

Selected biochemical examinations in patients with diabetes mellitus (1st Faculty of Medicine, Charles University, VL, 2nd year)

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Disorders of energy metabolism, especially obesity, diabetes mellitus, conditions that precede diabetes (prediabetes) and so-called. metabolic syndrome, They are of extraordinary medical importance. Today, diabetes alone affects about 10% of the population of developed countries and its incidence is still growing. At the same time, it is a disease that is associated with a large number of complications and dramatically increases mortality and morbidity. Understanding diabetes and knowing the principles of its diagnosis and treatment is therefore essential for any healthcare professional.

Glycaemic control

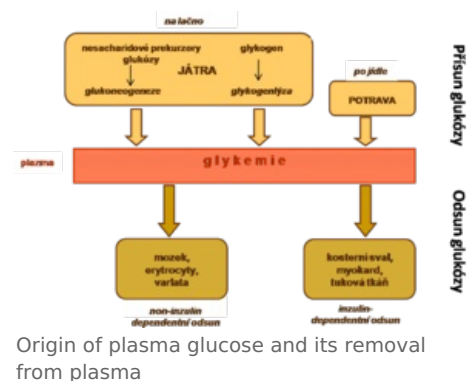
The concentration of glucose in blood (**blood glucose**) is maintained in a narrow range of 3.9-5.6 mmol/l on an empty stomach and after a meal lower than 10 mmol/l. It is tightly regulated by a number of mechanisms: insulin, which lowers blood glucose, and anti-insulin hormones - glucagon, catecholamines, glucocorticoids and growth hormone which increase blood glucose. The liver is also significantly involved in the regulation of glucose homeostasis. Maintaining a constant blood glucose level is essential for the activity of the CNS and other tissues and cells (eg erythrocytes).

Sources of glucose

The exogenous **glucose source** for the body is the Disaccharides and Polysaccharides in the diet. Glucose is formed by their breakdown in the small intestine and is utilized in the liver, muscle, adipose and brain tissue as a direct source of energy. Non-oxidized glucose is stored in the form of glycogen or converted to fatty acids and triacylglycerols. In the fasted state, normal glucose concentration is maintained by glycogen cleavage by glycogenolysis and glucose formation from non-saccharide precursors (amino acids, glycerol and lactate in the gluconeogenesis process).

Changes in blood glucose concentration

- A drop in blood glucose below 3.2 mmol/L is referred to as **hypoglycemia**. In hypoglycemia, the supply of glucose to brain tissue is compromised. It can occur during various diseases, most often in overdose antidiabetics, more rarely in long-term starvation, in some endocrine tumors or inherited metabolic disorders that also affect glucose metabolism (eg in antidiabetics). glycogenosis [glycogenosis]]. Severe hypoglycaemia is accompanied by restlessness, sweating and tremor;
- Glycaemia elevated above the reference range is referred to as **hyperglycemia**. Chronic hyperglycemia is an underlying manifestation of *diabetes*. However, we may also encounter transient **non-diabetic hyperglycaemia**. All situations where there are elevated levels of catecholamines, glucocorticoids and other stress hormones lead to it, including a number of acute diseases. A change in the regulation of glucose metabolism leading to hyperglycemia also accompanies inflammatory conditions. Hyperglycemia can also be induced iatrogenically, most often as a result of treatment with steroid hormones and their analogues.



Links

Related articles

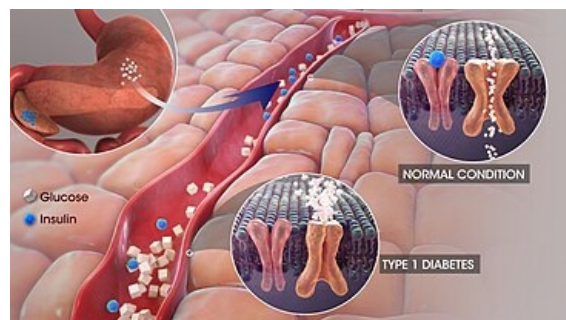
- Glycaemia determination
- The blood glucose assessment is discussed together with the assessment of oGTT
- Hepatogenous diabetes

■

Diabetes mellitus

Diabetes mellitus (DM) is a chronic metabolic disease with high morbidity and mortality, with the major manifestation of hyperglycemia due to absolute or relative insulin insufficiency. In the last decade, there has been a significant and steady increase in the incidence of diabetes mellitus worldwide, including in the Czech Republic. Especially in economically developed countries, the cause of this phenomenon lies in the lifestyle of the population, such as excessive energy intake and reduced physical activity.

