Lipid degradation and ketone bodies metabolism

Contents of the subchapter:

Introduction to lipid degradation and ketone bodies metabolism

__ Introduction to lipid degradation and ketone bodies metabolism Triacylglycerols (TAG) store large amounts of chemical energy. They are very advantageous as energy stores because 1g of anhydrous TAG stores six times more energy than 1g of hydrated glycogen. Complete oxidation of 1g of TAGs yields approximately **38kJ** of energy, while 1g of saccharides or proteins yields only 17kJ of energy. A 70kg-male storages in his TAGs approximately **400 000 kJ** of energy with a total weight of about 10,5 kg. These supplies could allow surviving even a few weeks of starvation. The main site of TAG accumulation is the cytoplasm of adipocytes.

Fatty acid oxidation

The different types of fatty acid oxidation are indicated by the Greek letters, which indicate the carbon atom on which the reactions take place. The β-oxidation taking place in the **mitochondria matrix** is of major importance. Enzymes catalyzing so-called ω- and α-oxidation are present on the membranes of the **endoplasmic reticulum**.

Conversion of fatty acids to glucose

Animals cannot convert fatty acids into glucose. FAs are a rich source of energy for gluconeogenesis, but their carbon atoms do not form glucose (except for odd-numbered fatty acids). **Acetyl-CoA** cannot be converted into either pyruvate or oxaloacetate - both carbons are split off as CO_2 during the Krebs cycle. The pyruvate dehydrogenase reaction is **irreversible**. In addition, the plants have two other enzymes that allow them to convert AcCoA to OAA, in the so-called **glyoxylate cycle**.

Lipids as a source of energy - intracellular TAG degradation, β-Oxidation of fatty acids.

__ Lipidy jako zdroj energie

Utilization of lipids for energy production takes place in three basic phases:

1. **Lipid mobilization** - hydrolysis of TAG to FA and glycerol and their transport by blood.
2. **Activation of FA** in the cytosol and **their transport** into the matrix of mitochondria.
3. **β-oxidation** - degradation of FA to acetyl ~ CoA, which enters the Krebs cycle or forms ketone bodies from it.

Lipid mobilization - lipolysis Hormone-sensitive lipase (HSL) enzymatically mobilizes storage lipids. It catalyzes the reaction:

TAG → 3 MK + glycerol

The released fatty acids bind to **serum albumin**, which transports them to their destination (eg to the liver). Glycerol is transported freely dissolved in plasma.

Regulation of lipolysis As the name suggests, the enzyme is under strict hormonal control. Its activity is stimulated by **phosphorylation** of its molecule. Insulin as an anabolic hormone causes its **inhibition**, counter-regulatory hormones (glucagon, catecholamines) or thyroid hormones on the contrary **activate it**.

Glycerol utilization

__ Využití glycerolu Glycerol obtained by hydrolysis of triacylglycerols is involved in energy metabolism through intermediates of glycolysis or gluconeogenesis. The first step is to phosphorylate it to glycerol-3-P using glycerol kinase. This is followed by dehydrogenation to dihydroxyacetone-P catalyzed by glyceraldehyde-3-phosphate dehydrogenase. It is an intermediate of glycolysis / gluconeogenesis.

Fatty acid transport across the cell membrane

__ Vstup mastných kyselin do buňky The way the cell membrane is crossed depends on the **length of the chain**. Short-chain fatty acids (↓ 12C) can cross the cell membrane by **simple diffusion**. Those with a longer chain use various **transport systems** in the membrane allowing their facilitated diffusion - eg **FATP** (fatty acid transport protein) or **FAT / CD36** (fatty acid translocase).

Fatty acid activation

__ Aktivace mastných kyselin Fatty acids are activated **in the cytosol, on the outer mitochondrial membrane**, immediately after their entry into the cell. Without activation, the involvement of their molecules in metabolism cannot be considered at all. Activation then simultaneously maintains a constant **concentration gradient** (analogous to glucose phosphorylation - see glycolysis). The principle of fatty acid activation is the ester binding of a fatty acid molecule to the **SH − group of coenzyme A** via an **acyl − CoA − synthetase** (fatty acid thiokinase):

FA + ATP + HS−CoA → acyl−CoA + AMP + 2 Pi

Fatty acid activation actually takes place in two phases. First, **acyl adenylate** (acyl-AMP) is formed and in the second phase, AMP is exchanged for **coenzyme A**.

Fatty acid import into mitochondria

__ Vstup mastných kyselin do matrix mitochondrie

The way fatty acids enter the mitochondria matrix depends on their **chain length**:

1. **below C10** enter the matrix freely;
2. **C12 to C18** enter via a carnitine transporter;
3. **above C18** do not pass.

Acyl-CoA with C12 – C18 can **pass freely** through the outer mitochondrial membrane, but the inner membrane is impermeable to it. Thus, the fatty acid must leave the bond to coenzyme A and bind to the new partner. That's **carnitine**. Fatty acid transfer between coenzyme A and carnitine is catalyzed by **carnitine acyltransferase I** (CAT I or carnitine palmitoyltransferase I - CPT I) located on the cytosolic side of the outer mitochondrial membrane.

The **carnitine-acylcarnitine translocase** in the inner mitochondrial membrane allows the subsequent exchange of carnitine for **acylcarnitine**, whereby the acylcarnitine enters the matrix of the mitochondria.

Here, the fatty acid is transferred back from the acylcarnitine to coenzyme A via **carnitine acyltransferase II** (CAT II). The released carnitine leaves the matrix by translocase in exchange for a new acylcarnitine. In this way, we transferred acyl-CoA to the mitochondrial matrix, where it undergoes β-oxidation.

