td>
<td>12–20 h</td>
</tr>
<tr>
<td>human - ultralente</td>
<td>4–6 h</td>
<td>8–16 h</td>
<td>18–24 h</td>
</tr>
<tr>
<td>glargin</td>
<td>2–4 h</td>
<td>flat curve</td>
<td>~24 h</td>
</tr>
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THE INDICATION OF INSULIN TREATMENT

a) acute treatment – diabetic coma

b) chronic treatment

DM 1.typu – standard therapy

DM 2.typu – failure of treatment PAD

alergy to PAD

acute status (operation, accident, infection)

pregnancy
Physiological daily profile of insulin
Copy of physiological profile combination of short- and long-term insulinu
Adverse reactions

- Hypoglycemic reaction – insulin overdose skipping meals or higher physical burdens

  *Sympatic reaction* (sweating, tachycardia, tremors, weakness)

  *Parasymatic reaction* (hunger, nauzea, ocluded vision)

- Long term therapy (mainly for old patients) – impairment of CNS functions (confusion, uncoordinated speach and bizarre behavior)

- Hypoglycemic coma – intravenous application of glucose (20-50 ml 40 % Glu) or glucagon (i.m., s.c.),
Application forms

Insuline syringes

- special plastic syringe 1 ml with fixed needle
- 1 unit scale corresponds to 1 unit insulinu
- Disposable
- Today exceptional application - mainly in adult diabetics
- lower price
Application forms

Insuline pens (applicators) standard therapy

- Applicators - size and shape of pen
- Insuline containers
- Especially suitable for intensive insuline therapy in multiple dose scheme
Application forms
Insuline pumps

- portable pump for subcutaneous infusion continuously supplying the soluble insulin with defined speed
- continuous monitoring of blood glucose
- precise control of glucose necessary
- **advantages**: Exchange of infusion set every 48 hours, plus the comfort to the patient
- **disadvantages**: high cost, need for repeated measurements of blood glucose during the day, plus the risk of skin infections (needle is introduced into the skin of the abdomen permanently)
Type 2. Diabetes mellitus
The importance of insulin resistance
Insuline resistance - T2DM

Glucose decrease

Plasmatic insulin

Normal reaction

Insuline resistance
Diabetic patients have the same CV risk, as nondiabetic after MI.
Antidiabetics (hypoglycemic agents)

- **Insuline resistance**
  - Metformin
  - Glitazons

- **Pancreas dysfunction**
  - Inadequate glucagon secretation (α-cell dysf.)
  - Inadequate insulin secretion (β-cell dysf.)
  - Progressive loss of function β-cell.

- **Analogs GLP-1, inhibitors DPP-4**

- Sulfonylureas
- Glinids

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ORAL ANTIDIABETICS
Peroral antidiabetics (PAD)

- **Insuline sensitisers**
  - biguanides (*metformin*)
  - glitazones – thiazolidindiones (*pioglitazon*)
  - *glitazars*

- **Insuline secretagogues**
  - sulfonylurea derivatives (*glimepirid,...*)
  - glinides (*repaglinide, nateglinide*), quick, short acting insuline sekretagogues

- Incretins and inhibitors DPP-4

- **Glucosidase inhibitors** - gut (*acarbose*)
INSULINE SENSITISERS
BIGUANIDES

Mechanism of action:

- ↓ glucose absorption from the gut
- liver gluconeogenesis inhibition
- stimulating effect of insulin in target tissues

Molecular mechanism not clear
biguanides - *metformin*

- As a first line treatment for GP
- PAD for obese patients – *improving prognosis*
- good long term tolerance,
- *minimum risk of hypoglycemia,*
- possibility of combination with other antidiabetics and favourable cost of treatment
Metformin increase glucose utilisation stimulation GLUT-4 striated muscle adipocytes without metformin

Insuline

Translocation into membrane

Glucosa

GLUT-4 activated

Synthesis de novo

GLUT-4
Metformin increase glucose utilisation stimulation GLUT-4 striated muscle adipocytes

with metformin

insuline

translocation

metformin

synthesis de novo

effect: ↑glucose utilisation ↓inzulin resistance
metformin – CV risk

Decrease of CV complications

- MI ↓ up to 40%
- CV+ ↓ up to 50%
- DM+ ↓ up to 40%
- Total risk ↓ 10 up to 35%

Metabolic memory – decreased mortality /morbidity after long term treatment - even after stopping
biganides - *metformin*

- **Adverse reactions:**
  - lactic acidosis – very rare
    (dyspnoe, diarrhoea, muscle pain, coma)
  - GIT intolerance, with diarrhoea (transitional)

- **contraindication:** renal insufficiency

- stop before the examination with RTG contrast media (nephrotoxicity)
metformin – decrease of CV risk

