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Учреждение образования
«Гомельский государственный медицинский университет»

Кафедра патологической физиологии
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МЕТОДИЧЕСКАЯ РАЗРАБОТКА
Для проведения занятия со студентами
3 курса ФПСЗС, обучающихся на английском языке
по патологической физиологии

Тема: Типовые нарушения обмена веществ. Нарушения обмена белков, витаминов, нуклеиновых кислот. Голодание

Theme: Typical metabolic disorders. Disorders of protein, vitamins, nucleic acids metabolisms. Starvation

Время 3 ак. часа

Actuality of the theme. For data of the WHO, more than half of population of globe chronically is undernourished. Therefore starvation is the social problem is considered not only as medical, but also as asocial problem. This pathological process accompanies with a number of diseases, mainly of digestive system. There is protein-calorie insufficiency more often.

The changes of metabolism for starvation are carried out nervous, endocrine and peripheral mechanisms of regulation. Due to such regulation there is a redistribution of nutritious substances for maintenance of functions of the vital bodies (heart, brain) and preservation of life on long time.

Learning goals of the lesson: to study etiology and pathogenesis of protein, nucleic acid metabolism disorders.

Educational goals of the lesson: formation of scientific outlook and theoretical basis of future specialists on the basis of fundamental knowledge and the latest achievements of pathological physiology.

Objectives of the lesson:

1. To know typical forms of violations of protein metabolism, causes and mechanisms of development of various types of protein deficiency.
2. To be able to explain causes of disruption of protein biosynthesis, final stages of protein metabolism.
3. Characterize violations of plasma protein composition.
4. To be able to explain pathogenetic mechanisms of disturbances in exchange of purine and pyrimidine bases.
5. To know causes and pathophysiological mechanisms of periods of complete starvation.

To repeat the following questions from related disciplines to ensure absolute mastery of the material:

1. Significance of proteins, fats, carbohydrates, water, vitamins for normal ability to live of an organism (biochemistry discipline)
2. Mechanisms of neuro-humoral regulation of metabolism and energy (normal physiology discipline)

Control questions of the lesson:

1. Typical forms of violations of protein metabolism. Positive and negative nitrogen balance.
2. Violations of final stages of protein metabolism: types, causes, mechanisms of development.
3. Violations of protein composition of blood plasma.
4. Violation of exchange of purine and pyrimidine bases.
5. Fasting: causes, types, periods of complete starvation. Alimenterapy.
6. Protein-caloric insufficiency, types.
7. Primary and secondary hypovitaminosis: causes, mechanisms of development, main manifestations. Antivitamins.

Calculation of study time

Total study time 3 ac.hours

№ п/п	Contents	Calculation of study time
1.	Introduction. Motivational characteristic of the theme	3 minutes
2.	Written control of students on the topic of the lesson	15 minutes
3.	Interviews with students about the topic of the lesson	60 minutes
4.	Self-managed student work	15 minutes
5.	Summing up the results of the lesson	5 minutes
6.	Decision of situational tasks	20 minutes
7.	Task for the next lesson	2 minutes

Additional materials:

Metabolism is a sum of substances from outside exposed to chemical conversions.

Division of complex and varied metabolism on the separate parts aggravates team approach to its analysis in conditions of norm and pathology. Such division of metabolism on different types (protein, lipid, carbohydrate) is artificial, as it lead to division of indivisible and also it renders understanding of pathogenic processes in metabolism in functional and morphologic functional impairments of organs and tissues (e.g., diabetes mellitus, atherosclerosis, prolonged protein starvation). From the other side, pathology of metabolism may be presented as a complicating factor in basic disease development. It is necessary to know that metabolism control is realized on various levels.

Protein metabolism character

1. Protein metabolism directly depends on nutrition as there is no protein depot in organism. Proteins are necessary for growth consistence of organism.

2. The source of protein synthesis is amino acids of exogenous and endogenous origin. Essential amino acids do not run in organism due to endogenous transformations, they are necessary for synthesis.

3. The source of energy is carbohydrates, lipids, in their insufficiency – proteins. In case of carbohydrate and lipid insufficiency for energy supply, amino acids will split up to substrates, instead of protein synthesis.

4. It is necessary to remember that protein supply of organism from several sources will lead to polyetiologic protein metabolism impairment.

In normal conditions proteins split up to oligopeptides and alpha – amino acids. Optimum Ph for protein splitting is provided by gastric hydrochloric acid. Protein kinases split the specific peptide links. In alkaline conditions of intestine trypsin, chemotrypsin and carboxypeptidase of pancreas hydrolyse peptases and peptones up to peptidases and aminoacids. Some proteins in small amount may be absorbed in unchanged state: products of hydrolysis, some amino acids. Amino acids are transported to liver by the portal vein system, than they are disturbed in other tissues and participate in functional protein restoration (albumins, globulins, hormones and others). Excess of amino acids is deamidized, nitrogen containing part is changed into urine in liver and is excreted by kidneys, carbohydrate of amino acids, as lipids and carbohydrates is acidified. One part of amino acids is referred to glycogenic, and other part – to ketogenic.

It is known that biological role of proteins is determined by efficiency of other utilization. Proteins with high biological value (e.g., essential amino acids) are distinguished by their quantity and characteristics and distribution favorable for re-synthesis of tissues and energy intensity. In protein insufficiency proteins of muscles can be destructed and become a source for enzyme run and maintenance need in brain tissue.

20% of an adult's body weight - proteins. Amino acids composing them are referred to essential running in cell protoplasm formation. Type, number and structure of amino acids determine characteristics of protein molecule. All amino acids are divided into essential and nonessential, semi-essential. Ten amino acids (threonine, amino isovaleric acid, leucine, isoleucine, lysine, tryptophan, phenylalanine, methionine, histidine, arginin) are referred to essential in first-year-old children. Besides, cystine and taurin are essential in children with low body weight aborning. There are eight essential amino acids in healthy adult (threonine, amino isovaleric acid, leucine, isoleucine, lysine, tryptophane, methionine).