Fatty acid β-oxidation

__ Beta oxidace mastných kyselin (FBLT)

β-oxidation takes place **only under aerobic conditions** - it is closely related to the respiratory chain. Individual β-oxidation reactions of fatty acids are catalyzed by **four enzymes**:

1. **Acyl ~ CoA** − dehydrogenase - prosthetic group is FAD;
2. **Enoyl ~ CoA** − hydratase;
3. **L-3-hydroxyacyl-CoA-dehydrogenase** - the coenzyme is NAD +;
4. **β-ketothiolase**.

The reactions can be summarized in the sequence **dehydrogenation - hydration - dehydrogenation - thiolytic cleavage**. The first three reactions are analogous to those occurring in the Krebs cycle starting with succinate (see Krebs cycle):

1. **Oxidation** of succinate to fumarate by **succinate dehydrogenase** - cofactor is FAD.
2. **Addition of water** to the double bond in the fumarate, malate is formed by **fumarate hydratase** catalysis.
3. **Oxidation** of malate to oxaloacetate by the enzyme **malate dehydrogenase** - cofactor is NAD +.

1.Acyl ~ CoA dehydrogenase - first oxidation This enzyme catalyzes the formation of a double bond between the 2nd (α) and 3rd (β) carbon of the fatty acid chain. It is a **stereospecific reaction** in which trans-enoyl-CoA is formed. The recipient of the electrons is **FAD**. There are different types of dehydrogenases in the cells, which differ in the length of the MK chain, which they oxidize:

- Short-chain fatty acids(4–6 C),
- Medium-chain fatty acids(6–10 C),
- Long-chain fatty acids(12–18 C).

2.Enoyl-CoA hydratase This enzyme catalyzes the **hydration of the trans-double** bond formed in the first step. The **hydroxyl group** - L-3-hydroxyacyl-CoA - is formed.

3.Hydroxyacyl-CoA dehydrogenase This enzyme catalyzes the **oxidation** of a hydroxyl group on the third (β) carbon to a keto group. Electrons are taken up by coenzyme NAD +.

4.β-ketothiolase The last step of one turn of β-oxidation is β-ketothiolase-catalyzed **thiolytic cleavage**. It attacks the SH − group of the coenzyme on the β-keto carbon of the fatty acid chain. The reaction leads to the formation of AcCoA and two carbons shorter acyl-CoA. **One round of β-oxidation** β-oxidation is a cyclic process, one round of which we can write as: **Acyl−CoA + FAD + NAD+ + HS−CoA → acyl−CoA (o 2 C kratší) + FADH2 + NADH+H+ + AcCoA** The intermediate (acyl − CoA 2 C shorter) enters the next round of β-oxidation. Most fatty acids have an even number of C, so the last turn transforms butyryl-CoA into two molecules of AcCoA. **The yield of complete oxidation of palmitate** To give an idea of the total yield of fatty acid oxidation, here is the equation and energy balance of complete palmitate oxidation:

Palmitoyl ~ CoA + 7 FAD + 7 NAD + + 7 HSCoA + 7 H2O → 8 AcCoA + 7 FADH2 + 7 NADH + H +

As can be read in the article on the respiratory chain and ATP production, we cannot determine exactly the amount of ATP produced in the respiratory chain during nutrient oxidation. Therefore, please perceive the following numbers only as an approximate and generally correct amount. We present them here so that you can compare them with the oxidation of other nutrients, such as glucose. In the respiratory chain, 2.5 (3) ATP is obtained from one NADH2 and 1.5 (2) ATP from one FADH2, which in total represents:

- 7 × FADH2 = 10, 5 (14) ATP,
- 7 × NADH = 17, 5 (21) ATP,
- Oxidation of 8 AcCoA in the Krebs cycle = 80 (96) ATP.

The total profit ended at the sum of 108 (131) ATP. However, we used **2 ATP** to activate the fatty acid, so the net gain is **106** (129) **ATP**.

Regulation of fatty acid beta-oxidation

__ Regulace beta-oxidace mastných kyselin Regulation of β-oxidation takes place at the level of fatty acid **entry into the mitochondria** - more precisely at the level of the carnitine transporter **carnitine acyltransferase I** (CAT I). This enzyme is inhibited by the fatty acid intermediate - **malonyl-CoA**. We are talking about so-called **cross-regulation**. The principle is that the synthesis of fatty acids takes place in the cytosol, just like the reaction catalyzed by CAT I. Malonyl-CoA is formed as a product of the first reaction of fatty acid formation. Cross regulation prevents the simultaneous course of synthesis and degradation of MK. Insulin inhibits β-oxidation, while counterregulatory hormones activate it.

Fatty acids with odd C number

__ Oxidace mastných kyselin s lichým počtem uhlíků Oxidation of odd-chain fatty acids produces **propionyl-CoA** in addition to AcCoA. It is first carboxylated to **methylmalonyl-CoA**, which is converted to **succinyl-CoA** - an intermediate of the Krebs cycle. Through conversion to oxaloacetate, it can be involved in gluconeogenesis - glucose can be synthesized from these fatty acids. However, very few fatty acids with an odd number of carbon atoms are present in the body.

Unsaturated fatty acids degradation

__ Oxidace nenasycených mastných kyselin Most unsaturated fatty acids in the human body and in food have the **cis configuration** of double bonds. Their degradation in β-oxidation proceeds by the process described above until their double bond comes into contact with enoyl-CoA-hydratase. This is because it only requires **trans isomers** - so it is necessary to convert the cis isomer to trans using **isomerase**.

