Pharmacological options for influencing diabetes

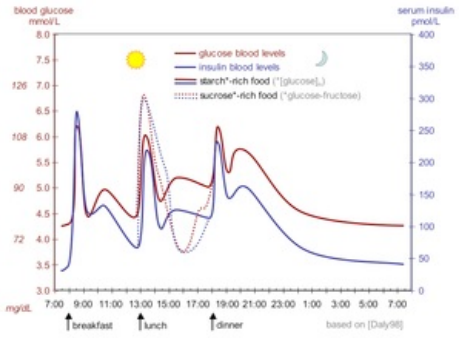
Therapies for each type of diabetes vary to a large extent. While in type 1 diabetes we are dependent on insulin therapy, in type 2 diabetics , depending on the degree of insulin resistance, diet, oral antidiabetic drugs are used, and only in complicated diabetes do we resort to insulin therapy. The cornerstone of the treatment of type 1 diabetes mellitus is insulin substitution, which must be supplemented with dietary and regimen measures.

Cooperation between the doctor and the patient is essential, as an individual treatment plan is drawn up for the patient, which consists of:

- diet regime with detailed instructions;
- lifestyle changes;
- education;
- psychosocial care;
- pharmacological treatment of diabetes and associated diseases;
- regular checks.

We start insulin therapy on an outpatient basis or during hospitalization. We always apply lower doses at the beginning to prevent hypoglycemia , because endogenous insulin secretion still persists. We collect a large glycemic profile , which consists of: glycemia always before a meal and after a meal, at 10 p.m. and at 3 a.m. Based on regular glycemic profiles, we adjust the dosage to set the optimal compensation.

After application, insulins do not bind to plasma proteins in the vascular bed , therefore they quickly leave the circulation and bind to insulin receptors. Exogenous insulin is more than 60% degraded in the kidneys, the rest of the degradation is realized in the liver (unlike endogenous insulin, which is degraded for the most part in the liver). Only a small part of the administered insulin is excreted unchanged in the urine.



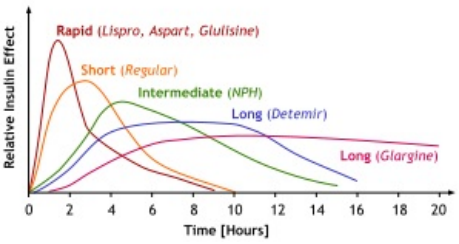
How the physiological response of insulin to increased sugar levels after meals, during the day and at night works

Types of insulins by origin

Animal insulins have been used for the longest time, previously isolated from beef or pig pancreases, today monocomponent and highly purified. Beef insulin differs from human insulin by three amino acids, and pork insulin by one amino acid. Due to the risk of BSE , bovine insulins are no longer used. Human insulin was prepared by recombinant DNA transfer technologies into *Escherichia coli* . Compared to animal insulins, human insulin is more polar, has faster absorption from the site of administration and a shorter duration of action. By administering human insulin, we better copy the physiological function of this hormone, but we hide some of the warning signs of hypoglycemia, which are otherwise present when animal insulins are administered.

Insulin analogs , which are biosynthetics differing in amino acid sequence and pharmacokinetics, are also used .

Types of insulin according to duration of action



Comparison of the length of action of individual insulins

Insulins with different durations of action have been developed to best compensate for diabetes.

Short-acting insulins

Short-term insulins are produced to manage acute situations of hyperglycemia as well as for intensified insulin therapy as clear water-soluble solutions of crystalline insulin complexes with zinc at a neutral pH. For acute intervention in the case of hyperglycemic ketoacidotic coma and during anesthesia or other extreme loads in diabetics, it can also be administered intravenously, which has a practically immediate effect. As part of intensified insulin therapy, it is then administered subcutaneously, when it works within 15-30 minutes, the peak effect occurs in 1-3 hours and lasts 4-6 hours. Short-acting insulins include:

- Insulin lispro – its advantage is a lower tendency to form hexamers and dimers, which facilitates absorption and accelerates the onset of action. It can therefore be applied just before a meal, and thanks to their short effect, the risk of hypoglycemia is reduced.
- Insulin aspart – has similar properties to insulin lispro.

Intermediate-acting insulins

They are cloudy suspensions (mixtures of crystalline and non-crystalline insulin) intended for subcutaneous administration only.

- Amorphous insulin : a mixture of porcine or human insulin with 2 μm particles with a duration of action of 8–12 hours
- Zinc-insulin suspension : 30% amorphous insulin and 70% crystalline insulin, the duration of the effect varies (from 7 to 24 hours).
- Isophan insulin (NPH insulin or protamine-zinc-insulin): protamine is a mixture of peptides isolated from brook trout sperm. The ratio of protamine molecules to insulin is approximately 1:6.
- Stabilized insulin mixtures are mixtures of short-acting insulin and isophane insulin. The advantage is a quick onset and a prolonged effect.

Long-acting insulins

These insulins are slowly absorbed because they contain large zinc-insulin crystals, so their effect starts slowly but also lasts a long time (26-28 hours). They are applied subcutaneously, rarely intramuscularly. For example, insulin glargine is used , which has a duration of action of up to 36 hours, and must not be mixed with other insulins in the same syringe due to large crystals.