**IM**
- metformin
  - P = 0.01
  - 39% ↓

**CV+**
- metformin
  - P = 0.02
  - 50% ↓

UKPD st.
Thiazolidindiones (glitazons)
Thiazolidinediones (glitazones) - PPARγ agonists

Rosiglitazone
- increase CV mortality – out not marketed in EU

Pioglitazone
- favourable effect on CV mortality
Thiazolidinediones (glitazones)

- **mechanisms of action**: sensitization of peripheral receptors to insulin

- **selective stimulation** PPARγ receptors (peroxisome proliferator-activated receptors)
  - **stimulation of glucose utilisation** (*increase sensitivity to insulin*) and decrease hepatic gluconeogenesis
Glitazones stimulation GLUT-4 adipocytes

with glitazones

insuline

translocation

glitazones

synthesis de novo

glucosa

effect: \( \uparrow \) glucose utilisation
\( \downarrow \) inzulin resistance
Thiazolidinediones (glitazones)

- Indication when intolerance or contraindication of metformin
- Benefit in combination with metformin or other PAD
- Good tolerance, hypoglycemia rare
- Water retention – attention for heart failure
- Only pioglitazone
GLITAZARS

Mechanism of action

- Dual agonists PPARα/γ (peroxisome proliferation-activated receptors)
- Antihyperglycemic and hypolipidemic
- Increase HDL
- Decrease blood pressure
GLITAZARS

Indications

- high insuline resistance
- fasting hyperglycemia
- diabetic dyslipidemia
- obesity
GLITAZARS

Under clinical trials only

- muraglitazar – increased CV risk
- tesaglitazar – hepatic toxicity
- aleglitazar – promising
SECRETAGOGUES
DRUGS RELEASING INSULIN
Drugs releasing insulin secretagogues

**sulfonylureas** – long acting

**glinides** - short-term, fast-acting

- Effect mediated block ATP-dependent potassium channel in pancreatic β-cells
- Decreased glycemia, mainly postprandial
- Insulin resistance is not influence
Sulfonylurea derivatives

- Mechanism of action:
  
  stimulation of basal and postprandial insulin secretion from $\beta$-cells

- Effect depends on functional $\beta$-cells

- AE: hypoglycemia, increase in weight
Insuline secretion by \( \beta \)-cells

GLUT2

Glucokinase

\[ \text{Glucose metabolism} \]

\[ \text{ADP/ATP} \]

Potassium channel (\( K_{\text{ATP}} \)) closed

Sulfonylureas

Insuline granula

Calcium channel open

\[ \text{Ca}^{2+} \]

Insuline secretion

\[ \text{Ca}^{2+} \]
Sulfonylurea derivatives

1. **generation** Tolbutamide, Chlorpropamide) **not used**

2. **generation**

   GLIBENKLAMIDE (Maninil, Glucobene)

   GLIPIZIDE (Minidiab)

   GLIKLAZIDE (Diaprel, Diaprel MR)

   GLIQUIDONE (Glurenorm)

   GLIMEPIRIDE (Amaryl)
NONSULFONYLUREA SECRETAGOGUES

METIGLINIDES (GLINIDES)

Repaglinide (Novonorm)
Nateglinide (Starlix)

Characteristics:
- quick onset
- correction of postprandial glycemia
Glinides

- **Mechanism of action**: stimulation of insulin secretion depending on actual glycemia inhibition ATP-dependent potassium channel
- **half-life of action**: 60-90 min,
- **repaglinide, nateglinide**
- **Adverse events**: hypoglycemia,
  - GIT symptoms
Glinides

Sulfonylurea rec.

140 kDa

65 kDa

K+

membrane β - cell.

K_{ATP} channel

K+

sulfonylureas

glinides

glimepiride
INCRETINS
INCRETINS

Intestinal hormones stimulating insuline secretion

- Glukagon-like peptide (GLP 1)
- Glucose dependent insulinosotropic polypeptide (GIP)
- Cholecystokininine
Different Responses to Oral vs IV Glucose

Oral Glucose Tolerance Test and Matched IV Infusion

N=6

IV=intravenous
GLP-1 and GIP Are Synthesized and Secreted from the Gut in Response to Food Intake

GLP-1 and GIP Are Synthesized and Secreted from the Gut in Response to Food Intake

GIP = glucose-dependent insulinotropic peptide; GLP-1 = glucagon-like peptide-1
Adapted from Drucker DJ. Diabetes Care. 2003; 26: 2929–2940.
GLP-1: Glucagon-Like Peptide-1

GIP: Glucose-Dependent Insulinotropic Peptide

Amino acids shown in gold are homologous with the structure of glucagon.
Incretin effect is reduced for Type 2. diabetic patients

*P ≤ .05 ve srovnání s příslušnými hodnotami po perorální zátěži.