Very long-chain fatty acids degradation

__ Oxidace mastných kyselin s velmi dlouhým řetězcem Oxidation of very long-chain fatty acids (more than 18 carbons) takes place in peroxisomes. The first step is catalyzed by **flavoprotein dehydrogenase**, which transfers electrons to O2 - H2O2 is formed:

1. FADH2 from the first step is reoxidized not in the respiratory chain, but by reaction with O2: **FADH2 + O2 → FAD + H2O2**
2. Peroxisomal catalase decomposes H2O2: **2 H2O2 → 2 H2O + O2**

Oxidation ends with octanoyl-CoA, which is transported from peroxisomes in binding to carnitine and goes to β-oxidation. The reactions described above **do not lead** to the formation of ATP.

α-oxidation and ω-oxidation

__ Alfa-oxidace a omega-oxidace mastných kyselin **These are minor pathways** of fatty acid oxidation. During ω-oxidation, reactions occur at the terminal carbon of the chain. During α-oxidation, oxidation occurs on α-carbon.

Omega oxidation takes place in the enoplasmic reticulum. Hydroxylation of the terminal methyl group occurs, which is further oxidized to the carboxyl group. A dicarboxylic acid is formed, which can be degraded to a dicarboxylic acid with 6-10C. It is already sufficiently soluble in water.

Ketone bodies formation and utilization

Ketone bodies formation and function

__ Tvorba ketolátek Ketone bodies include **acetoacetate, β-hydroxybutyrate** and **acetone**. The main site of their formation is the mitochondria of hepatocytes. Ketone bodies are a water-soluble transport form of acetyl. It is formed when there is an **excess of acetyl-CoA** produced by liver beta-oxidation - the liver "chews" fatty acids and provides the body with ketone bodies as an **alternative energy source**. The entry of AcCoA into the Krebs cycle depends on the availability of oxaloacetate. Which is formed by carboxylation of pyruvate. During starvation or diabetes mellitus, OAA is consumed in the process of gluconeogenesis. Carbohydrate deficiency leads to a reduction in the amount of OAA and thus to a slowing down of the Krebs cycle. You could say that "fats burn in a fire of carbohydrates".

Conditions for ketogenesis Before we get to the specific reactions of ketone body formation - **ketogenesis**, we describe the situation in the organism in which it takes place. Initially, lipolysis is activated by **hormone-sensitive lipase** (HSL). After activation of lipolysis, plasma concentrations of fatty acids increase, which enter liver cells to an increased extent. In them, they undergo **β-oxidation**, which produces an **excess of AcCoA**. It cannot be sufficiently applied in other pathways and therefore enters ketogenesis. Thus, the source of carbon atoms in ketogenesis is only **acetyl-CoA**.

The course of ketone bodies formation The course of ketone body formation can be described by the following reactions:

1. Condensation of two molecules AcCoA → acetoacetyl ~ CoA.
2. Reaction with additional AcCoA → 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA).
3. Cleavage of HMG ~ CoA → AcCoA and acetoacetate.
4. Reversible conversion of acetoacetate and β-hydroxybutyrate.
5. Decarboxylation of acetoacetate.

β-Ketothiolase β-Ketothiolase catalyzes the last step of β-oxidation of fatty acids - **thiolytic cleavage**. During the formation of ketone bodies, the **reaction is reversed** and one molecule of acetoacetyl-CoA is formed from two molecules of AcCoA. The reaction takes place in the **matrix of the mitochondria**.

3-hydroxy-3-methylglutaryl-CoA synthase This enzyme catalyzes the condensation of acetyl-CoA with acetoacetyl-CoA. The condensation takes place on the third carbon of acetoacetyl-CoA to give 3-hydroxy-3-methylglutaryl-CoA. This important intermediate occurs not only in the metabolism of ketone bodies, but also occurs during the synthesis of cholesterol.

3-hydroxy-3-methylglutaryl-CoA lyase This enzyme catalyzes the **cleavage of HMG-CoA** to acetoacetate and AcCoA. This creates the **first ketone body**.

β-hydroxybutyrate dehydrogenase This enzyme catalyzes the **reversible conversion** of two ketone bodies - acetoacetate and β-hydroxybutyrate. The cofactor is NAD +. In the massive formation of ketone bodies, **β-hydroxybutyrate** is quantitatively the most important ketone body in the blood, ie most acetoacetate is converted to it.

Decarboxylation of acetoacetate Some molecules of acetoacetate **spontaneously**, ie non-enzymatically decarboxylates to **acetone**, which has no use in the human body and is **excreted** by respiration or urine.

Ketone bodies activation and utilization

__ Využití ketolátek Ketone bodies are the product of the breakdown of fatty acids under certain metabolic conditions (eg starvation). Ketone bodies include acetate, beta-hydroxybutyrate and acetone. They occur only in the liver and are used by extrahepatic tissues as a temporary source of energy.

Chemical processes

Ketone bodies are polar and are therefore transported freely in plasma. Their utilization occurs only extrahepatically, because hepatocytes do not contain the enzyme needed for their activation. First, β-hydroxybutyrate is oxidized to acetoacetate, which is subsequently activated by the transfer of coenzyme A from

succinyl-CoA. Acetocetyl-CoA is converted to AcCoA (part of β-oxidation, catalyzed by thiolase), which enters the Krebs cycle.

Utilization of ketone bodies by individual organs

The heart muscle, skeletal muscle and renal cortex prefer the oxidation of ketone bodies to the oxidation of glucose. During starvation, the brain adapts to the burning of ketone bodies - during long-term starvation, up to 50% of its energy requirements are covered by the oxidation of ketone bodies.