It is very important that amino acid insufficiency occurs not only in case of one or several essential amino acids, but also in case of essential nonessential amino acid ratio impairment in organism. Protein energy malnutrition refers to a range of clinical syndromes characterized by an inadequate dietary intake of protein and calories to meet the body's need.

Semi-essential amino acids are called semi-essential because of their deficiency develops very quickly in pathological conditions. Glutamin (it is necessary for synthesis of nucleotides, skeletal muscle protein, ammonia in kidneys, gluconeogenesis in hepatocytes); arginin (it is a substrate for contra-insulin hormones, insulin, insulin is also necessary for protein synthesis).

Nonessential proteins may be synthesized in organism, so they are not supposed to contain in food.

Types of protein insufficiency:

1. Alimentary (exogenous, primary)

- quantitative
- qualitative

2. Endogenous (secondary)

- in protein split (impairment in gastro-intestinal tract)
- in protein absorption impairment
- in change of amino acid admission rate
- in organs and tissues
- in change of protein dissimilation rate
- in interstitial amino acid metabolism impairment
- the end point stages of protein metabolism impairment

Exogenous develops in:

- low bioactivity
- essential amino acid deficiency
- starvation (complete or partial)

Protein structure synthesis

There are different processes in base of protein metabolism in organism, but the main is protein structure synthesis. Protein synthesis is the central part of metabolism, and specificity of protein biosynthesis. General regularity of protein synthesis is an active metabolism.

Types of protein synthesis (according to V.N. Nikitin)

1. Synthesis of growth. It is caused by organ growth. It has physiologic limits and it finishes at the moment of physiologic growth stopping.
2. Stabilizing synthesis associated with self-renewing tissue proteins. It is realized as long as life endures.
3. Regeneration synthesis: post accidental. It is presented in period of recovery after blood loss, starvation
4. Functional synthesis. It is directed on specific organ function (synthesis of specific enzymes, hemoglobin).

Causes of protein biosynthesis impairment

I. Hereditary

II. Acquired

1. alimentary insufficiency
2. protein split impairment in gastro-intestinal tract
3. amino acid absorption impairment
4. amino acid synthesis impairment in cell

Pathology of protein synthesis occurs not only in form of general impairments. In this respect we shall discuss blood serum protein pathology. There are 150 individual proteins are identified in blood serum. In physiological conditions general protein is heterogeneous. Heterogeneity becomes more expressed in pathological conditions.

Consequences of protein biosynthesis impairment:

- development of dystrophic and atrophic disorders in organs and tissues due to lack of updating of structural proteins;
- deceleration regeneration processes;
- growth retardation, physical and mental development;
- ↓ synthesis of various enzymes and hormones (growth hormone, antidiuretic and thyroid hormones, insulin, and others.) → endocrinopathy, violation of other types of metabolism (carbohydrate, water-salt, base);
- ↓ oncotic pressure in the blood → edema;
- ↓ production of antibodies and other protective proteins → ↓ immunological reactivity of the organism;

Functions of blood proteins

- a. transport
- b. oncotic pressure support
- c. defence
- d. buffer
- e. blood flow property
- f. injuring (cryoglobulins, etc.)

Pathology of blood serum protein content

Pathology of blood serum protein content associated with water exchange and plasma protein content impairment. It is presented by different changes in measurements of serum proteins.

1. hypoproteinemia
2. hyperproteinemia
3. defectoproteinemia
4. dysproteinemia

Quantitative and qualitative changes of protein content are referred.

Quantitative changes of protein biosynthesis have a great role in different disease pathogenesis (e.g., hemoglobinopathia).

Hemoglobinopathia is a hereditary abnormality of hemoglobin synthesis. These abnormalities are presented by primary structure impairments or normal hemoglobin chain ratio impairment (quantitative and qualitative hemoglobinopathias). Some hemoglobinopathias result in development of lethal outcome (sickle cell anemia, thalassemia). Majority of hemoglobinopathias do not have clinical importance (in case of latent carriage of abnormal hemoglobin, when there is a complex of normal and abnormal hemoglobin in erythrocyte).

Hyperproteinemia – increase in measurement of all or separate types of proteins.

- **relative**, as a result of hemoconcentration
- **absolute** variant happens in some types of leukemia with formation of anomalous proteins (paraproteins).

Hypoproteinemia – decrease in measurement of all or separate types of proteins. Due to:

- lower entering of proteins into the organism,
- disorder of protein digestion and suction,
- increased loss of proteins,
- increased disintegration of proteins,
- decreased protein synthesis.

Defectoproteinemia: Paraproteins, pyroglobulins, cryoglobulins may appear in blood serum in pathologic conditions.

Paraproteins are pathological monoclonal immunoglobulins which are distinguished from normal immunoglobulins by physical chemical properties, antigenic structure, activity and other signs.

Paraprotein appearance in blood takes place in plasma cell neoplasms. Plasma cell neoplasms are B-lymphocyte system tumors. B-lymphocyte differentiates up to stage of monoclonal immunoglobulin secretion. To plasma cell neoplasm we refer: multiple myeloma, solitary myeloma, Woldenström Macroglobulinemia, plasmoblastic leukemia, lymphoma with paraproteinemia).

Pyroglobulins are globulins undergone coagulation in case of heating up to 56°C. They are revealed in sarcoidosis, syphilis, systemic lupus erythematosus.

Cryoglobulins are globulins sedimented in cooling and then dissolve in heating up to 37°C. They are revealed in cirrhosis, autoimmune diseases, idiopathic cryoglobulinemia.

Dysproteinemia – disbalance between different fraction of serum proteins (albumin/ α -globulin/ β -globulin).