At present, more than 10% of the population are diagnosed with diabetes mellitus in the Czech Republic (approximately 990,000 individuals). Estimates suggest that at least 5% more of the population with diabetes mellitus remains undiagnosed. These are most often type 2 DM (93% of cases), type 1 DM makes up about 5%, and other types are less common.



DM Type 1

Classification of diabetes mellitus

- **Diabetes mellitus type 1**
 - Autoimmune
 - Absolute lack of insulin production by the pancreatic beta cells of Islet of Langerhans
 - Usually affecting the younger population
 - Requires administration of insulin
- **Diabetes mellitus type 2**
 - Resistance to the action of insulin
 - Usually affecting adults and the older population
 - The production of insulin could even be increased in the earlier course of the disease, with reduction in the later course of the disease
 - Weight management, diet control and exercising are essential, if still insufficient, diabetic medications or insulin therapy might be required
- **Gestational diabetes mellitus**
 - DM that occurs during pregnancy, which resolves soon after delivery
 - Pregnant women should undergo a 2 phase screening:
 - Phase I: In the first trimester of pregnancy (up to the 14th week), assessment of fasting blood glucose
 - Phase II: Women who test negative for Phase I are subjected to Phase II of screening. Oral glucose tolerance test (oGTT) is evaluated.
 - Women who experience gestational DM have increased risk of developing DM type 2 later on in life
- **Other specific types of diabetes mellitus**
 - DM in endocrinopathies (acromegaly, pheochromocytoma, hypercortisolism, hyperthyroidism, etc.)
 - Drug and chemical induced DM (glucocorticoids, nicotinic acid, thyroid hormones)

Pathogenesis

Disruption of glucose metabolism occurs with:

- Impaired insulin production or secretion (insulin deficiency)
- Impaired response to insulin (insulin resistance)
- Possibly a combination of both mechanisms

Insufficient insulin function disrupts the transport of glucose from the blood to the cell, leading to hyperglycemia and glucose deficiency intracellularly. Insufficient glucose utilization leads to a change in the mechanisms for ATP gain. **Gluconeogenesis** and **glycolysis** are stimulated, while lipolytic breakdown of triacylglycerols into fatty acids and glycerol increases in adipocytes. Degradation of fatty acids by β -oxidation produces excess acetyl-CoA, from which ketones (acetacetate, 3-hydroxybutyrate and acetone) are formed in the liver. Acetacetate can serve as a source of energy for muscle and brain activity instead of glucose.

If the production of ketone bodies exceeds their utilization by peripheral tissues, **ketoacidosis** develops (with characteristic clinical sign of fruity breath). Because ketone bodies are soluble in water and excreted in the urine, **ketonuria** could occur as well. When the plasma glucose concentration threshold (10-12 mmol/L) is exceeded, the transport capacity of the proximal tubule is disrupted and glucose is excreted into the final urine. As glucose and ketone bodies are osmotically active, this leads to osmotic diuresis, which causes additional water to be loss in urine bringing about **polyuria**.

Clinical aspects

The characteristic signs include:

- DM type 1: thirst, polydipsia, polyuria, weight loss
- DM type 2: is often associated with obesity
-

Psychological aspects of treatment

Due to the need for comprehensive treatment of the disease, cooperation at the doctor-patient level is important. A patient with DM may experience problems such as those associated with the necessary precautions (ie. restrictive diet), or related secondary complications that may lead to diabetic distress. It is appropriate for the doctor to focus on the psychological aspects of this disease as well.