Regulation of ketogenesis

__ Regulace ketogeneze Regulation of ketogenesis takes place in **four stages**:

1. Hormone-sensitive lipase - lipolysis in adipose tissue.
2. Carnitine acyltransferase I - entry of fatty acids into the mitochondria, where their β-oxidation takes place.
3. Direction of AcCoA from β-oxidation to ketogenesis and not to the Krebs cycle.
4. Mitochondrial HMG-CoA synthase.

High levels of ketone bodies in the blood signal the presence of large amounts of AcCoA. It results in inhibition of lipolysis.

Plasma ketone bodies concentration and ketoacidosis

__ Koncentrace ketolátek v plazmě

The maximum rate of ketone body formation is reached at a plasma concentration of 12 mmol / l.

Links

Related articles

- Slimming diet
- β-oxidation
- Diabetes mellitus
- Acetyl-CoA

Ketoacidosis Diabetic ketoacidosis (DKA) is a life-threatening complication of diabetes mellitus. The cause is an absolute or relative insulin deficiency. It occurs in 20-40% of newly diagnosed diabetics. DKA mortality is <2%. **The predominant symptoms** are dehydration, metabolic acidosis and hyperglycemia. Stressful situations (most often infectious diseases, sudden abdominal events, etc.) lead to an increase in insulin resistance. Although hyperglycaemia occurs, ketosis occurs only when insulin doses are not increased sufficiently. In practice, it is quite possible to encounter such a gross error that in case of anorexia and vomiting the insulin dose is reduced or the dose is completely omitted.

Pathophysiology

Insulin is an anabolic hormone that leads to the production of glycogen in the liver and allows lipogenesis. Insulin deficiency is caused by insufficient secretion or substitution of insulin (newly formed DM I. type, incorrectly conducted therapy, a technical problem of insulin administration). **Insulin deficiency leads to a failure of adequate glucose supply to cells** (mainly muscle and adipose tissue) with subsequent cellular starvation. This situation initiates the rise of **counter-regulating hormones** - glucagon, corticosteroids, catecholamines, and growth hormone in **an effort to strengthen energy sources**. Thus, paradoxically, there is a further increase in hyperglycemia, escalation of lipolysis, proteolysis, glycogenolysis and gluconeogenesis. If the reabsorption capacity of the renal tubules is exceeded (usually glycemia> 10 mmol / l), glycosuria occurs, which **induces osmotic diuresis**. The result is hyperosmolar (hyperglycemic) dehydration. In most cells of the body, the hypertonic state of DKA enhances intracellular dehydration in order to preserve intravascular volume. Brain cells adapt to hyperosmolality by increasing intracellular osmotically active solutes, idiogenic osmols (so-called osmoprotection). These osmoprotective molecules help maintain nerve cell volume despite high hyperosmolality. The rapid decrease in osmolality that occurs when an excess of free water is administered can cause brain swelling by the initial movement of water and not electrolytes through the endothelium of brain capillaries into osmotically adapted brain cells. Insulin deficiency is the reason why glucose cannot be used as an energy substrate. Lipolysis is activated, and plasma levels of free fatty acids increase in plasma and hepatocytes. Fatty acids are degraded by β-oxidation faster than the formed acetylcoenzyme A can enter the Krebs cycle. Excess acetylcoenzyme A gives ketone bodies (acetone, acetoacetate and 3-β-hydroxybutyrate). Ketone bodies are an alternative usable source of energy in the absence of glucose intracellularly. Ketone bodies are a product of both lipolysis and proteolysis. Their disadvantage is that they are acidic in nature and lead to metabolic acidosis (MAc). 3-β-hydroxybutyrate is not a chemical structure ketone, but in practice is included among ketones.

Chemicaly

- acetyl-CoA → CoA + acetyl,
- acetyl + acetyl → acetoacetate (reduction of acetoacetate gives 3-β-hydroxybutyrate),
- 3-β-hydroxybutyrate → acetone.

This metabolic situation is partially compensated by hyperventilation and hyperpnea, which leads to a decrease in pCO2 at already low bicarbonate levels. Manifest hyperventilation - Kussmaul's breathing, is a picture of the body's futile efforts to compensate for MAc. Kussmaul's breathing, especially in the youngest children, is associated with increased muscle work and therefore DKA is often associated with lactic acidosis (dehydration with hypoperfusion also contributes to this). Increasing amounts of ketone bodies and lactate lead to a deepening of the MAc.

Intracellularly stored potassium is leached from the cells due to acidosis. Another reason for potassium efflux from cells is the negative nitrogen balance in protein catabolism. Potassium is then lost through osmotic diuresis. Volume depletion leads to secondary hyperaldosteronism, which further enhances potassium excretion in the kidney. The result is marked potassium depletion, although serum potassium levels may not correspond to this at first. Potassium depletion can lead to paralytic ileus. Fluid losses also lead to the depletion of other ions - calcium, phosphate, and magnesium.

The reduction of circulating volume caused by osmotic diuresis, hyperventilation, and vomiting is masked by the transfer of fluids from the intracellular space to the extracellular (ie also intravascular) and the skin turgor, therefore, remains for a long time. When ketoacidosis is corrected, the levels of acetoacetate and acetone increase in relation to β-hydroxybutyrate, while acidosis worsens, the opposite happens. Routine laboratory tests for the presence of ketone bodies detect only acetone and acetoacetate, not β-hydroxybutyrate. Therefore, in DKA, it initially appears that ketone bodies are absent and, conversely, the detected ketone bodies may increase even with the remission of severe acidosis. It follows that there is greater objectivity when using β-hydroxybutyrate to determine the severity of DKA.

