Disorders of glucose metabolism

An increase in blood glucose above 7.77 mmol/l is referred to as **hyperglycemia**; on the contrary, a reduction below 2.5 mmol/l is **hypoglycemia**. Under physiological conditions, the average glucose consumption of an adult, is 38 mmol/h (= 6.8 g/h), is balanced by its production in the liver at 39 mmol/h (= 7.0 g/h).

Hypoglycemia

Hypoglycemia is a condition in which the glucose level falls below 2.5 mmol/l. This limit is 1.7 mmol/l in neonates and 1.1 mmol/l in preterm infants. The main danger of hypoglycemia is an insufficient energy supply to the brain (neuroglycopenia), with symptoms such as hunger, headaches, falling asleep, mental confusion, hallucinations and finally convulsions and coma. The second group of symptoms stems from the activation of the adrenergic system and increased secretion of catecholamines (palpitations, anxiety, tremors, sweating).

Hypoglycemia is caused by increased utilization of glucose by extrahepatic tissues (e.g. excessive physical exertion) or by reduced carbohydrate intake. Brain tissue is most at risk of a sudden drop below 2.5 mmol/l (in adults) (an intracellular glucose supply to the brain is only 10-15 minutes).

According to the causes based on the physiological regulation of glycemia, we can divide hypoglyacemia into two groups:

1. from insufficient glucose supply to the bloodstream;
2. from too rapid uptake from circulation.

However, the division into the following types is more practical.

Hypoglycemia during fasting

Are caused by:

- *Langerhans islet β-cell tumours* (carcinoma, adenoma) or their hyperplasia (nesidioblastosis); *extrapancreatic tumours* (secreting or non-secreting insulin);
- *endocrinopathies* causing counter-insulin hormone deficiency (panhypopituitarism, isolated growth hormone or adrenocorticotropin deficiency, hypoadrenalism, hypothyroidism, glucagon defect);
- *liver cirrhosis* (hepatitis, congestive liver failure);
- *glycogenoses* (type I, VII, IX) and a defect in gluconeogenic metabolism enzymes;
- *lack of glucose precursors* (alanine) - pregnancy hypoglycemia, ketosis hypoglycemia of infants, uremia, severe malnutrition.

Hypoglycemia in newborns and infants

In neonates, glycemia is lower than in adults (on average 1.94 mmol/l) and shortly after birth, it decreases further (as the liver glycogen supply is depleted) to values of around 1.66 mmol/l at full term and 1.11 mmol/l. prematurity without clinical manifestations of hypoglycemia. The most common causes of neonatal hypoglycemia are prematurity, respiratory distress syndrome (paediatrics), maternal diabetes mellitus, pregnancy toxaemia, hypothermia, and polycythemia. Hypoglycemia is usually transient.

In infants, it may no longer be transient and is usually caused by hereditary metabolic disorders (galactosemia, glycogenosis, hereditary fructose intolerance, gluconeogenesis enzyme deficiency) or ketosis hypoglycemia, which occurs during starvation or feverish conditions. Other causes may be hypersensitivity to leucine, endogenous hyperinsulinism, Rey's syndrome or idiopathic hypoglycemia (McQuarrie's syndrome).

Postprandial hypoglycemia

- alimentary (in patients with gastrectomy, gastrojejunostomy, etc.);
- early-stage diabetes mellitus;
- functional idiopathic hypoglycemia;
- leucine-induced hypoglycemia;
- fructose-induced hypoglycemia (fructose-1-phosphate-aldolase deficiency or fructose-1,6-bisphosphaldolalase deficiency).

Drug-induced hypoglycemia

- insulin;
- oral antidiabetics;
- salicylates, propranolol;
- alcohol (ethanol inhibits gluconeogenesis).