Disorder of nitrogen balance

Nitrogen balance is the integral index of protein balance.

Positive nitrous balance reflects the intensification of protein synthesis (predominance of protein anabolism above catabolism).

1. At normal conditions:

- Growth
- pregnancy
- Intensive regeneration
- lactation, pregnancy

2. Pathology:

- polycythemia
- large benign tumors
- Some malignant tumors
- hypersecretion of growth hormone
- treatment with anabolic hormones (somatotrophic, androgens)

Negative nitrogen balance reflects the intensification of protein disintegration (catabolism) or their loss:

- starvation
- infection, protein loss with urine (proteinuria in renal pathology)
- malnutrition
- diabetes mellitus type 1
- hypercortisolism
- lack of any essential amino acids
- extreme conditions, stress
- burns
- diarrhea
- thyreotoxicosis,
- treatment by thyroxin, cortisole
- fever

Violations of the final stages of protein metabolism

The final stages of protein and nucleic acid metabolism lead to the formation of excreted from the body of nitrogenous compounds - ammonia, urea, uric acid, creatinine, indican. The main indicator of excretion and formation of nitrogenous products is the level of residual nitrogen, which normally ranges from 14.3 to 28.6 mmol / L and 50% consists of urea nitrogen; the other 50% is residual (non-urea) nitrogen which is part of the amino acids (25%), ammonia and other nitrogenous compounds.

Disorder of urea synthesis

Ammonia is produced in all tissues as a result of aminoacids metabolism. Ammonia is toxic, its accumulation causes damage of cellular cytoplasm. For its binding and neutralization two mechanisms exist – urea is formed from ammonia in the liver, in other tissues ammonia bind to glutamine acid and glutamine is formed. Further, glutamine rebound ammonia for synthesis of new aminoacids, which transformation is completed by urea formation, which excreted with urine.

Under the pathological conditions ammonia neutralization and elimination from organism is failed. Hepatic and renal insufficiency lead to such disorder. Increase of residual nitrogen in the blood – hyperazotemia – may be a result of disordered urea synthesis in the liver (production hyperazotemia) or secretory function of kidneys (retention hyperazotemia). These events are the important components of hepatic and uremic coma pathogenesis.

Activity of the enzyme of urea synthesis is disordered in hepatic diseases (hepatitis, cirrhosis), hypoproteinemia, inhibition of oxidizing phosphorylation as well as due to genetic reasons. In such cases ammonia is accumulated in tissues and blood, and intoxication develops.

Cells of nervous system are the most sensitive to ammonia. Together with direct damaging effect of ammonia on nervous cells, ammonia is bounded with glutamine acid which thus gets excluded from metabolism. In accelerated transamination of aminoacids with alpha-ketoglutaric acid the latter does not include into Krebs cycle. Oxygen consumption gets decreased. Oxidation of pyruvic and acetic acid gets

limited. Inhibition of Krebs cycle leads to inhibition of acetyl-CoA utilization, which causes comatous state transforming into ketone bodies.

Disorders are manifested as dystrophic changes in the liver, hypoxia. They may be as genetically determined defect (disorder of enzymes of synthesis).

Hyperazotemia

- **production hyperazotemia** - in violation of the urea synthesis its number in blood and urine decreases and increases the content of residual nitrogen. Excess of ammonia can be eliminated a certain extent by the increased formation of glutamine and joining the α -ketoglutaric acid, which is thus converted into glutamic and its oxidation in the TCA cycle is significantly reduced. This reduces the formation of ATP.
- **retention hyperazotemia** - with impaired renal excretory function or impaired passing of the urinary tract. The concentration of residual nitrogen in the blood rises to 140-215 mmol / l, and the content of non-protein nitrogenous products in urine decreased. The retention hyperazotemia is one of the factors that play a role in the development of uremic coma.
- **mixed (combined) hyperazotemia** - a combination of increased protein degradation in tissues with inadequate excretion of nitrogenous products with urine. This combination possible at acute renal failure, which developed on the basis of septic abortion, or the extensive compression of tissues (crush syndrome). By the combined form hyperazotemia refers hypochlorinemic hyperazotemia arising in uncontrollable vomiting, pyloric stenosis, and profuse diarrhea.

Protein glycosylation

This refers to the process by which glucose chemically attaches to the amino group of proteins, without the aid of enzymes. Glucose forms chemically reversible glycosylation products with protein (named Schiff bases) that may rearrange to form more stable Amadori type early glycosylation products, which are also chemically reversible. The degree of enzymatic glycosylation is directly related to the level of blood glucose. Indeed, the measurement of glycosylated hemoglobin (HbA_{1c}) levels in blood is a useful adjunct in the management of diabetes mellitus.

Also you have to pay attention to that fact that hyperglycemia causes nonenzymatic covalent glycosylation not only of short-lived, but also of long-lived proteins and enzymes participating in viable physiologic functions of organism. Non-enzymatic glycosylation result in these protein functioning impairment. Pathophysiological presentations of protein glycosylation are specified in table 1.

Protein	Pathological physiology presentations
Proteins of erythrocyte membrane	Erythrocyte deformation
The clotting system proteins	The blood clotting impairment
Protein of endothelial cellular membrane	Vascular permeability impairment
Proteins of lens and its capsule	Eye-sight impairment
Proteins of glomerula base membrane	Glomerula pathology
Collagen	Wound scarring impairment
Myelin	CNS pathology
Appoproteins Lipoproteins of low-density	Impaired binding of low-density proteins with receptors
Appoproteins Lipoproteins of high-density	Increased elimination from blood

So the early glycosylation products on collagen and other long-lived proteins in interstitial tissue and blood vessel walls, rather than dissociation, undergo a slow series of chemical rearrangements to form irreversible advanced glycosylation end products, which accumulate over the life time of the vessel wall. Advanced glycosylation end products have a number of chemical and biologic properties that are potentially pathogenic.

