Glucose metabolism disorders

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

Hypoglycemia

Hypoglycemia refers to conditions in which the glucose level falls below 2.5 mmol/l. This limit is 1.7 mmol/l for newborns and 1.1 mmol/l for premature babies. The main danger of hypoglycemia is 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 activation of the adrenergic system and increased secretion of catecholamines (palpitations, anxiety, tremors, sweating).

Hypoglycemia occurs when increased utilization of glucose by extrahepatic tissues (e.g. excessive physical exertion) or when the intake of saccharides is restricted. Brain tissue is most at risk of a sudden drop below 2.5 mmol/l (in adults) (intracellular glucose supply for the brain is only sufficient for 10-15 minutes).

Hypoglycemia can be divided into two groups according to the causes based on the physiological regulation of glycemia:

1. from insufficient supply of glucose into the blood circulation;
2. from too rapid absorption from the circulation.

However, it is more practical to divide it into the following types.

Hypoglycemia during fasting

Are caused by:

- *β-cell tumors* of the islets of Langerhans (carcinoma, adenoma) or their hyperplasia (nonsidioblastosis); ``extrapancreatic tumors *(insulin-secreting or non-insulin-secreting);*
- *endocrinopathies* causing a lack of counter-insulin hormones (panhypopituitarism, isolated deficiency of growth hormone or adrenocorticotropin, hypoadrenalism, hypothyroidism, [[glucagon] defect]]at);
- *liver cirrhosis* (hepatitis, liver congestion in heart failure);
- *glycogenoses* (type I, VII, IX) and *defect of enzymes of gluconeogenetic metabolism*;
- *lack of glucose precursors* (alanine) − pregnancy hypoglycemia, ketosis hypoglycemia of infants, uremia, severe malnutrition.

Hypoglycemia in neonates and infants

In newborns, glycemia is lower than in adults (on average 1.94 mmol/l) and shortly after birth it drops further (as the liver glycogen supply is depleted) to values of around 1.66 mmol/l in full-term infants and 1.11 mmol/l in premature infants without clinical manifestations of hypoglycemia. The most common cause of neonatal hypoglycemia is prematurity, Respiratory distress syndrome (pediatrics), diabetes mellitus in the mother, pregnancy toxemia, hypothermia, polycythemia. Hypoglycemia is usually transient.

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

Postprandial hypoglycemia

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

Drug-induced hypoglycemia

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

Reactive hypoglycemia

It is a clinical syndrome manifested postprandial (after a meal) by signs from the autonomic nervous system (weakness, shaking, cold sweat, nausea, feeling of hunger, epigastric discomfort), accompanied by hypoglycemia (below 2, 5−2.77 mmol/l), usually during the day. Reactive hypoglycemia must be distinguished from hypoglycemia arising from hunger. Reactive hypoglycemia is a benign condition and can also be understood as a physiological situation. Determination of blood glucose at the time of the 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.) that are often attributed to hypoglycemia, but this has never been proven.

Causes of hypoglycemia

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

Hyperglycemia

Diabetes mellitus

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

Type 1 diabetes mellitus (formerly known as insulin-dependent or juvenile type, IDDM)

IDDM is a *polygenic autoimmune disease*. Genetic predisposition combined with certain external factors such as viral infection, toxins, 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 itself as *insulitis* (lymphocyte infiltration of islet cells, inflammation). Insulitis gradually reduces the number of functional β-cells, which causes disorders of insulin synthesis and secretion. Diabetes is clinically manifested when up to 60-70% of pancreatic β-cells are destroyed by autoimmune inflammation. The population at risk 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% for a diabetic father and 2% for a diabetic mother), but also adults (parents of a diabetic child). There are about 5-10% of undiagnosed type 1 diabetics whose disease did not manifest until adulthood (slowly progressive autoimmune insulitis = LADA), but who can be treated as type 2 diabetes with potentially catastrophic consequences.

Markers of progressive insulitis include several types of antibodies directed against different types of islet antigens such as the isoform of glutamate decarboxylase (GAD65) or autoantibodies against insulin and proinsulin, against the cells of the islets of Langerhans. Also, the first phase of insulin secretion is reduced even before the obvious 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. An isoform of glutamate decarboxylase known as GAD65 appears to be the most suitable predictive marker. An association between type 1 diabetes and HLA genetic markers (HLA-DR/DQ) has been demonstrated.