Clinical picture

During the first detection of diabetes mellitus, we find a history of polyuria and polydipsia in children, which preceded acute decompensation. Despite the increased appetite, there is a weight loss. Children have nausea, vomiting, abdominal pain, thirst, weakness, vertigo. In young children, we can find significantly soaked diapers. In these cases, polydipsia may be absent and polyuria can easily escape attention. In older children, we may find nocturia or secondary enuresis. Less than 10% of children with DKA are admitted to hospital in a coma, but a much higher percentage have a significant impairment of consciousness.

Incipient diabetes can often be misdiagnosed. Abdominal pain leads to suspicion of acute appendicitis or other types of acute abdomen (sometimes we can also find weakened peristaltic), hyperpnea leads to suspicion of pneumonia or asthma, polyuria leads to suspicion of urinary tract infection. Symptoms such as enuresis, polydipsia, and increased irritability are often classified as psychosomatic disorders. In the circulatory system, we find a prolonged capillary return, cold periphery, and intangible peripheral pulsations. However, blood pressure remains normal for a long time. Tachycardia is often present. In diagnosed diabetics, the symptoms develop earlier. In the anamnesis, we find data on intercurrent illness, incorrect management of insulin administration, including non-compliance of patients.

Diagnosis

As part of the physical examination, it is necessary to pay attention to the symptoms of dehydration, ie dryness of mucous membranes and the skin turgor (however, the skin turgor can be preserved for a relatively long time). In some cases, patients show symptoms of hypovolemic shock. Acetone odor of breath and hyperpnea (Kussmaul's breathing) are characteristics, which indicate ketoacidosis. Patients may have impaired consciousness ranging from somnolence to deep coma. Abdominal pain with abdominal wall rigidity (pseudoperitonitis diabetica) resembles the symptomatology of an acute abdomen.

Hyperglycemia without ketoacidosis with hyperpigmentation (acanthosis nigricans) on the back of the neck leads to the suspicion of diabetes mellitus II. type. In laboratory tests hyperglycemia, ketonemia and ketonuria, usually also glycosuria are present. MAc is defined as pH <7.3 and HCO3 <15 mmol / l Glucose measurement by glucometer is acceptable to monitor changes in glycemia during treatment, but venous blood glucose testing should be performed at the start of treatment.

Hyperosmolarity

Hyperosmolarity is a typical finding. Serum osmolality is also increased by the accumulation of so-called idiogenic osmols in a severe catabolic state. Therefore, the value of the calculated osmolality increases less significantly compared to the osmolality measured by an osmometer. The calculated osmolality can be found using the following equation:

S-osmolality = 2 × Na + glycemia + urea standard: 280–295 mosmol / kg

Within DKA, it is useful to determine the osmolal / osmotic gap (OG), which expresses the difference between the directly measured osmolality by osmometer and the calculated osmolality, which can be found using the equation above.

Osmotic gap in mmol / l = measured - calculated osmolality the physiological value of the osmotic gap is 4–12 mmol

OG exists because some solutes that are measured by an osmometer are not included in the formula. If the plasma contains a significant amount of these uncounted osmotically active substances (idiogenic osmols in DM ketoacidosis), a large difference arises between the measured and calculated value of osmolality. The value of the osmotic gap in DKA increases significantly and is a reflection of the degree of catabolism, on the contrary, the gradual fall to normal values indicates successful treatment of ketoacidosis.

MAC within DKA The clinical findings are the aforementioned Kussmaul's breathing, acetone breath, and raspberry red mucosa. For DKA the accumulation of keto acid is typical (β-hydroxybutyrate and acetoacetate) and MAc is characterized by a high value of the anion gap ("anion window").

anion gap (AG) = (Na + K) - (Cl + HCO3) the physiological value of AG is 13–17 mmol / l

Tissue hypoperfusion in a generally severe condition and excessive respiratory work during Kussmaul breathing also lead to an increase in lactate and MAc in this case is a combination of ketone bodies and lactate accumulation. After metabolization of accumulated anions - ketone bodies, alkalization occurs by bicarbonate production in the liver, and therefore we correct acidosis with bicarbonate only at extremely low pH values. ABR examinations are usually performed by taking arterialized capillary blood, which is an easier way, but with the availability of an arterial catheter, arterial values are certainly more accurate.

Pseudohyponatremia Usually, lower values of plasma sodium ("pseudohyponatremia")are detected, because the present hyperglycemia has a diluting effect. It is therefore necessary to determine the corrected sodium. To about 3 mmol / l glucose above the reference value we add about 1 mmol / l sodium. Natremia then tends to increase as therapy proceeds. Insufficient increase in sodium or even decrease signals an increased risk of cerebral edema.

Sodium decreases by 1 mmol for every 3 mmol increase in blood glucose.

Hyperkalemia Normokalaemia or even hyperkalaemia is a regular finding in advanced DKA, although total potassium levels are reduced (see pathophysiology). With rehydration and insulin substitution, the patient is at risk of developing rapid hypokalaemia, so potassium substitution is another priority in DKA therapy. There are algorithms for potassium depletion concerning its current serum level (see therapy). Potassium losses are around 5 mmol / kg, in the heaviest forms of DKA up to 10 mmol / kg!