Excess taking of proteins

- Clinical manifestations of protein excess taking are not noted

- Excess taking of proteins in case of adequate amount of water absence may result in protein fever
- Protein intoxication may be observed in children with liver diseases
- In treatment of children with marasmus by high-caloric diet may cause hyperammonemia

Starvation

Starvation is a pathologic condition characterized by energy and body weight deficiency in organs and cell elements. Starvation develops in malnutrition and increased metabolic processes.

Types of starvation

I. Exogenous

- a. Absolute – complete absence of food and water
- b. Complete – absence of food, but present of water
- c. Incomplete – caloric capacity of food less than energy expense
- d. Partial – caloric capacity of food equals energy expense, absent of single amino acids, vitamins etc.

II. Endogenous

- a. increased
- b. stress

III. Alimenterotherapy

In present day incomplete and partial starvation is often met. Absolute and complete starvation is often met. Absolute and complete starvation mechanisms of impairment and staging of processes arising in organism in food absence are observed.

Exogenous starvation

In physiologic adaptation to this type of starvation staging of metabolic changes occurs. In the process of starvation change of the main energy sources take place.

Pathogenic periods of complete starvation:

First period (initial) device (1-2 days) - the body needs energy consumption is provided by reserve carbohydrates (respiratory quotient (RQ) = 1); ↓ tissue protein biosynthesis, ↓ intensity of des- and transamination of amino acids in the liver, ↓ formation of citrulline and arginine, respectively ↓ formation of urea and uric acid. Develops negative nitrogen balance.

Second period (steady-state) - a period of relatively uniform consumption of self-proteins, energy substrates and the organism's adaptation to life during starvation (up to 70 days) - mainly a lipids are oxidated (RQ = 0.7); ↓ basal metabolism, negative nitrogen balance, ↑ conjugation of oxidative phosphorylation. Economy of energy exchange during starvation is achieved due to the decay of mitochondries. There ↓ mass of various organs (adipose tissue, spleen, testes). 6-8 day starvation occurs spontaneous secretion of digestive glands. In the blood develops hypoproteinemia, which contributes to the development of starvation edema. Reduced immune defenses of the body.

Third period (terminal) in 45-50 % loss of body weight, last 3-5 days ending coma and death. Characterized by a progressive increase in breakdown of proteins of vital organs. Death occurs from intoxication and lack of nutrients in the body.

Conditions affecting life expectancy during starvation:

1. sex
2. age (children < older)
3. general state (reactivity, neuro- humoral regulation)
4. reserve of proteins and fats
5. metabolic rate

Stages of compensatory changes in organ and tissues of man in complete starvation

Organ	In 2-72 hours from the beginning of complete starvation	After 72 hours from the beginning of complete starvation
Brain	Biologic oxidation as a source of glucose	Biologic oxidation of not only glucose, but also ketone bodies
Liver	Amino acids, free fat acids consumption by hepatocytes, gluconeogenesis, ketogenesis, glycogenolysis. Release of glucose and ketone bodies by hepatocytes	Intensive gluconeogenesis and ketogenesis in nearly complete stop of glycogenolysis
Adipocytes of fat tissue	Lipolysis, i.e. split of triglycerides up to glyceride and free fat acids	Lipolysis
Skeletal muscles	Biological oxidation of free fat acids and ketonic bodies in myocytes and amino acid release	Oxidation of free fat acids. Proteolysis and amino Acid release

Adaptation to complete starvation consists of consecutive use of energy reserves of organism. Energy substrate of “the first turn” is triglyceride of fat tissue and glycogen. In physical adaptation to starvation the main source of free energy is triglycerides (in men with normal body weight 80% of all energy reserves in triglycerides, in men with adiposity up to 95%). Triglycerides are the high-concentrated reserve of metabolic energy. In complete oxidation of fat acid the output quantity is 9 large caloric/g, carbohydrates and proteins – 4 large caloric/g. It is explained by the following state: fat acid are much more deoxidized compounds, they possess strongly expressed nonpolarity and are reserved in almost dehydrated form (carbohydrates and proteins are more polar and more high-hydrate).

Kwashiorkor

Kwashiorkor is a disease caused by the deficiency of protein. It suffers mainly the children under five years of age. The children lack enough protein after stopping breastfeeding as a result of next birth. Then, they will be malnourished in the lack of breast milk because breast milk contains enough and high quality protein. The patients are suffered from loss of appetite, swelling and diarrhea.

Symptoms

Swelling (edema) of body due to retention of water. It starts from feet to head. But the skin of hip and legs are wrinkled.

Retardation of physical growth and underweight.

Skin cracks, descaling and wound.

Different skin color. In some places, it is dark whereas in some place, it is light.

Preventive measure

Increase community awareness on nutrition. Identify the patients and support for the treatment of them.

Support for the treatment of them.

In order to increase protein in the body, provide the food like milk, fish, meat, egg, beans (soyabean, gram, pea etc.) which are rich in protein.

Physical check up and measurement of height and weight regularly.

Provide nutrition and healthy education to parents.

Provide local food and seasonal fruits instead of expensive instant food with low nutritive value.

Alimentary marasmus

Marasmus is a protein-energy malnutrition. It causes children lean and thin because of the lack of enough food and essential nutrients (both carbohydrates and protein) for a long time. This disease mainly suffers the children. The skin of children wrinkles due to the loss of fat. Average weight of children becomes 60 percent less than other healthy children of similar age.

Symptoms

Getting lean and thin

Faces wrinkle like old person

Low weight for age (underweight)

Regular reduction in fat and muscle

Suffering from diarrhea

Not interested on food despite the hunger.

Preventive measure:

Increase community awareness on nutrition. Identify the patients and support for the treatment of them.