Complications

- **Acute complications**
 - Hypoglycemia,
 - Diabetic hyperosmolar hyperglycemic coma,
 - Diabetic ketoacidosis
 - Ketoacidotic coma
 - Lactic acidosis,
 - Lactacidotic coma.
- **Chronic complications**
 - Diabetic kidney disease
 - Diabetic retinopathy,
 - Diabetic neuropathy,
 - Diabetic foot syndrome
 - Atherosclerosis

History of the treatment of DM

One of the most important events in the history of diabetes treatment was in the year 1921, when Frederick Grant Banting and his assistant, medical student Charles Herbert Best, discovered a substance in the animal pancreas that caused the dogs' plasma glycemia levels to drop. This substance was named 'insulin'. The experiment was later repeated on a 13-year-old boy suffering from DM type 1, Leonard Thompson, who became the first person to be injected with insulin.

References

Sources

1. ČEŠKA, Richard, et al. *Interna*. 3. vydání. Praha : Triton, 2020. 970 s. ISBN 978-80-7553-780-5.

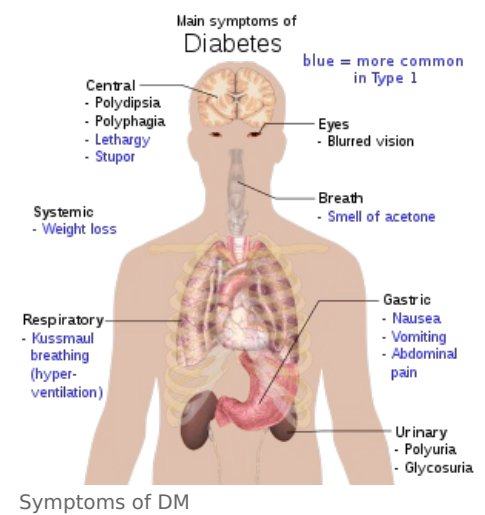
Type 1 diabetes mellitus

Type 1 diabetes mellitus is characterized by absolute or almost complete lack of endogenous insulin and life dependence on exogenous insulin. Patients are prone to ketoacidosis.

The disease results from the selective destruction of pancreatic **islet β -cells** by an autoimmune process in genetically predisposed individuals. The triggering mechanism of the autoimmune process is probably a viral infection or contact with another exogenous or endogenous agent.

The clinical picture of type 1 diabetes mellitus depends on the aggressiveness of the autoimmune process. *In childhood and adolescence*, when most diseases develop, the last stage of β -cell destruction tends to be very rapid, so diabetes is manifested by classic *acute symptoms* (including ketoacidosis). At a *later age*, the disease tends to have a much *slower* onset and only eventually results in complete insulin dependence. Insulin secretion may be reduced for several years, but sufficient to prevent ketoacidosis. The clinical course of the disease therefore resembles type 2 diabetes mellitus and it is stated that about one in ten patients originally classified as type 2 diabetes has slow-onset type 1 diabetes - **latent autoimmune diabetes of adults (LADA)**.

Type 1 DM is a less common form of diabetes that occurs in about 7% of diabetics. The classic symptoms of type 1 DM are thirst, polyuria and weight loss.



Metabolic consequences of insulin deficiency or inadequate insulin function

Type 1 diabetes mellitus		Type 2 diabetes mellitus
	LADA	
insulin secretion is missing	gradual cessation of insulin secretion	insulin resistance, impaired insulin secretion
a typical beginning in childhood and adolescence	a typical beginning in adulthood	a typical beginning after 40 years
ketoacidosis		
more often lower BMI		more often higher BMI
positive autoantibodies		autoantibodies are missing
C-peptide is missing	C-peptide reduced	C-peptide normal or elevated
immunoreactive insulin is missing	immunoreactive insulin reduced	immunoreactive insulin normal or elevated

Type 2 diabetes mellitus

Type 2 is the predominant form of Diabetes Mellitus. Patients are **not dependent on exogenous insulin for life**, because insulin production is not reduced, or is reduced less than in the case of type 1 DM.