Other laboratory findings In determining laboratory parameters of dehydration, urea concentration is more important than creatinine concentration. Severe noninfectious leukocytosis is present. Other typical laboratory findings include elevations in serum amylases, which, together with abdominal pain, may lead to a false diagnosis of pancreatitis, transaminase elevations, or creatine kinase. Phosphate, calcium and magnesium levels may initially be within the reference range, but a significant deficit is very likely. State of consciousness is evaluated according to the Glasgow coma scale (GCS). GCS <12 b. is evaluated as a disorder of consciousness. A decrease in GCS during treatment is a warning sign of the development of cerebral edema.

Differential diagnostics

- Methanol poisoning,
- ethanol poisoning,
- paraldehyde poisoning,
- salicylate poisoning,
- metformin poisoning
- starvation,
- uremia,
- differential diagnosis of lactate MAC.

Therapy

Securing the patient

It is ideal to provide 2 i.v. lines, one serving as a route for the administration of rehydration solutions and the other for the linear and accurate dosing of insulin. Patients with severe impairment of consciousness, severe MAC, or shock should also have an arterial line, especially due to frequent sampling and higher validity of ABR examinations. In children with impaired consciousness, the insertion of a nasogastric tube is also necessary. A urinary catheter is used in all children with severe DKA. It allows accurate determination of diuresis with hourly balance. This is especially important at the outset, as patients may lose a large amount of urine due to osmotic diuresis despite significant dehydration. An accurate balance of diuresis will allow adequate rehydration therapy. Intubation and mechanical ventilation are used only in the most extreme case, with severe unconsciousness or cerebral edema. Setting the UPV mode is very difficult in terms of ventilation parameters because even a small change in pCO2 threatens a significant pH shift.

Expansion of volume and correction of fluid deficit

Volume adjustment is a top priority. Saline solution 1/1 of 20 ml / kg i.v. is administered during the first hour. The dose is repeated until pulse frequency is decreased and until the capillary return is normal. In shock, a dose of 10–20 ml / kg i.v. within 20-30 minutes is preferred. After adjustment of the intravascular volume, other fluids are administered with caution. If the calculated S-osmolality is <320 mosmol / l, we can compensate for the fluid deficit within 24 hours. However, if the S-osmo is> 345 mosmol / kg and the corrected sodium is> 145 mmol / l, we will extend the fluid replenishment to 48-72 hours. DKA is usually associated with an average fluid loss of about 10% by

weight. The severity of dehydration may be worse than clinical estimation because serum hyperosmolality leads to intracellular water transfer extracellularly. Besides, continuous losses of polyuria should be taken into account until the glycemia is <10 mmol / l.

It is extremely important to cover ongoing losses at the same time. Especially the initially present polyuria despite dehydration can lead to the failure of our rehydration strategy. Therefore, a urinary catheter should be inserted, and the monitoring of hourly fluid balance should be started. Potassium losses are estimated as if 20 mmol of potassium is lost per 1 liter of urine. The patient's control weighing informs us about the adequacy of our rehydration, at least at intervals of 12 hours. Further weight loss during infusion therapy is a serious warning of poor rehydration.

When the glycemia drops <15 mmol / l, a 5% glucose solution with the added necessary ions should be administered. We administer fluids parenterally until the child is able to receive them orally.

Ion correction

Sodium correction Hyponatremia is a common finding. The cause is both pseudohyponatremia with severe hyperglycemia, but real loss of sodium also occurs, which can be as much as 10 mmol / kg. Due to practical considerations, 0.45% NaCl solution is administered after the initial correction of the intravascular volume. After the start of volume expansion, an adequate increase in sodium is expected. If sodium is <135 mmol / l and decreases further with adequate rehydration and requires administration of highly concentrated NaCl solutions, the development of SIADH with concomitant cerebral edema should be considered.

As part of the adjustment of sodium, it is necessary to calculate the so-called effective osmolality and then the increase in sodium during treatment should be assessed in correlation with the decrease in glycemia.

Effective osmolality (= S-tonicity) = 2 × (Na + glycemia)

A gradual decrease in effective osmolality should occur during treatment with a gradual increase in serum Na and a concomitant decrease in glycemia. During treatment, serum sodium levels should increase by approximately 1-2 mmol / l with each decrease in blood glucose by 5-6 mmol / l. The calculated sodium value corrected in this way should remain constant for each simultaneous determination of glycemia and sodium during treatment. If the measured serum sodium concentration is higher, it is necessary to evaluate the increase in the need for free water, i.e. the increase in the rate of fluids administered. If the measured sodium is lower and does not rise with a concomitant decrease in blood glucose, it is probably caused by excessive administration of free water. The administration of free water should be immediately reduced, ie the rate of infusion should be decreased. A drop in effective osmolality caused by excessive administration of free water can lead to cerebral edema. In this respect, a decrease in serum osmolality of more than 3 mOsml / l / h is dangerous.

Hypernatremia should not be corrected until significant hyperglycemia has gone and the infusion rate should be decreased to ensure an appropriate, but not very rapid, lowering in sodium levels. It can take more than 48 hours. Hypernatremia is usually corrected if the glycemia reaches values <20 mmol / l.

Potassium correction All children with DKA have potassium depletion (average 5 mmol / kg) and therefore potassium replacement is an important part of DKA treatment. As already mentioned, due to severe MAC normal or slightly elevated serum potassium levels can be detected even with severe total depletion of this ion. After initiation of rehydration, and in particular, in connection with insulin administration, potassium is rapidly transferred back to the cells and the patient is at risk of hypokalaemia. Potassium is administered after correction of intravascular volume, in the absence of hyperkalemia and its signs on the ECG. Diuresis must be present at the same time. A sufficient supply of potassium is usually ensured by adding 40 mmol of KCl to each liter of fluid administered. Kalemia should correlate with acid-base balance and ECG curve. If potassium is <3.5 mmol / l and it is not possible to increase it, it is advisable to discontinue insulin therapy until the level reaches an adequate increase.