Support for the treatment of them.

In order to increase protein in the body, provide the food like milk, fish, meat, egg, beans (soyabean, gram, pea etc.) which are rich in protein.

Physical check up and measurement of height and weight regularly.

Provide nutrition and healthy education to parents.

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Purine and Pyrimidine Metabolism

Overview

One of the important specialized pathways of a number of amino acids is the synthesis of purine and pyrimidine nucleotides. These nucleotides are important for a number of reasons. Most of them, not just ATP, are the sources of energy that drive most of our reactions. ATP is the most commonly used source but GTP is used in protein synthesis as well as a few other reactions. UTP is the source of energy for activating glucose and galactose. CTP is an energy source in lipid metabolism. AMP is part of the structure of some of the coenzymes like NAD and Coenzyme A. And, of course, the nucleotides are part of nucleic acids. Neither the bases nor the nucleotides are required dietary components. We can both synthesize them de novo and salvage and reuse those we already have.

Nitrogen Bases

There are two kinds of nitrogen-containing bases - purines and pyrimidines. **Purines** consist of a six-membered and a five-membered nitrogen-containing ring, fused together. **Pyrimidines** have only a six-membered nitrogen-containing ring. There are 4 purines and 4 pyrimidines that are of concern to us.

Purines

- Adenine = 6-amino purine
- Guanine = 2-amino-6-oxy purine
- Hypoxanthine = 6-oxy purine
- Xanthine = 2,6-dioxy purine

Adenine and guanine are found in both DNA and RNA. Hypoxanthine and xanthine are not incorporated into the nucleic acids as they are being synthesized but are important intermediates in the synthesis and degradation of the purine nucleotides.

Pyrimidines

- Uracil = 2,4-dioxy pyrimidine
- Thymine = 2,4-dioxy-5-methyl pyrimidine
- Cytosine = 2-oxy-4-amino pyrimidine
- Orotic acid = 2,4-dioxy-6-carboxy pyrimidine

Cytosine is found in both DNA and RNA. Uracil is found only in RNA. Thymine is normally found in DNA. Sometimes tRNA will contain some thymine as well as uracil.

Purine Catabolism

The end product of purine catabolism in man is **uric acid**. Other mammals have the enzyme urate oxidase and excrete the more soluble allantoin as the end product. Man does not have this enzyme so urate is the end product for us. Uric acid is formed primarily in the liver and excreted by the kidney into the urine.

Pyrimidine Catabolism

In contrast to purines, pyrimidines undergo ring cleavage and the usual end products of catabolism are beta-amino acids plus ammonia and carbon dioxide. Pyrimidines from nucleic acids or the energy pool are acted upon by nucleotidases and pyrimidine nucleoside phosphorylase to yield the free bases. The 4-amino group of both cytosine and 5-methyl cytosine is released as ammonia.

Gout

Gout is a painful condition that occurs when the bodily waste product uric acid is deposited as needle-like crystals in the joints and/or soft tissues. In the joints, these uric acid crystals cause inflammatory arthritis, which in turn leads to intermittent swelling, redness, heat, pain, and stiffness in the

joints. The normal serum concentration of uric acid 0,12-0,24 mmol/l. Hyperuricemia in gout. In men, the disease occurs when the concentration of blood uric acid level greater than 0.42 mmol/l for women - 0.36 mmol/l.

In many people, gout initially affects the joints of the big toe (a condition called podagra). But many other joints and areas around the joints can be affected in addition to or instead of the big toe. These include the insteps, ankles, heels, knees, wrists, fingers, and elbows. Chalky deposits of uric acid, also known as tophi, can appear as lumps under the skin that surrounds the joints and covers the rim of the ear. Uric acid crystals can also collect in the kidneys and cause kidney stones.

Uric acid is a substance that results from the breakdown of purines. A normal part of all human tissue, purines are found in many foods. Normally, uric acid is dissolved in the blood and passed through the kidneys into the urine, where it is eliminated.

There are two forms of the disease.

- primary gout
- secondary gout

Primary or idiopathic gout is a genetically determined disease. The structure of genes responsible for the synthesis of enzymes involved in the metabolism of purines has been disrupted. In some patients, a decrease in the activity of hypoxanthine phosphoribosyltransferase (Lesch-Naikhan syndrome), adenine phosphoribosyl pyrophosphate synthetase, glucose-6-phosphatase, an increase in the activity of 5-phosphoribosyl-1-synthetase is registered. Such disorders are accompanied by excessive synthesis of uric acid. Genetic defects are linked to the X chromosome, so almost exclusively men are prone to gout.

Secondary gout arises as a concomitant pathology in diseases accompanied by intensive decay of nucleic acids or impaired urate excretion through the kidneys. These diseases include diabetes mellitus, hemoblastosis and other disseminated tumors, hemolytic anemia, psoriasis, sarcoidosis, chronic renal failure, etc. Secondary gout may appear in patients taking long-term medications - euphyllin, caffeine, dimedrol, aspirin, saluretics, cytotoxic drugs, corticosteroids, vitamin B12, etc., when lead salts are poisoned.