The cause of this type of diabetes lies in the **malfunction of insulin action**. This is the so-called **resistance to insulin** (insulin resistance) due to a malfunction of the insulin receptor or a malfunction in the transmission of the insulin signal to the cell.

Blood insulin concentrations are initially elevated due to insulin resistance. In the further course of the disease, a disorder of insulin secretion also occurs, β -cells gradually lose their ability to respond to increased glucose levels by synthesizing insulin.

The disease manifests mainly in **adulthood**, usually over the age of 40. Type 2 Diabetes Mellitus has a high heritability, so a family history is often evident. Unlike type 1, patients are **not prone to ketoacidosis**. In 60-90% it is associated with obesity.

Links

related articles:

- Diabetes mellitus
- gestational diabetes mellitus
- diabetes mellitus type I
- metabolic syndrome and insulin resistance

Gestational diabetes

Gestational diabetes mellitus (GDM) is a disorder of various stages of glucose metabolism that occurs during pregnancy and resolves spontaneously during the sixth week. In addition to GDM, so-called overt diabetes mellitus (DM) can also be detected during pregnancy, which meets the diagnostic criteria of diabetes valid for the general population and usually persists after the sixth week. Caring for pregnant women with overt diabetes is the same as caring for pregnant women with pregestational diabetes.

All pregnant women, except those already treated for diabetes, are subjected to a **two-phase GDM** screening provided by an outpatient gynaecologist. In the first trimester of pregnancy (up to the 14th week), **fasting venous blood glucose** is determined. If a pregnant woman has fasting blood glucose repeatedly (i.e. 2 consecutive days) $\geq 5.1 \text{ mmol} \cdot \text{l}^{-1}$, she is diagnosed with GDM, no longer has to undergo oGTT and is referred to a diabetologist. All women with a negative result in the 1st trimester then undergo a three-point **oral glucose tolerance test (oGGT)** with a load of 75g of glucose between 23 + 1 and 27 + 6 weeks of pregnancy if they have a fasting blood glucose lower than $5.1 \text{ mmol} \cdot \text{l}^{-1}$. Standard glycemia in oGTT is $<10.0 \text{ mmol} \cdot \text{l}^{-1}$ at 60 minutes and $<8.5 \text{ mmol} \cdot \text{l}^{-1}$ at 120 minutes. At higher values, GDM is diagnosed and the woman is referred to diabetology. Depending on the severity of the GDM, diet, metformin or insulin are used to compensate for blood glucose. ^[1]

References

Related articles

- Diabetes Mellitus/type 2

Reference

1. Česká gynekologická a porodnická společnost. Gestační diabetes mellitus. - [online]. 2019, roč. -, vol. -, s. -, dostupné také z <<http://www.gynultrazvuk.cz/data/clanky/6/dokumenty/2019-05-gestacni-diabetes-mellitus-dp-cgps-cls-jep-revize.pdf>>.

Basic biochemical examinations in patients with diabetes mellitus

Determination of blood glucose concentration is an examination that will provide basic information about carbohydrate metabolism. Capillary or venous blood is collected and glucose is determined in whole blood, plasma or serum. When determining glucose in whole blood, the values are 10–15% lower (depending on hematocrit), in arterial blood they are 10% higher than in venous (arteriovenous difference). To prevent glycolysis, NaF (2.5 mg per ml of whole blood) is added to the collection vials.

The glucose test in blood has the necessary information value only if the time interval between blood collection and food intake is known.

Blood glucose testing is performed:

- **fasting** (blood is taken at least 8 hours after a meal) - indicated when searching for diabetics and diagnosing DM;
- **randomly** measured blood glucose (blood is taken without a time relation to food intake) - performed when hypoglycemia or hyperglycemia is suspected;
- postprandial - **postprandial** glycaemia (1 hour after a meal containing carbohydrates) - indicated to monitor the effectiveness of DM treatment;
- as **glycemic profile** - glycemia is determined several times a day, usually before main meals, sometimes after meals and at night.