Amylin is a peptide hormone produced by pancreatic islets that affects blood glucose levels: it reduces glycemia after an oral load in connection with slowing gastric emptying. **Pramlintide**, a human amylin analog, favorably affects glycemic homeostasis in both IDDM and NIDDM patients treated with insulin.

Pathogenesis of type 1 diabetes

Metabolic consequences of lack of insulin

Metabolism of carbohydrates	Metabolism of lipids	Metabolism of proteins	Electrolytes, ph, H_2O
reduced utilization of glucose by tissues	increased lipolysis	reduced protein synthesis	reduced entry of K^+ 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)

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

Hyperglycemia is caused by a combination of insulin resistance and a relative lack of insulin (abnormal insulin, antibodies against insulin). Resistance to insulin action may be the result of a reduced number of plasma membrane receptors on target cells or a consequence of a postreceptive blockade of intracellular glucose metabolism (reduced number of receptors or reduced affinity; reduced activity of the complex; abnormal signal transduction or abnormal phosphorylation reactions for excessive production of TNF_α). The degree of insulin insufficiency is a reflection of the gradual loss of the ability of β-cells to respond to glucose; however, responsiveness to sulfonylurea and other stimulants remains.

Pathogenesis of type 2 diabetes

Although the pathogenesis of type 2 diabetes is not fully understood, 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 progressive decline in the functional capacity of β-cells. 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 by increased production of insulin resistance begin to have more permanent hyperglycemia, which worsens in further development and amplifies the pre-existing dysfunction of β-cells.

MODY *(Maturity Onset Diabetes of the Young)*

It is adult-type diabetes occurring in juveniles. It manifests as mild hyperglycemia without a tendency to ketosis. Autosomal dominant inheritance with three variants of mutations is assumed: 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 of the gene for glucokinase on the short arm of chromosome 7. Glucokinase is a key enzyme for glucose metabolism in the β-cells of the pancreatic islets, where it acts as a "glucose sensor", i.e. it regulates insulin secretion according to the glucose level.

Diabetes in pregnancy

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

Conditions with hyperglycemia or impaired glucose tolerance other than diabetes mellitus

These diseases are:

- *endocrine (https://www.wikiskripta.eu/w/Kardiovaskulárn%C3%AD_autonomn%C3%AD_neuropatie_(KAN)?veaction=edit#Auton.C3.B3mna_neuropathy_.28AN.29) diseases* (acromegaly, Cushing syndrome, thyrotoxicosis, pheochromocytoma, glucagonoma);
- *pancreatic diseases* (pancreatitis, hemochromatosis, cancer);
- *liver diseases* (cirrhosis, tumors);
- *severe acute diseases* (acute coronary insufficiency, cerebrovascular accident, trauma, infection);
- *hyperglycemia after medication* (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 below 30	usually above 30
Frequency (% of all diabetics)	10−20%	80−90%
Emergence of symptoms	acute or subacute	slow
Obesity	not common	very common
Precipitating factors	altered immune response after viral infection	obesity, pregnancy, stress
Pancreatic insulin content	absent or traces	low, normal, high
Glucagon in plasma	high but insulin suppressible	high but insulin resistant
Antibodies against pancreatic islets	present in 85% of cases	less than 5%
Primary insulin resistance	minimal	usually prominent
Response to insulin treatment	+++	+ to -
The answer to dietary treatment itself	minor	always present, but varying degrees
Response to treatment with oral antidiabetic drugs	absent	present
Common acute complications	ketoacidosis	hyperosmolar coma
Association with HLA	yes	no

Complications of diabetes

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

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

We have to treat both ketoacidosis, dehydration and demineralization (i.e. 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 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 amount of food (skipped) or glucose consumption (increased physical exertion). If the glucosemia is not increased (above 3.5 mmol/l), brain damage can occur (chemical energy in the brain tissue is covered only by glucose, not by fatty acids). If this happens more often, serious malfunctions may occur. Hypoglycemia is much less common in NIDDM (insulin in these cases is still subject to physiological control).