A number of risk factors are associated with hyperuricemia and gout. They include:

- **Alcohol consumption.** Drinking too much alcohol can lead to hyperuricemia, because alcohol interferes with the removal of uric acid from the body.
- **Diet.** Eating too many foods that are rich in purines can cause or aggravate gout in some people. (High-Purine Foods)
- **Lead exposure.** In some cases, exposure to lead in the environment can cause gout.
- **Other health problems.** Renal insufficiency, or the inability of the kidneys to eliminate waste products, is a common cause of gout in older people. Other medical problems that contribute to high blood levels of uric acid include:
 - high blood pressure
 - hypothyroidism (underactive thyroid gland)
 - conditions that cause an excessively rapid turnover of cells, such as psoriasis, hemolytic anemia, or some cancers
 - Kelley-Seegmiller syndrome or Lesch-Nyhan syndrome, two rare conditions in which the enzyme that helps control uric acid levels either is not present or is found in insufficient quantities.
- **Medications.** A number of medications may put people at risk for developing hyperuricemia and gout. They include:
 - **Diuretics**, which are taken to eliminate excess fluid from the body in conditions like hypertension, edema, and heart disease, and which decrease the amount of uric acid passed in the urine
 - **Salicylate-containing drugs**, such as aspirin
 - **Niacin**, a vitamin also known as nicotinic acid
 - **Cyclosporine**, a medication that suppresses the body's immune system (the system that protects the body from infection and disease). This medication is used in the treatment of some autoimmune diseases, and to prevent the body's rejection of transplanted organs.
 - **Levodopa**, a medicine used to support communication along nerve pathways in the treatment of Parkinson's disease.

If there is diminished filtration and decreased excretion and/or overproduction of uric acid, the levels can rise in the body. This causes hyperuricemia – increased uric acid and urates in the blood and tissue fluids.

Once the uric acid levels become very high, it may precipitate and form crystals that are jagged. This occurs in the tissue of the joint and within the synovial fluid in the joint space. The reason why this is more likely to occur in the synovial fluid is that this fluid is a poor solvent for uric acid compared to blood plasma. It is therefore more likely to become supersaturated and for crystal precipitation to occur. However, uric acid crystals can occur in these sites yet not lead to joint inflammation and pain. This may be explained by the coating around the uric acid crystals that prevents it from binding to surrounding cells and irritating the tissue. When these crystal are uncoated, it may irritate the tissue and become phagocytosed by macrophages and lead to a series of reactions that facilitate inflammation at the site.

Gout can progress through four stages:

1. **Asymptomatic (without symptoms) hyperuricemia.** In this stage, a person has elevated levels of uric acid in the blood (hyperuricemia), but no other symptoms. Treatment is usually not required.
2. **Acute gout, or acute gouty arthritis.** In this stage, hyperuricemia has caused the deposit of uric acid crystals in joint spaces. This leads to a sudden onset of intense pain and swelling in the joints, which also may be warm and very tender. An acute attack commonly occurs at night and can be triggered by stressful events, alcohol or drugs, or the presence of another illness. Attacks usually subside within 3 to 10 days, even without treatment, and the next attack may not occur for months or even years. Over time, however, attacks can last longer and occur more frequently.
3. **Interval or intercritical gout.** This is the period between acute attacks. In this stage, a person does not have any symptoms.
4. **Chronic tophaceous gout.** This is the most disabling stage of gout. It usually develops over a long period, such as 10 years. In this stage, the disease may have caused permanent damage to the affected joints and sometimes to the kidneys. With proper treatment, most people with gout do not progress to this advanced stage.

Three versions of gout:

- Metabolic. By high intensity of synthesis in the body of uric acid (greater than 3.6 mmol / day).
- Kidney. There is a decrease in excretion of uric acid (daily uraturia least 1.8 mmol).
- Mixed version. Determined in patients with increased synthesis of uric acid combined with reduced excretion of urate.

Orotic aciduria

Orotic aciduria refers to an excessive excretion of orotic acid in urine. In addition to the characteristic excessive orotic acid in the urine, patients typically have megaloblastic anemia which cannot be cured by administration of vitamin B12 or folic acid.

It also can cause inhibition of RNA and DNA synthesis and failure to thrive. This can lead to mental and physical retardation.

Its hereditary form, an autosomal recessive disorder, can be caused by a deficiency in the enzyme **UMPS (Uridine monophosphate synthetase)**, a bifunctional protein that includes the enzyme activities of orotate phosphoribosyltransferase and orotidine 5'-phosphate decarboxylase.

It can also arise secondary to blockage of the urea cycle, particularly in ornithine transcarbamylase deficiency (or OTC deficiency).

Reasons of hypovitaminosis

I Alimentary vitamin deficiency:

1. the low content of vitamins in the daily diet
2. destruction of vitamins because of their long and improper storage and cooking
3. effect of antivitamins in food
4. the imbalance of the chemical composition of diets and violation of optimal balance between vitamins;
5. food perversion and religious prohibitions imposed on the number of products in some races.

6. anorexia.

II. Inhibition of the normal intestinal microflora, producing a number of vitamins:

1. Disorders of the gastrointestinal tract
2. Irrational chemotherapy

III. Violations of the assimilation of vitamins:

1. Malabsorption of vitamins in GIT:

- stomach diseases;
- bowel diseases;
- the failure of the hepatobiliary system;
- competes with the absorption of other vitamins and nutrients;
- congenital defects of transport and enzyme mechanisms of vitamins absorption;
- abuse of laxatives.

2. Utilization of dietary vitamin with intestinal parasites and pathogenic intestinal microflora.

3. Disturbance of the normal metabolism and formation of biologically active forms of vitamin:

- genetic abnormalities;
- acquired diseases, the effect of toxic and infectious agents.

4. Violation of formation of transport forms of vitamins.

5. Antivitamins action of drugs.

IV. The increased need for vitamins:

1. Special physiological condition of the body (intensive growth, pregnancy, lactation);
2. Intense exercise;
3. A significant neuropsychiatric load stress conditions;
4. Infectious diseases and intoxication;
5. Diseases of internal organs and endocrine glands (diabetes, thyroid disease);
6. Smoking, drinking alcohol;
7. Specific climatic and environmental conditions;
8. Increased excretion of vitamins.

There are 3 stages of vitamin deficiency:

Stage I – prehypovitaminosis (subnormal supply of vitamins) - manifested nonspecific general changes some functions of internal organs, reducing the overall tone, body resistance, serviceability.