Modes

Conventional modes

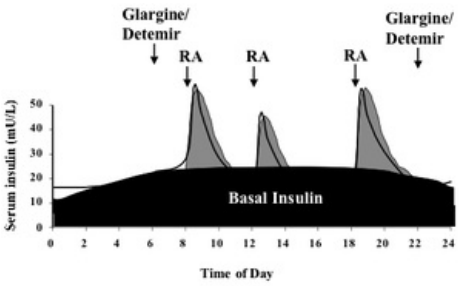
If a certain degree of endogenous insulin secretion is still preserved, the following schemes are used:

- Two-dose regimen : rapid and medium-acting insulin in two daily doses, 2/3 of the total daily dose in the morning and 1/3 in the evening.
- Three-dose regimen :
  - morning: fast insulin + medium fast insulin,
  - before dinner: rapid insulin,
  - at bedtime: medium-rapid insulin.

Intensified modes

In patients with type 1 DM, we try to ensure that exogenous insulin delivery mimics insulin secretion from the pancreas of healthy people as best as possible. These schemes are also used in type 2 DM with a complicated course.

- **Scheme for rapid compensation of diabetes** , also suitable for more labile diabetes: short-acting insulin before main meals, medium-acting insulin before bedtime.
- **Basal-bolus schedule** : short-acting insulin before main meals and long-acting insulin in one or two daily doses.



- A scheme of short-acting insulin in at least four daily doses.
- Insulin pump : continuous subcutaneous infusion of fast-acting insulin.

Methods of administering insulin

Insulin is administered as an injection solution, most often subcutaneously (rapid insulin can also be administered intravenously). Since insulin therapy is permanent, it is necessary to instruct patients precisely and teach them the application technique so that their diabetes is fully compensated. To administer insulin, it is used:

- Insulin syringe (so-called insulin pen),
- insulin pen,
- Insulin pump .

Therapy of type 2 diabetes mellitus

More detailed information can be found on the page Diabetes mellitus type 2 (endocrinology) .

Non-pharmacological therapy

- diet
- physical activity
- bariatric treatment

Oral antidiabetics

Oral antidiabetic drugs (PAD) are drugs used in the therapy of diabetes mellitus . The mechanism of their action is dependent on the production of endogenous insulin , and therefore they **cannot be used in patients with type 1 diabetes .**

According to the place of action, PAD can be divided into 4 groups:

- **insulin sensitizers** – increase the sensitivity of cells to insulin (biguanides , thiazolidinediones);
- **insulin secretagogue** - they increase the release of insulin from β-cells of the pancreas (sulfonylurea derivatives , glinides);
- **Intestinal glucosidase inhibitors** - reduce the absorption of glucose from the intestine - alpha-glucosidase inhibitors ;
- **inhibitors of glucose reabsorption in the proximal tubule** − increase glycosuria (gliflozins).

Insulin sensitizers

They increase the sensitivity of cells to insulin. They do not cause hypoglycemia , and are therefore referred to as *"euglycemic drugs"* .

Biguanides

Metformin is the main PAD today. It is well tolerated and can be advantageously combined with other antidiabetic drugs. It reduces cardiovascular mortality independent of compensation for diabetes and has positive late consequences of treatment (treatment can be started already in the period of prediabetes). It does not cause an increase in body weight (unlike secretagogues and thiazolidinediones), so it is also beneficial for obese patients. It is a cheap drug without a prescription restriction.

Mechanism of action

They increase the sensitivity of tissues (especially liver and skeletal muscle) to insulin and reduce glycemia:

- by supporting glucose utilization in skeletal muscles and fat tissue (stimulation of glycolysis),
- suppression of gluconeogenesis in the liver,
- by reducing the absorption of glucose from the intestine.

Side effects

They support glycolysis and thus the formation of lactate . ***Lactic acidosis*** can therefore be a serious complication . Individuals with failing kidneys, cardiopulmonary insufficiency, liver insufficiency (alcoholics) are predisposed to it. In these cases, biguanides are contraindicated. **Gastrointestinal problems** may appear at the beginning of treatment . Intravenous administration of iodinated contrast media can lead to **renal failure** . This can cause accumulation and increase the risk of lactic acidosis. The use of biguanides must therefore be discontinued 48 hours before the examination. They are also discontinued prior to surgery. They are not recommended for the treatment of diabetes during pregnancy. Insulin should be used to maintain blood sugar levels to minimize the risk of fetal malformation.

Thiazolidinediones

Mechanism of action

They have similar effects to biguanides. Through the nuclear receptor PPAR-γ, they activate the transcription of genes responsible for carbohydrate and fat metabolism.

Side effects

They cause mild fluid retention (which is why diuretics are sometimes added), so they are not given to patients with heart failure , edema conditions, or during pregnancy. Pioglitazone is contraindicated in hematuria of unclear origin. They require regular monitoring of liver tests . There is often an increase in weight (fluid retention, increase in adipose tissue). An eye examination is also recommended before use, due to the risk of worsening diabetic macular edema.