Potassium should be restored as potassium chloride and potassium phosphate in a ratio of 2: 1.

Correction of other ions Phosphorus, calcium, and magnesium values may be in the reference range, but their significant deficiency is very likely. In severe DKA, 1 mmol / kg of these ions are given within 24 hours. Inadequate treatment with phosphates can lead to hypocalcemia, on the other hand, administration of phosphates in severe hypophosphatemia reduces muscle weakness and myocardial depression.

MAC correction

The most important step in MAC correction is adequate volume expansion and insulin therapy. Bicarbonate administration remains controversial, as it leads to paradoxical acidosis in the CNS and thus to depression of CNS functions. The cause of paradoxical acidosis is the metabolism of bicarbonate, where its' combination with hydrogen ions (H +) leads to carbonic acid (H2CO3) formation. This acid decomposes immediately into water (H2O) and carbon dioxide (CO2). The blood-brain barrier is more permeable to CO2 than to HCO3-, and this leads to the accumulation of CO2 in the CNS and results in a deepening of acidosis in the CNS. Bicarbonate treatment is preserved for children with pH <7.0, HCO3 <8 mmol / l, for children with v.s. cardiac depression associated with MAC and for those who are no longer able to compensate for MAC hyperventilation. The adequacy of the compensation can be determined if we know the value of pCO2 and HCO3 according to the so-called Winter formula. If the pCO2 value is greater than a result of the formula: (1.5 × HCO3-) + 8, then the respiratory effort is no longer sufficient to compensate for the degree of acidosis, and bicarbonate administration is justified. Adjust the pH to pH 7.1–7.15 and HCO3 15 mmol / l.

at pH <7.0 or HCO3 <8 mmol / l we administer bicarbonate in the dose: 0.1 × BE × kg t.h. corrected to pH 7.1–7.15, administered in KI, ie NOT as a bolus.

Insulin treatment

Insulin treatment is necessary to stop the formation of ketone bodies, which is the primary cause of DKA. In addition to crystalloid substitution, an initial bolus of human fast-acting insulin is administered i.v. 8-12 units. Insulin administration should be initiated after stabilization of the circulation (supplementation of fluid deficiency) and at an adequate kalemia value concerning pH. During the first 60-90 minutes of rehydration treatment, blood glucose drops significantly even without insulin administration. Therefore, we start continuous insulin administration approximately 1 hour after the initial volume therapy. As shown, the previously recommended immediate initiation of continuous insulin administration is associated with a higher risk of developing cerebral edema. An initial bolus of insulin is no longer recommended.

Number of insulin units = 5 I.U./kg to 50 ml 1 / 1FR, then 1 ml / h. = 0.1 I.U./kg/hour

Before starting the infusion, the infusion set should be flushed with 20 ml of this solution because insulin binds to the wall of the set. If it is not possible to administer the insulin intravenously, the fast-acting insulin can be administered intramuscularly or subcutaneously at a dose of 0.1 I.U./kg/hr. effectively.

Glycaemia should decrease gradually, ie by 3-5 mmol / l / h. (A decrease of 5-6 mmol / l / h is also safe if the sodium level increases by 1-2 mmol / l / h at the same time). It is not desirable to lower blood glucose by more than 6 mmol / l / h. When your blood glucose decreases below 15 mmol / l, glucose-containing saline solutions should be started. Most often, 5% glucose with the addition of sodium at the level of 1/2 FR + other necessary ions is recommended. The goal is to maintain blood glucose 8-12 mmol / l. If there is no decrease in blood glucose within 2 hours, increase the insulin dose to 0.2 U.I./kg/h.

If, on the other hand, the blood glucose decreases too fast or falls below 8 mmol / l with the MAC present, the insulin delivery rate should not be decreased, but instead, the glucose concentration should be increased to 10%, ev. and more. The rate of insulin delivery should only be slowed down (to a maximum rate of 0.05 I.U./kg / h - an even lower rate threatens the recurrence of ketosis) when the glycemia remains below the target level despite glucose supplementation.

Oral fluid intake should not be initiated until the clinical condition has significantly improved, although mild ketosis may still persist. Once oral fluids are tolerated, intravenous fluid intake should be reduced. Subcutaneous insulin administration can be initiated with p.o. supply and disappearance of ketosis. A subcutaneous dose of fast-acting insulin is usually given 10-30 minutes before each meal. I.v. Insulin delivery should be continued for approximately 30-60 minutes after the first subcutaneous dose, which controls glycaemia until sufficient injected insulin is obtained.

At glycaemia <10 mmol / l and pH> 7.35 it is possible to switch to s.c. insulin administration.

Monitoring

The unambiguous indication for admission to the ICU in patients with DKA is age <1 year, GCS <12b., Calculated S-osmolality> 320 mosomol / l, sodium> 145 mmol / l and potassium <4 mmol / l.

Blood pressure, heart and respiratory rate, fluid intake, and output (hourly balances) should be monitored. The state of consciousness, reactivity, and shape of the pupils should be carefully and regularly evaluated. ECG monitoring is required for the risk of arrhythmias in hypo- or hyperkalemia. Glycemia during the first 2 hours every 30 minutes should be checked, checkings are performed every 1 hour for the duration of insulin administration i.v. Kalemia is monitored every 2-4 hours until acidosis and hyperglycemia return to normal. More frequent controls are required if the potassium is outside the physiological range or when bicarbonate is administered. We perform arterial blood gas analysis(ABG) initially, then at intervals of 2-4 hours, and always about 30 minutes after administration of bicarbonate. As acidosis subsides and hydration improves, the state of consciousness improves, nausea and vomiting start to disappear.