Stage II - hypovitaminosis - is the result of a relative deficiency of vitamin. Characterized by overt clinical manifestations, depending on the predominant deficiency of concrete vitamin.

Stage III - avitaminosis. Manifested the characteristic significant clinical picture

VITAMIN A

Fat soluble

Functions

- Vision: integrity of eye & formation of rodopsin necessary for dark adaptation
- essential for the correct functioning of epithelial cells, glycoprotein synthesis
- Regulation of gene expression: vital to cell differentiation & physiologic processes
- needed for normal haemopoiesis, immunity: important for activation of T lymphocyte, maturation of WBC & integrity of physiological barrier
- Production of human growth hormone

Sources

- Retinyl esters derived from animal sources (liver, milk products, eggs, fish oils)
- Provitamin A carotenoids (B-carotene) in leafy green and yellow vegetables

Cooking, canning and freezing results in only small losses

Zinc deficiency interfere with vitamin A metabolism

Deficiency

- Night blindness & xerophthalmia
- Growth retardation

- Acquired immune deficiency
- Keratinization of epithelia in RT, GIT and UT with increased risk of malabsorption, infections of RT and UT.

Hypervitaminosis

Clinical manifestations include anorexia, painful bones/joints, alopecia; increased intracranial pressure, vomiting, headaches, papilledema (pseudotumor cerebri) and neuropsychiatric symptoms

Symptoms develop over several weeks to months

VITAMIN D (vitamin D2 – ergocalciferol, vitamin D3 – cholecalciferol)

Fat soluble

Functions

Calcitriol promotes bone mineralization, absorption of calcium, phosphates in intestine and reabsorption in kidney. It also promotes bone collagen synthesis.

Sources

Sunlight exposure

Deficiency

Rickets is characterized by the production of soft pliable bones due to defective mineralization secondary to calcium deficiency. Vit D deficiency is also characterized by low concentration of calcium in blood in association with increased serum alkaline phosphatase.

Hypervitaminosis

Clinical manifestations are secondary to hypercalcemia and include hypotonia, irritability, constipation, polydipsia, polyuria; hypercaliuria & kidney stones may develop; osteopetrosis on radiographs

VITAMIN E (tocopherol)

Fat soluble

Functions

- Antioxidant properties (protects against oxygen free radical damage to cellular membranes)
- Essential for maintenance of the nervous system, retina and skeletal muscle
- Helps to prevent atherosclerosis by inhibiting oxidation of LDL and inhibits platelet activity

Sources

The richest source is vegetable oils and nuts. Green plants, milk and eggs

Deficiency

Muscle weakness, double vision, loss of position sense, ataxia, hyporeflexia, and hemolytic anemia (premature infants)

Hypervitaminosis

Not clear yet

- increased bleeding, decreased activity of vitamin K
- weakness
- myalgia

VITAMIN K

Fat soluble

Functions

Essential for synthesis of prothrombin and coagulation factors II, VII, IX and X, proteins C and S.

Sources

- from intestinal bacteria (intestinal flora produces adequate amounts (except in neonates))
- leafy vegetables, soybean oils, fruits, seeds and milk

Deficiency

Hemorrhagic disease, especial in newborn — spontaneous bleeding usually from GIT, nasal, intracranial, umbilical

Hypervitaminosis

GIT disorders, increased coagulation, anemia

VITAMIN B1 (thiamine)

Water soluble

Functions

Thiamine functions in all cells as the coenzyme cocarboxylase, thiamine pyrophosphate, which participates in the oxidative decarboxylation of pyruvic acid to acetate for entry into the tricarboxylic acid (TCA) cycle. Thiamine pyrophosphate is also a coenzyme in direct oxidation of glucose occurs in the cytoplasm of cells via the pentose phosphate pathway.

Thiamine is essential for good appetite, normal digestion, growth and fertility. It is needed for normal functioning of the nervous tissue and the requirement is determined by the caloric density of the diet.

Sources

Seeds, nuts, wheat, leguminous plants (rich source) and lean meat

Deficiency

- Beriberi (irritability, peripheral neuritis, ataxia, hyporeflexia, congestive cardiac failure and low plasma albumin)

Hypervitaminosis

Injection of more than 100 mg of thiamine parenterally possible inhibits of the enzyme cholinesterase and histaminase, which is manifested by muscle relaxant effects and allergic reactions, the patients have tremors, restlessness, sweating, shortness of breath, decreased blood pressure, the body of an itchy rash appears.

VITAMIN B2 (riboflavin)

Water soluble

Functions

- component of the flavin coenzymes, FAD and FMN
- mainly used in the energy metabolism of sugars and lipids

Sources

Meats, Nuts, Legumes, Milk, fish, egg etc

Deficiency

- photophobia, keratitis
- inflammation of the corner of mouth (angular stomatitis), cheilosis
- painful glossitis of tongue
- scaly dermatitis

Hypervitaminosis

Almost does not occur, excessive administration as can sometimes occur itching, numbness or a slight burning sensation, but it passes quickly.

VITAMIN B3 (nicotinic acid, niacin, nicotinamide, vitamin PP)

Water soluble

Functions

essential for NAD/NADPH

Sources

- can be synthesized from tryptophan
- milk, lean meat, unrefined grains, cereals, legumes, coffee & tea

Deficiency

- pellagra (dermatitis, diarrhea, dementia)
- burning sensations, numbness, dizziness, gingivitis, stomatitis, failure of growth, loss of weight and anemia

Hypervitaminosis

Redness of the skin is due to increase of blood pressure in the vessels of the skin (subcutaneous expansion of larger vessels on the face and other body parts), nausea, diarrhea, impaired liver function, low blood cholesterol levels.

VITAMIN B5 (Pantothenic acid, coenzyme a)

Water soluble

Functions

Part of CoA. Necessary for breaking down carbohydrates, proteins, and fats.