Reactive hypoglycemia

It is a clinical syndrome that manifests itself postprandially (after a meal) with signs from the autonomic nervous system (weakness, tremor, cold sweat, nausea, hunger, epigastric discomfort), accompanied by hypoglycemia (below 2.5-2.77 mmol / l), normally during the day. Reactive hypoglycemia must be distinguished from hunger hypoglycemia. Reactive hypoglycemia is a benign condition and can be understood as a physiological situation. The diagnosis of glycemia at the time of onset of clinical symptoms will help with the diagnosis; a 5-6 hour glucose tolerance test is less suitable.

„Nonhypoglycemia“

Non-specific clinical symptoms (fatigue, weakness, palpitations, muscle spasms, numbness, sweating, pain, etc.), are usually attributed to hypoglycaemia, which has never been proven.

Causes of hypoglycemia

A. Decreased glucose intake	B. Increased glucose utilization
decreased hepatic gluconeogenesis	increased physical activity
hereditary metabolic disorders	hyperinsulinism
alcohol intoxication	β-cell tumour
poisoning	lack of insulin antagonists
malabsorption	M. Addison
starvation	hypopituitarism
	sulfonylurea treatment
	insulin overdose

Hyperglycemia

Diabetes mellitus

This disease, characterized by absolute or relative insulin deficiency, has several forms and several stages, which must be distinguished for both prognostic and therapeutic reasons.

Type 1 diabetes mellitus (formerly referred to as insulin-independent or juvenile type, IDDM)

IDDM is *a polygenic autoimmune disease*. Genetic predisposition combined with certain external factors such as viral infection, toxins, and stress can induce a prediabetic phase of the disease, which lasts for several years. At this time, there is a slow destruction of β-cells of the islets of Langerhans mediated by activated T-lymphocytes and cytokines, which manifests as insulitis (lymphocyte infiltration of islet cells, inflammation). Insulitis gradually reduces the number of functional β-cells, causing impaired insulin synthesis and secretion. Diabetes is clinically manifested at a time when up to 60-70% of pancreatic β-cells are destroyed by autoimmune inflammation. The at-risk population includes not only siblings of diabetic children (with a relative risk of around 12% with a large individual variance) and children of diabetic parents (relative risk of about 6% in diabetic fathers and 2% in diabetic mothers), but also adults (diabetic child's parents). There are about 5-10% of unrecognized type 1 diabetics who did not develop the disease until adulthood (slowly progressing autoimmune insulitis = LADA), but who can be treated as type 2 diabetes with possibly catastrophic consequences.

Progressive insulitis markers include several types of antibodies directed against various types of islet antigens, such as the glutamate decarboxylase (GAD65) isoform or autoantibodies to insulin and proinsulin, against islet cells. The first phase of insulin secretion is also reduced before the apparent clinical manifestations of diabetes. The presence of autoantibodies is not the cause of β-cell destruction, but their examination is important for predicting the risk of IDDM. The glutamate decarboxylase isoform, termed GAD65, appears to be the most suitable predictor of the marker. An association between type 1 diabetes and HLA genetic markers (HLA-DR / DQ) has been demonstrated.

Amylin is a peptide hormone produced by the pancreatic islets that affect blood glucose levels: it lowers blood glucose after oral exercise in connection with slowing gastric emptying. **Pramlintide**, a human amylin analogue, has a beneficial effect on glycemic homeostasis in both IDDM and NIDDM patients treated with insulin.

Metabolic consequences of lacking insulin

Carbohydrate metabolism	Lipid metabolism	Protein metabolism	Electrolytes, ph, H_2O
decreased tissue glucose utilization	increased lipolysis	decreased protein synthesis	reduced K^+ entry into cells
increased glycogenolysis	increased fatty acid oxidation	increased protein catabolism	osmotic diuresis (for hyperglycemia)
increased gluconeogenesis	increased production of ketone bodies		acidosis (to increase the level of ketone bodies)

Type 2 diabetes mellitus (formerly non-insulin-dependent or adult type, NIDDM)

Hyperglycemia is caused by a combination of insulin resistance and relative lack of insulin (abnormal insulin, anti-insulin antibodies). Insulin resistance may be the result of decreased plasma membrane receptors on target cells or post-receptor blockade of intracellular glucose metabolism (decreased receptor number or decreased affinity; decreased complex activity; abnormal signal transduction or abnormal phosphorylation reactions for TNFα overproduction). The degree of insulin deficiency reflects the gradual loss of β-cell responsiveness to glucose; however, the ability to respond to sulfonylurea and other stimulants remains.