Methods for determining blood glucose

Determination of glycemia in laboratory conditions

Various methods are used to determine glucose concentration. Enzyme methods are widely used. Glucose can be determined by any enzyme that metabolizes it. Another article discusses the possibilities of Non-invasive blood glucose measurement

Glucose oxidase reaction

The recommended routine method uses *glucose oxidase-coupled enzyme reactions* (**GOD** , 4.html EC 1.1.3.4 (<http://www.sbcs.qmul.ac.uk/iubmb/enzyme/EC1/1/3/>)) and **peroxidase (POD**, /7.html EC 1.11.1.7 (<http://www.sbcs.qmul.ac.uk/iubmb/enzyme/EC1/11/1/>)) . *In the first reaction, the enzyme "glucose oxidase" catalyzes the oxidation of glucose by atmospheric oxygen to form gluconic acid, which is converted to the inner ester gluconolactone. It is known that 36% of glucose is known to be in the form of the α -anomer and 64% in the form of the β -anomer. GOD is highly specific for β -D-glucopyranose. In order for both anomers to be oxidized, a mutation of the α - to β -anomer is required, which occurs spontaneously during a sufficiently long incubation. An equimolar amount of "hydrogen peroxide" is formed as a by-product of the glucose oxidase reaction.*

File:Glucose oxidase reaction.png
Glucose oxidase and peroxidase reactions

In **another peroxidase-catalyzed reaction**, the resulting hydrogen peroxide is reacted with a suitable chromogen, which is oxidized to a reactive intermediate, which is coupled with another substance to a stable soluble dye. An example is the oxidative coupling of a phenol derivative with 4-aminoantipyrine to a red dye, the absorbance of which is measured after the reaction equilibrium has stabilized.

Other methods utilize the measurement of oxygen depletion that occurs during a glucose oxidase-catalyzed reaction and can be monitored electrochemically with an oxygen electrode or an enzyme electrode.

Hexokinase reaction

The hexokinase method is characterized by high specificity. **Hexokinase** (EC 2.7.1.1 (<http://www.sbcs.qmul.ac.uk/iubmb/enzyme/EC2/7/1/1.html>)) phosphorylates glucose in the presence of ATP to **glucose-6-phosphate**. In the next step, glucose-6-phosphate is oxidized by "glucose-6-phosphate dehydrogenase" against NADP⁺ to 6-phosphogluconolactone. The reduction of NADP⁺ to **NADPH** can be evaluated by direct UV photometry on the principle Warburg optical test.

Determination of glycemia in non-laboratory conditions

Glycemia is one of the parameters that is often examined even without a laboratory background. Rapid guideline blood glucose determination is common in emergency care. Patients treated with insulin also preferably have their blood glucose monitored regularly with a personal glucometer, and treatment is adjusted based on the measured values. Blood glucose levels are among the parameters most commonly determined by "point of care testing" ("POCT") techniques. However, it must be borne in mind that POCT methods, although improving the quality of care and patient comfort, do not replace regular medical examinations or laboratory tests.

Rapid blood glucose methods use several principles. The starting material is usually a drop of whole capillary blood that is applied to a **test strip**.

The oldest bands were based on the same reactions as the photometric measurement of glucose concentration. The reaction zone contained "glucose oxidase", "peroxidase" and the appropriate chromogen. The evaluation was performed either visually by comparison with a color scale or using a glucometer - single-purpose reflection

photometer. Most meters today use "enzyme electrodes"^{[1] [2]}.

The **first generation** sensors appeared in the 1960s. The oldest system was based on the glucose oxidase reaction. He used two electrodes, one covered with an enzyme. The oxygen concentration in the sample and the rate of its decrease during the reaction was measured by the so-called Clark method: oxygen is reduced at the platinum cathode, the current intensity between the cathode and the anode corresponds to its concentration:



Later, hydrogen peroxide production was determined electrochemically instead of oxygen consumption. Even in this case, it is a simple electrochemical reaction, this time taking place at the anode:



The analyzers constructed in this way were simpler and could be miniaturized more. However, amperometric measurement of hydrogen peroxide production is influenced by a number of substances: ascorbate, uric acid, many drugs, etc. Another problem of many first-generation sensors was the dependence of the measurement results on the oxygen saturation of the sample.