Complications

Brain edema The most serious complication of DKA is cerebral edema (most often developing in the first 12-24 hours of therapy). It occurs in about 1% of patients with DKA. The cause of the DKA is not fully understood. Several factors are involved in its development: the length and severity of DKA before starting therapy, too aggressive volume expansion, use of bicarbonate, too fast insulin administration, osmolality fluctuations with a sharp decrease in Na, Cl, urea, cerebral hypoxia and degree of hyperglycemia. Typical clinical signs of developing cerebral edema include headache, irritability, confusion, impaired consciousness, small and anisocoral pupils, hypertension with bradycardia, decreased SaO2, cranial nerve palsy, Cheyne-Stokes ventilation pattern, occasional changes in the ocular background (disappearance of venous pulsations, papilloedema). Unfortunately, only 50% of children show prodromal symptoms of brain edema, very unfavorable is the sudden development of convulsions or respiratory arrest. If brain edema is suspected, the child requires resuscitation care. Hypoglycemia must be ruled out first. Therapeutically administer hypertonic sodium solutions (if there is no concomitant hypernatremia), slow the infusion rate to half, consider the administration of steroids. If there is a risk of brain stem compression, 20% mannitol 5 ml / kg within 20 minutes should be administered, intubated, and hyperventilated. After stabilization, CT or MRI imaging of the brain should be performed, as other causes of exacerbation may occur - hemorrhage, thrombosis, and infarction. Brain edema is the leading cause of death in DKA.

Other complications Another common complication in the treatment of DKA is hypokalaemia. Rare complications include ARDS, rhabdomyolysis, and acute renal failure. Some patients may report blurred vision, which is caused by a rare complication - lens dislocation due to fluid shifting during volume replacement.

Diabetic hyperosmolar coma, DHC

Pathophysiology of DHC The balance between the capacity of gluconeogenesis and glycosuria occurs at glycemic values of 30–35 mmol / l, the finding of higher glycemia is always a manifestation of severe hyperosmolar dehydration. In this situation, there is an extremely high risk of cerebral edema during rehydration therapy, often also the development of SIADH. It is a hyperosmolar diabetic coma with a high glycemic value> 40 mmol / l without ketosis or with only mild ketosis. It can occur in children with little residual insulin secretory capacity and at the same time an inability to achieve adequate fluid intake and in hyperosmolality due to hyperglycemia. Typically, this condition can occur in very young children or children with mental disabilities, in children treated with high doses of glucocorticoids, or in children treated with diazoxide due to hypoglycemia. The measured S-osmolality can reach extreme values of 360-380 mosmol / kg. After initiation of rehydration therapy, β-oxidation of fatty acids increases and, paradoxically, the MAC deepens.

Laboratory criteria

- Glycaemia> 40 mmol / l,
- S-osmolality> 345 mosmol / kg,
- corrected for Na> 145 mmol / l.

Therapy The fluid deficit should be covered for at least 72 hours. Initially, lower insulin doses are preferred, ie 0.01–0.05 I.U./kg/h. Increase to the usual 0.1 I.U./kg/hour. indicated only when the glycemia drops <30 mmol / l. During the development of SIADH, fluids are reduced by another 20-25%. There is a significantly higher risk of cerebral edema than with typical DKA. The treatment of cerebral edema is described above.

Infections in patients with diabetes mellitus.

Type I diabetes mellitus, especially in long-term hyperglycemia, is characterized by an increased risk of severe bacterial, viral, or fungal infection. Hyperglycemia in disease detection or inadequate diabetes control has been shown to be a major cause of decreased immunoreactivity. The function of polymorphonuclear cells is altered, chemotaxis and adherence are depressed, bactericidal activity with defective production of hydrogen peroxide and NADPH is present. Dermal reactivity to T-antigens is also reduced. After reaching the euglycemic state, the transient impairment of phagocytic functions and cellular immunity gradually returns to normal. Staphylococcus aureus is the most common cause of cutaneous pyoderma (carbuncles, furuncles), subcutaneous abscesses, fasciitis, muscle abscesses, respiratory tract infections (bronchopneumonia, pleuropneumonia, lung abscesses), urogenital system infections (pyelonephritis, abscesses). Other agents may be involved in the severe infectious complication of Streptococcus pneumoniae, E. coli, Salmonella enteritidis, less commonly Mycobacterium tuberculosis. Invasive infection caused by staph aureus spreads mainly hematogenously. Nasal colonization of diabetics by Staphylococcus aureus is often cited as a source of infection. Poor compensation of the underlying disease with glycosylated hemoglobin values> 9% is considered to be a risk factor for increased staphylococcal colonization. Violation of aseptic insulin administration principles is a common cause of bacterial infection. Diagnosis of disseminated staphylococcal infection with the formation of multiple abscesses is very difficult in the first days of infection. The use of all imaging methods (USE, CT, MRI) is very beneficial. With a more focal process, gallium scintigraphy can also contribute to the correct diagnosis. It has recently been found that reduced polymorphonuclear function, which is considered to be a major risk factor for invasive staphylococcal infection, can be treated therapeutically by administration of recombinant growth factor for rhG-CSF granulocytes. Vaccination against pneumococci and influenza virus is recommended for all patients with diabetes according to some treatment algorithms.

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