Pathogenesis of type 2 diabetes

Although the pathogenesis of type 2 diabetes is not fully elucidated, the transition from normal glucose tolerance to type 2 diabetes in genetically predisposed individuals is thought to be due to insulin resistance, dysregulation of hepatic glucose production, impaired glucose tolerance and a gradual decrease in β-cell function. . Some individuals, even if they are obese and have increased insulin secretion, escape the clinical development of diabetes. Those individuals whose β-cells are unable to compensate for the increased production of insulin resistance will begin to have more persistent hyperglycemia, which worsens in further development and exacerbates pre-existing β-cell dysfunction.

MODY *(Maturity Onset Diabetes of the Young)*

It is adult-type diabetes that occurs in adolescents. It is manifested by mild hyperglycemia without a tendency to ketosis. Autosomal dominant inheritance is thought to have three mutation variants: the gene for MODY 1 is located on the long arm of chromosome 20, for MODY 3 on the long arm of chromosome 12, MODY 2 is caused by a mutation in the glucokinase gene on the short arm of chromosome 7. Glucokinase is a key enzyme for glucose metabolism in pancreatic islet β-cells, where it acts as a "glucose sensor", ie it regulates insulin secretion according to glucose levels.

Diabetes in pregnancy

Decreased glucose tolerance in pregnancy is common and is probably due to placental lactogen production. In addition, glomerular filtration is increased by 50-100% during pregnancy, so that the tubules receive a higher dose of glucose than their resorption capacity, so glycosuria is a common phenomenon in pregnancy. However, for the first time, real diabetes can manifest itself during pregnancy, which must be recognized not only from the point of view of the mother but also of the fetus.

Conditions with hyperglycaemia or reduced glucose tolerance other than diabetes mellitus

These diseases are:

- **endocrine diseases** (acromegaly, Cushing's syndrome, thyrotoxicosis, pheochromocytoma, glucagon);
- pancreatic diseases (pancreatitis, hemochromatosis, carcinoma);
- liver diseases (cirrhosis, tumours);
- severe acute illnesses (acute coronary insufficiency, cerebrovascular accident, trauma, infection);
- drug hyperglycemia (salicylates, contraceptives, corticosteroids, thiazide diuretics).

The most common cause of hyperglycemia is diabetes mellitus. This disease must be distinguished from impaired glucose tolerance (oral glucose tolerance test).

Differences between types of diabetes

	Type 1	Type 2
Age	usually under 30	over under 30
Frequency (% of all diabetics)	10−20 %	80−90 %
The onset symptoms	acute or subacute	slow
Obesity	not usual	very common
Triggering factors	altered immune response after viral infection	obesity, pregnancy, stress
Pancreatic insulin content	absent or traces	low, normal, high
Plasma glucagon	high but suppressive by insulin	high but insulin resistant
Anti-pancreatic islet antibodies	present in 85% of cases	less than 5%
Primary insulin resistance	minimal	usually pronounced
Insulin response	+++	+ to -
The answer to dietary treatment	alone	is always present, but to varying degrees
Response to oral antidiabetic	absent	present
Obvyklé akutní komplikace	ketoacidosis	hyperosmolar coma
HLA association	ano	ne

Complications of diabetes

Diabetic ketoacidosis is a very dangerous complication of type 1 DM. It arises as a consequence of a sequence of metabolic events, the beginning of which is insulin deficiency:

1. insulin deficiency → decreased glucose utilization → hyperglycemia → hyperosmolarity → osmotic. diuresis → **dehydration, demineralization**
2. insulin deficiency → decreased glucose utilization → glucagon excess → gluconeogenesis, lipolysis → ketogenesis → **ketoacidosis**
3. ketoacidosis + dehydration, demineralization → **diabetic ketoacidotic coma.**

We must treat both ketoacidosis and dehydration and demineralization (ie insulin + infusion therapy) at the same time.