The **second generation** sensors are also based on the **glucose oxidase** reaction, but instead of molecular oxygen, another substance is the electron acceptor - the so-called *mediator*. Another possibility is the oxidation of glucose to gluconolactone by another bacterial enzyme, **glucose dehydrogenase**, whereby electrons are again transferred to a suitable mediator. In both cases, the reduced mediator is reoxidized at the anode and either the current flowing between the cathode and the anode is measured (amperometric determination) or the resulting anode charge (coulombometric determination). A number of specific test strip configurations are used, and various substances are used as mediators (eg, ferric cyano, ruthenium hexamine, osmium complexes, phenanthrolinequinone).

Links

Reference

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Oral glucose tolerance test

Glycated proteins

A direct consequence of elevated blood sugar levels is its intense protein binding, which is the essence of **non-enzymatic glycation**. The glycation process is conditioned by the presence of free amino groups in the protein molecule.

The rate of glycation is mainly affected by the concentration of glucose and its duration of action. It also occurs in healthy individuals. Glycation takes place on all serum proteins and leads to the formation of glycated derivatives. Both soluble and structural proteins are glycated.

Non-enzymatic glycation takes place in several phases of the so-called **Maillard reaction** .

- The sequence of glycation reactions is initiated by the aldehyde group of the reducing sugar, which binds to the amino group of the protein. A **labile aldimine** of type **Schiff base** is created (*early glycation products*). Schiff's formation is quick, reaching equilibrium within hours. This reaction is reversible.
- Schiff's base then slowly, within a few days, undergoes chemical rearrangement. A more stable *glycation transition product* is formed, the so-called **Amadori product**, which has the character of a **ketoamine**. This produces a keto group on the second carbon of the sugar, which is characteristic of fructose. The concentration of **fructosamines** formed can be determined by reaction with nitrotetrazolium blue (see below). Amadori's products are also **somewhat reversible**, although the balance is shifted considerably in the direction of their formation. Steady state is reached in a few weeks. The amount of ketoamines can be reduced by normalizing glycemia.
- Aldose, which is two carbons shorter than the original protein-bound sugar, can also be cleaved from Schiff's base. A di-carbon residue remains attached to the protein, which is further oxidized and reacts with another amino group of the protein. The chain of other reactions results in the formation of highly reactive glyoxal-type dialdehydes.
- Amadori products are reactive substances. In weeks and months, regardless of the presence of glucose, Amadori products are formed by reactions mainly with long-lived proteins (eg collagen, elastin, nerve myelin) **advanced glycation products** (*advanced glycation end-products, AGE*). These processes are **irreversible**.

Non-enzymatic glycation in long-term hyperglycemia is one of the causes of tissue damage in some organs in patients with diabetes mellitus.

The determination of Amadori-type glycation products is a suitable indicator of long-term glucose concentration and provides **indirect information about the course of glycaemia over a period of time that corresponds to the biological half-life of the protein. Glycated hemoglobin and glycated proteins** are commonly determined.

The determination of glycated hemoglobin and glycated proteins is used to control diabetes mellitus and to diagnose persistent hyperglycemia. Elevated glycated derivatives indicate that elevated blood glucose levels have prevailed in the patient in recent weeks and that diabetes mellitus has not been adequately controlled.

Glycated hemoglobin

Glycated hemoglobin (HbA_{1c}) is considered **the best way to control glucose levels in diabetics**. Glycated hemoglobin concentration indicates blood glucose values in the previous 2-3 months (erythrocyte lifespan). It is determined by chromatographic or immunochemical methods.