Today, only one **pioglitazone** preparation is used (rosiglitazone does not have a favorable effect on cardiovascular mortality and is currently withdrawn from the market), it is well tolerated, and is suitable when metformin is contraindicated.

Insulin secretagogue

They increase the release of insulin from the β-cells of the pancreas. They are risky in terms of the possible induction of **hypoglycemia** and cause an **increase in body weight** .

Sulfonylurea derivatives

Mechanism of action

Increased release of insulin from β-cells of the pancreas is achieved by blocking ATP-sensitive K + channels in the membrane. This will reduce the current of potassium from the cell, depolarize the membrane and open Ca 2+ channels. The influx of Ca 2+ ions causes a washout of insulin.

Side effects

The most serious complication can be hypoglycemia, especially with longer-acting substances. This group of drugs also increases appetite, so treatment is often associated with weight gain.

II drugs are used in practice. generation (**glipizide**) and III. generation (**glimepiride**). Most often in combined therapy with metformin (mainly in case of insufficient compensation of type II DM monotherapy with metformin).

Glinides

Newer drugs also **block the ATP-sensitive K + channel** in β-cell membranes. They act quickly, making them ideal for taking with food to offset postprandial hyperglycemia. Examples of substances are **repaglinide** and **nateglinide** .

Intestinal glucosidase inhibitors

They are used to suppress postprandial hyperglycemia. The basic substance used in this group is **acarbose** .

Mechanism of action

By inhibiting enzymes, they limit and slow down the absorption of carbohydrates in the small intestine. The blocked enzyme does not break them down and therefore cannot be resorbed (absorption of monosaccharides remains unchanged).

Side effects

Flatulence, diarrhea and abdominal pain, which are caused by the action of microbial intestinal flora on undigested complex carbohydrates.

If the patient develops hypoglycemia due to other drugs, it cannot be treated orally with sucrose, but exclusively with glucose.

Gliflozin

Empagliflozin in combination with metformin for oral use

Mechanism of action

They inhibit the SGLT-2 transporter in the proximal tubule of the nephron, thereby blocking the reabsorption of glucose and increasing glycosuria. Thus, there is a shift in the renal threshold for glucose and a reduction in glycemia. Increased glucose losses lead to energy depletion and patient weight loss. At the same time, they reduce glycated hemoglobin , uricemia, slightly increase HDL cholesterol and, due to osmotic diuresis, there is a slight drop in blood pressure.

Adverse effects Increase in the frequency of infections of the urogenital tract. Most often, these are fungal infections in women. Due to increased diuresis, caution is warranted in patients at risk of hypotension or volume depletion.

The risk of hypoglycemia is minimal during treatment with gliflozin.

Dapagliflozin , **canagliflozin** and **empagliflozin** are available in the Czech Republic .

Incretins

Newly, substances modulating the effects of incretins can be used in the treatment of type 2 diabetes . They are very effective, safe, but expensive. They increase insulin secretion, inhibit glucagon and act only in hyperglycemia.

Exenatide is a synthetic analogue of GLP-1 (glucagon-like peptide 1), an analogue of incretins . It is applied sc, so it does not belong to PAD.

Dipeptidyl peptidase 4 (DPP-4) inhibitors block the enzyme that inactivates endogenous incretins. They are less effective than incretin analogues, but are cheaper and can be administered orally. Example of substance: **sitagliptin** , **linagliptin** .

Comparison of therapeutic options

The strategy for the treatment of type 2 diabetes mellitus with oral antidiabetic drugs depends, among other things, **on the patient's comorbidities - cardiovascular risk** and renal insufficiency are taken into account the most . Cardiovascular risk can be assessed using the ASCVD SCORE table, and the presence of heart failure is also assessed. If the patient does not have these comorbidities, therapy is chosen individually according to other goals, e.g. elimination of hypoglycemic episodes, weight loss, more favorable price. A summary of the therapy is written in the following diagram.

The following table summarizes the individual PADs and their advantages and disadvantages.

Pharmacy	Advantages	Adverse effects, contraindications
Metformin	initial therapy	gastrointestinal problems, lactic acidosis, KI in renal insufficiency
Sulfonylurea	potent medicine	weight gain, hypoglycemia
GLP-1 agonists	reduction of CVD risk, weight reduction	gastrointestinal problems, need for injections, high price
Thiazolidinediones	pioglitazone: modification of the lipid spectrum, lower CVD risk	fluid retention, weight gain, bladder cancer risk (pioglitazone)
Glinide	potent medicine	weight gain, hypoglycemia, must be taken 3 times a day
SGLT-2 inhibitor	weight loss, lowering of blood pressure, improvement of cardiovascular and renal prognosis	vaginal candidiasis, urinary tract infection, risk of fractures, risk of amputations
DPP-4 inhibitor	weight neutral	high price
Alpha-glucosidase inhibitor	weight neutral	frequent gastrointestinal problems, dosage 3 times a day

Links

Related articles

- Diabetes mellitus
- Diabetes mellitus type 1
- Diabetes mellitus type 2 (endocrinology)
- Diabetes mellitus type 2 (biochemistry)
- Insulin

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