Hyperosmolar (nonketoacidotic) coma is much more common in non-insulin dependent DM. Residual insulin secretion is sufficient to prevent ketoacidosis, but it does not prevent hyperglycemia (due to glucagon predominance) → hyperosmolarity → osmotic diuresis → dehydration and demineralization. This situation, together with insufficient water intake (especially in the elderly), leads to hyperosmolar coma. Lethality is high (30-50%).

Hypoglycemia is another sudden metabolic event. It occurs when the dose of insulin (or its effect) is not balanced with the dose of food (omission) or glucose consumption (increased physical exertion). If glucosemia is not increased (above 3.5 mmol/l), brain damage can occur (chemical energy in the brain tissue is replaced only by glucose, not by fatty acids). If this happens more often, serious malfunctions can occur. Hypoglycaemia is much less common in NIDDM (insulin in these cases is still under physiological control).

Long-term complications of DM

- **Diabetic nephropathy** occurs 2 to 5 years after the onset of DM. It can be detected in the preclinical stage by examination of so-called microalbuminuria (urinary albumin values higher than 20 mg/l but lower than 250-300 mg/l - increased albumin above this value is already provable by a common paper test such as Albuphan = macroalbuminuria). The increased permeability of albumin in glomerular capillaries is explained by the reduced content of negatively charged anionic proteoglycans in the basement membrane (negative charges of carbohydrate chains prevent the passage of medium-sized molecules with a negative charge such as albumin).
- **Diabetic ophthalmopathy** (retinopathy, cataract, etc.).
- **Diabetic neuropathy** - cardiovascular autonomic neuropathy

The pathogenesis of these complications is explained by several possible mechanisms:

1. Accumulation of polyols (sorbitol), which are formed to an increased extent in hyperglycemia (the key enzyme aldose reductase has a relatively low affinity for its substrate, i.e. glucose, is therefore applied at higher glucose concentrations). The effect of polyols can be osmotic (in the lens of the eye).
2. Oxidative stress is caused by the accumulation or insufficient removal of superoxides or free radicals that damage cells.
3. Non-enzymatic glycation of proteins - is caused by the addition reaction of glucose with the free amino group of peptide chains (lysine); in the first phase of this reaction, a labile Schiff base (aldimine) is formed, in the next phase of the Amadori rearrangement a stable ketoamine is formed.