Evaluation of glycated hemoglobin concentration (HbA_{1c})
in diabetics

Compensated DM	≤ 45 mmol/mol
The need for a change in therapy	≥ 53 až 70 mmol/mol

Glycated hemoglobin concentration refers to total hemoglobin concentration and is expressed in **mmol HbA_{1c} per mole of total hemoglobin**. You can also find a percentage expression HbA_{1c} of total hemoglobin (1 % ± 10 mmol/mol). The assessment of glycated hemoglobin concentration in the table above is indicative. Target concentrations vary according to the risk of hyper-/hypoglycemia in a particular patient.^[3]

The glycated hemoglobin assay can also be used to screen for diabetes mellitus. At concentration HbA_{1c} over 39 mmol/mol we suspect diabetes mellitus^[4]. Je-li koncentrace HbA_{1c} vyšší než 48 mmol/mol, můžeme diagnózu diabetu mellitu považovat za potvrzenou.^[5]

Evaluation of glycated hemoglobin concentration
(HbA_{1c}) in diabetes mellitus screening

Physiological values	< 39 mmol/mol
Suspicion of diabetes mellitus	39–48 mmol/mol
Diabetes mellitus	≥ 48 mmol/mol

Fructosamines

Glycated proteins or **fructosamines** have a shorter half-life and their levels reflect the average glucose concentration for the period of 2-3 weeks before examination. Their main component is glycated albumin. Hypoproteinemia may falsely reduce the results. Today, determination of fructosamine concentrations is not a routine test in diabetics.

Evaluation of glycated protein concentration (S-
glycated proteins)

Physiological values:	205–285 μmol/l
Good compensation DM:	285–320 μmol/l
Satisfactory compensation DM:	321–370 μmol/l
Bad compensation DM:	nad 370 μmol/l

Principle of determination of glycated proteins (fructosamine)

Examination of glycated proteins uses the reducing properties of fructosamine in an alkaline environment. In the presence of carbonate buffer, fructosamine rearranges to its tautomer - eneaminol, reacts with nitrotriazolium blue (NBT). During the reduction, the heterocyclic rings of NBT are opened and colored formazan is formed. The rate of formazan formation is directly proportional to the fructosamine concentration.

Like any method that utilizes the reducing properties of some serum components, this test is non-specific. It therefore begins with a few minutes of incubation to remove the effect of fast-reacting reducing agents. In commercial kits, the agent includes the enzyme uricase, which eliminates the reduction of NBT by uric acid.

Glucose in urine

Glucose in urine

Ketone bodies in urine

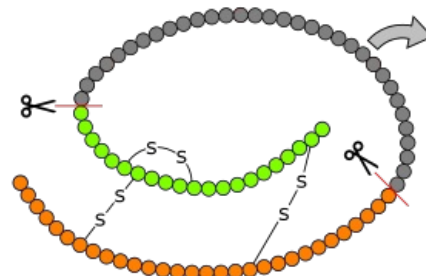
Ketone bodies in urine

Additional laboratory examinations of patients with diabetes

Insulin (Whereas the method of determination also **immunoreactive insulin, IRI**). Due to large fluctuations in levels during the day, interference with possible autoantibodies and the inability to distinguish endogenous insulin from insulin administered medicinally, it is usually determined during stress tests (oGTT). Values are reduced in type 1 diabetics, while insulin resistance syndrome is elevated.

C-peptide is the part of the **proinsulin** molecule that is cleaved before insulin secretion. Its serum concentration corresponds to insulin secretion. It is not taken up by the liver and, as there is no C-peptide in the injected insulin, the results are not affected by the treatment. It crosses the **glomerular membrane** and therefore its concentration increases in renal insufficiency.

Type 1 diabetes is also associated with positivity **autoantibodies** against the islets of Langerhans (**ICA**), against insulin (**IAA**) and in particular against one isoform of glutamate decarboxylase (**GAD 654**).



Proinsulin schematic topological diagram

Links

Related Articles

- Blood glucose
- Diabetes mellitus
- Type 1 diabetes mellitus
- Type 2 diabetes mellitus
- Gestational diabetes
- Borderline glycoregulation disorders
- Glycaemia/determination
- Oral glucose tolerance test
- Glycated proteins
- Glucose in urine
- Ketone bodies in urine
- C-peptide

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