Long-term complications of DM

- **Diabetic nephropathy** develops 2-5 years after the onset of DM. It can be detected even in the preclinical stage by means of the examination of so-called microalbuminuria (values of albumin in the urine higher than 20 mg/l, but lower than 250-300 mg/l - albumin increased above this value is already demonstrable by a common paper test such as, for example, 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 (the negative charges of the 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 occur to an increased extent during hyperglycemia (the key enzyme aldose reductase has a relatively low affinity for its substrate, i.e. glucose, therefore it is used at higher glucose concentrations). The effect of polyols can be osmotic (in the lens of the eye).
2. Oxidative stress, which 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 a free amino group of peptide chains (lysine); in the first stage of this reaction, a labile Schiff base (aldimine) is formed, in the next stage of the Amadori rearrangement, a stable ketoamine is formed.

Glycated Hemoglobin

Hemoglobin from adult human erythrocytes can be separated by cation exchange chromatography into eight components designated as A_{1a}, A_{1b}, A_{1c}, A_{1d}, A_{1e}, A_2 (principal component), A_{3a} and A_{3b}. It was found that especially the component A_{1c} is increased in diabetics. Glycation of the hemoglobin molecule results from a non-enzymatic reaction of glucose-6-phosphate or glucose with the NH_2-group of the terminal valine β-chain of hemoglobin. First, a Schiff base (aldimine) is formed, which is labile and easily dissociable; rearranges to a stable ketoamine. It follows from the reaction balance that the amount or rather the proportion of glycated hemoglobin formed *in vivo* is proportional to the concentration of free glucose. Therefore, in patients with diabetes mellitus, in whom the glucose level is permanently elevated, a greater amount of glycated hemoglobin is formed. The reaction is slow and gradual; in addition, hemoglobin is located in erythrocytes, so the events that take place on its molecule are tied to the life of the red blood cell (ie, normally 120 days). Determination of the proportion of glycated hemoglobin (mainly Hb_{1c}) is therefore a kind of "biochemical memory" preceding hyperglycemia. In other words, one determination of glycohemoglobin indicates the average state of glycemia over a period of 4-8 weeks. The situation is not quite so simple. It has been shown that the value of glycated hemoglobin may not be constant and may fluctuate even during the glycemic curve; this is due to the fact that some methods cannot distinguish the labile form (Schiff's base - aldimine), which is formed relatively quickly (reflects the situation in 24 hours), from the stable form (ketoamine), which is already stable (reflects the average value of glycemia in 4 −6 weeks). However, with a chronic increase in the body, not only hemoglobin is glycated, but also other proteins. This mechanism is associated with damage to some organs and tissues as a manifestation of complications of diabetes (glycation of the proteins of the basement membrane of the glomeruli, glycation of the collagen of the vessel wall or joints, glycation of the proteins of the eye lens, etc.). Determination of glycohemoglobin is therefore a valuable indicator of the success of diabetes compensation (it indicates the status of diabetes compensation over the last 8 weeks).

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

- Glycohemoglobin − sum of carbohydrate adducts at the N-terminal end of amino acids or ε-amino group of lysine in hemoglobin.
- HbA_{1c} − valine glucose adduct at the N-terminal end of the β-chain of hemoglobin; corresponds to N-[1-deoxyfructosyl] hemoglobin.
- HbA_1 − sum of different minor fractions of hemoglobin (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 total Hb)
- HbA_1: 4.7−8.8%

Pathological changes:

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

Indications for determining glycohemoglobin:

- labile diabetes (large fluctuations in glucose);
- "problem patient" (undisciplined in life management);
- new patient without information on previous results;
- patient with intercurrent disease (e.g. bronchopneumonia);
- confirmation and proper conduct of self-control;
- clarification of "stress" hyperglycemia (e.g. during an acute myocardial infarction, after a more difficult surgical procedure).

Glycated protein (= fructosamine) is created similarly, only its half-life of catabolism 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 deoxymorpholinfructose.

AGE products (Advanced Glycation End Products) - these are products of the non-enzymatic reaction of glucose with some proteins in vivo (see HbA_{1c}). 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 a mechanism for the development of disorders leading to late complications of diabetes. It is thought (Berg, 1997) that the cause of diabetic microalbuminuria may be the stimulation of mesangial cells in the renal glomeruli.

Microalbuminuria

Microalbuminuria is an early indicator of the onset of diabetic nephropathy. It covers the "grey zone" of proteinuria between 30-150 mg/l, when the test strip does not yet react positively. The examination 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.

Links

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