Glycated haemoglobin

Haemoglobin from adult human erythrocytes can be separated by ion-exchange chromatography on cation exchange resin into eight components designated A_{1a}, A_{1b}, A_{1c}, A_{1d}, A_{1e}, A_2 (major component), A_{3a} and A_{3b}. It has been found that the A1c component, in particular, is elevated in diabetics. Glycation of the haemoglobin molecule is caused by a non-enzymatic reaction of glucose-6-phosphate or glucose with the NH2-group of the terminal valine of the β-chain of haemoglobin. First, a Schiff base (aldimine) is formed, which is unstable and easily dissociable; switches to stable ketoamine. The reaction equilibrium shows that the amount or better the proportion of glycated haemoglobin formed in vivo is proportional to the concentration of free glucose. Therefore, patients with diabetes mellitus who have persistently elevated glucose levels develop more glycated haemoglobin. The reaction proceeds slowly and gradually; in addition, haemoglobin is located in erythrocytes, so that the events that take place on its molecule are tied to the lifespan of the red blood cell (i.e. normally 120 days). Thus, determining the proportion of glycated haemoglobin (especially Hb_{1c}) is a kind of "biochemical memory" of previous hyperglycemia. In other words, one glycohaemoglobin test indicates a mean blood glucose level over 4-8 weeks. The situation is not so simple. It has been shown that the value of glycated haemoglobin may not be constant and may fluctuate even during the glycemic curve; This is due to the fact that some methods fail to distinguish the labile form (Schiff base - aldimine), which forms relatively quickly (reflects the situation in 24 hours), from the stable form (ketoamine), which is already stable (reflects the mean glycemic value in 4 hours). −6 weeks). However, in the case of a chronic increase, not only haemoglobin but also other proteins are glycated in the body. This mechanism is associated with damage to some organs and tissues as a manifestation of a complication of diabetes (glycation of glomerular basement membrane proteins, glycation of collagen walls or joints, glycation of ocular lens proteins, etc.). Glycohaemoglobin determination is therefore a valuable indicator of the success of diabetes compensation (it indicates the state of diabetes compensation in the last 8 weeks).

There are several terms used in the literature that can be confused - for better understanding we define them:

- Glycohaemoglobin - the sum of carbohydrate adducts at the N-terminus of amino acids or the ε-amino group

of lysine in haemoglobin.
- HbA_{1c} - glucose adduct of valine at the N-terminus of the β-chain of haemoglobin; corresponds to N- [1-deoxyfructosyl] haemoglobin.
- HbA_1 −the sum of various minor haemoglobin fractions (glycated) including HbA_{1c}, such as $HbA_{1a1/a2}$, $HbA_{1b1/b2/b3}$, $HbA_{1d1/d2/d3}$ and HbA_{1e}.

Physiological values:

- HbA_{1c}: 3, 1−6, 3 % (of the total Hb)
- HbA_1: 4, 7−8, 8 %

Pathological changes:

- $HbA_1 < 9$ → diabetes compensation: very good;
- $HbA_1 = 9−11$ → good comepnsation;
- $HbA_1 = 11−13$ → poor comepnsation;
- $HbA_1 > 13$ → completely insufficient.

Indications for glycohaemoglobin determination:

- labile diabetes (large fluctuations in glucosemia);
- "Problem patient" (undisciplined in life management);
- a new patient without information about previous results;
- a patient with an intercurrent illness (e.g., bronchopneumonia);
- confirmation and proper conduct of self-inspection;
- clarification of "stress" hyperglycemia (eg in acute myocardial infarction, after major surgery).

Glycated protein (=fructosamine) is formed similarly, only its half-life is shorter, so it reflects the situation (i.e. previous periods of hyperglycemia) 1-3 weeks before the determination. Values are usually expressed in mmol/l deoxymorpholine fructose.

AGE products (Advanced Glycation End Products) - are products of the non-enzymatic reaction of glucose with some proteins in vivo (see HbA1c). Proteins modified in this way (AGE-collagen, AGE-LDL) can be captured by specific receptors on the surface of some cells, which can stimulate the production of cytokines, growth factors and the synthesis of extracellular matrix proteins. This may be the mechanism of disorders leading to late complications of diabetes. Stimulation of mesangial cells in the renal glomeruli is thought to be the cause of diabetic microalbuminuria (Berg, 1997).

Microalbuminuria

Microalbuminuria is an early indicator of diabetic nephropathy. It covers the "gray band" of proteinuria between 30-150 mg/l, when the test strip does not yet respond positively. The test is best performed in three consecutive overnight urine collections. Start the investigation no earlier than 2 years after the onset of diabetes; then 3 times a year.

External links

Sources

1. MASOPUST, Jaroslav a Richard PRŮŠA. *Patobiochemie metabolických drah.* 2. vydání. Univerzita Karlova, 2004. 208 s.