INCRETINS

Typ 2 diabetes

- Sekretion GIP - normal
- Sekrece GLP 1 - reduced
Incretins physiological effects

- ↑ postprandial insulin secretion
- ↓ glucagon secretion
- ↓ secretion HCl and GIT motility (slowdown gastric evacuation)
- ? β-cell protection and regeneration
Incretins

analogs and dipeptidylpeptidase 4 inhibitors

- secreted postprandially
  - intestinal endocrine cells

- stimulation insuline secretion

- Inhibition of glucagon secretion

- acting only at hyperglycemia,
  - but not at normoglycemia –
  - low risk of hypoglycemia
Incretins and control of glycemia

Food intake

GIT

Incretins release

Pancreas

β-bb. α-bb.

GLP-1 a GIP

Enzyme DPP-4 incretins degradation

Glucose dependent

↑ insulin (GLP-1 a GIP)

Glucose uptake

Regulation glycemia

decrease glucose output

glukagon α-cells (GLP-1)

Food intake

Miller S, St Onge EL. Ann Pharmacother 2006;40:1336-1343.
Incretin analogues

1. **Stimulation incretine receptores**
   - Exenatide, Liraglutid, Lixisenatid

2. **Decrease inactivation of incretines** - dipeptidyl peptidase (DPP-IV) inhibition
   - Sitagliptin, Vildagliptin, Saxagliptin
Exenatid – incretin analog GLP-1

- synthetic 53% homolog human GLP-1
  - from saliva lizards Gila monster
  - relatively expensive treatment
  - application
    - 2x daily s.c. inj
Lixisenatid
incretin, analog GLP-1

- Modified exenatid
- Resistant to DPP 4
- Injection
- CNS decreased food intake
- Application 1x daily
- Combination with other PAD
- Adverse reactions - GIT,
Liraglutid – incretin analog GLP-1

- synthetic 97% homolog human GLP-1
  - effective and safe antidiabetic
  - in comparison with exenatid more effective (greater decrease in glycemia)
  - combination with PAD (metformin, glitazones)
  - more expensive
  - application 1x daily s.c.
Albiglutid
incretin, analog GLP-1

- Resistant to DPP 4
- Application 1x weekly !!!
- Clinical trials only
Dipeptidylpeptidase (DPP-4-I) Inhibitors

- block the degradation of the natural incretines enhance and prolong their activity
- vildagliptin, sitagliptin, saxagliptin...
- Unlike analog incretines applied perorally
Vildagliptin: A Potent and Selective DPP-4 Inhibitor

- Highly selective DPP-4 inhibitor
- Has a high affinity for the human enzyme
- Reversible inhibition

X-ray crystallographic structure of vildagliptin (green) bound to the active site (yellow) of human DPP-4

DPP-4 = dipeptidyl peptidase-4
Vildagliptin Suppresses Endogenous Glucose Production

EGP=endogenous glucose production; PBO=placebo; vilda=vildagliptin

*P <0.05 vs PBO.

Vildagliptin Provides Potent Inhibition of DPP-4 in Patients with T2DM

DPP-4=dipeptidyl peptidase-4; T2DM=type 2 diabetes mellitus; vilda=vildagliptin

TRIHORMONAL REGULATION

Glucose appearance

HGP

Glucose disappearance

Plasma glucose

Food intake

GLUCAGON

- -

(Gastric emptying)

(analogue: Pramlintide)

INSULIN

Amylin

+ +
Exenatid enlarge the size of islets at diabetic mouse

Physiological solution

Exendin-4

Mean (SE).
DRUGS DECREASING HYPERGLYCEMIA

- decreased absorption
- increased excretion
Intestinal $\alpha$ glucosidase inhibitors

- **Mechanism of action:**
  - Inhibition intestinal $\alpha$-glucosidase splitting nonabsorbable oligosaccharides
  - Reduction and slowdown absorption of carbohydrates from GIT

- Decrease of postprandial glycemia,

- *acarbose* – pseudosaccharide with high affinity to enterocyte $\alpha$-glucosidase

- AE: flatulence, diarrhea
Influence of PAD to the weight of T2DM

- **PAD**

- **metformin**
- **SU**
- **glitazones**
- **glinides**
- **incretins**
- **metformin + SU**
- **metformin + glitazones**

- **change weight (kg)**

-3.8–0.5

-0.4–1.7

0.9–4.6

0.3–3.0

1.8–2.8

-0.3–1.9

0.8–2.1
GLIFLOZINS

Mechanism of action

• inhibition of glucose reabsorption in kidney
  – direct inhibition of sodium-dependent glucose cotransporter (SGLT 2) in kidney tubular system
GLIFLOZINS

- marketed
  - dapagliflozin, canagliflozin

- clinical trials only
  - florizin, sergliflozin, remigliflozin, ipragliflozin, empagliflozin,
FOUR PILLARS IN THE TREATMENT OF DIABETES

- PHYSICAL ACTIVITY
- DIET
- PSYCHOTHERAPY
- PHARMACOLOGICAL TREATMENT