Sources

- Plants: yeast, whole grain cereals, legumes
- Animals: eggs, liver, animal tissue

Deficiency

- allergies (e.g. stuffed or runny nose)
- adrenal insufficiency (Addison's disease)
- rheumatoid arthritis
- dermatitis, enteritis, alopecia

Hypervitaminosis

Because of the low toxicity of vitamin B5 clinical signs of hypervitaminosis are very rare - is nausea, vomiting, or diarrhea.

VITAMIN B6 (pyridoxine)

Water soluble

Functions

- balancing of Na⁺ and K⁺, promoting red blood cell production
- it is linked to cancer immunity and helps fight the formation of homocysteine.
- helps children with learning difficulties
- essential in normal brain metabolism
- may prevent dandruff, eczema, and psoriasis
- helps balance hormonal changes in women

Sources

- Plants: yeast, whole grain cereals
- Animals: liver

Deficiency

- pyridoxine-dependent infantile seizures
- peripheral neuritis, nerve damage, seizures
- dermatitis and sores in the mouth
- anemia
- pyroluria

Hypervitaminosis

Causes temporary deadening of certain nerves, sensory neuropathy/neuronopathy (proprioceptive nerves) and feeling of disembodiment common with the loss of proprioception. Sensory loss, paresthesias and pain

VITAMIN B7 (biotin or vitamin H)

Water soluble

Functions

Important in the catalysis of essential metabolic reactions to synthesize fatty acids, in gluconeogenesis, and to metabolize leucine.

Sources

- Plants: yeast
- Animals: seafood, liver, kidneys, milk, eggs

Deficiency

- hair loss which progresses in loss of eye lashes and eye brows.
- dry skin, seborrheic dermatitis, fungal infections.
- changes in mental status, depression, generalized muscular pains (myalgias), hyperesthesias and paresthesias

Hypervitaminosis

Cases hypervitaminosis B7 or any adverse effects of large doses of biotin in medical practice is not described.

VITAMIN B9 (folic acid, vitamin M)

Water soluble

Functions

Production and maintenance of new cells (especially during infancy and pregnancy), necessary for replicating DNA and synthesizing RNA. Both adults and children need folate to make normal red blood cells and prevent anemia.

Sources

The vitamin is abundant in leafy green vegetables such as spinach, so is named folic acid, from the same root as foliage, whole grain cereals and liver.

Deficiency

There may be also an **inhibition in DNA synthesis** due to decrease availability of purines and dTMP. This leads to arrest cells in S-phase. Inadequate folate levels during the early stages of **pregnancy increases the risk of neural tube defects (a type of birth defect) and spontaneous abortions.**

Megaloblastic anemia, diarrhea, loss of appetite, weight loss, weakness, sore tongue, headaches, heart palpitations, irritability, and behavioral disorders.

Hypervitaminosis

The first symptoms of hypervitaminosis are digestive disorders and irritability. Without treatment may develop severe kidney disease.

VITAMIN B12 (cobalamin)

Water soluble. Cyanocobalamin is the active form

Functions

coenzyme in metabolism of aminoacids, stimulates erythropoiesis

Sources

Synthesized by Microorganisms

Plants: breakfast cereals (only source for vegetarians)

Animals: Liver, shellfish, eggs, milk

Deficiency

- **Megaloblastic anemia**
- **Pernicious anemia** — autoimmune anemia (antibodies are directed against intrinsic factor).

Intrinsic factor is required for vitamin B12 absorption, so impaired absorption of vitamin B12 can result. The term pernicious anemia is sometimes used more loosely to include non-autoimmune causes of vitamin B12 deficiency. Clinical manifestation: severe **neurologic abnormalities** (demyelination of peripheral nerves, ataxia, hyporeflexia, coma), **macrocytic megaloblastic anemia, atrophy of intestinal cilia** (malabsorption in terminal ileum, diarrhea)

Hypervitaminosis

Hypervitaminosis may cause pulmonary edema, cardiac failure, thrombosis, and even anaphylactic shock. The first symptoms of hypervitaminosis B12 are irritability, palpitations, heart pain and urticaria.

VITAMIN P (bioflavonoids)

Water soluble

Functions

- cofactor of enzymes that are involved in carboxylation reactions (e.g. acetylCoA carboxylase, pyruvate carboxylase) helps to transfer carbon dioxide CO₂
- key role in the metabolism of lipids, proteins and carbohydrates
- it activates protein/amino acid metabolism in the hair roots and fingernail cells - the “beauty vitamin” - often recommended for strengthening hair and nails.
- role in DNA replication and transcription arising from its interaction with nuclear histone proteins

Sources

- synthesized by intestinal bacteria
- liver, egg yolk, nuts, seeds, soya

Deficiency

- hair loss,
- depression, halucination,
- muscle pain,
- dermatitis

Hypervitaminosis

Thrombosis, hypercoagulation

VITAMIN C (ascorbic acid)

Water soluble

Functions

- antioxidant
- is needed for the production of collagen in the connective tissue, bone and capillary formation
- required for synthesis of dopamine, noradrenaline and adrenaline in the nervous system or in the adrenal glands
- is needed to synthesize carnitine, important in the transfer of energy to the cell mitochondria

Sources

Citrus fruits, tomatoes, spinach and other green vegetables

Cooking has a destructive effect

Deficiency

- Fever, diarrhea
- Petechial hemorrhage
- Defective tooth dentin loosening of teeth
- Irritability with generalized tenderness
- "pseudoparalysis" (legs held in frog-like position)
- Edematous swelling along shafts of legs
- Bluish-purple swellings of mucous membranes (esp. by upper incisors)
- "rosary" of costochondral junctions; depression of sternum
- Scurvy (weakening of collagen fibers caused by the failure to hydroxylate proline and lysine)

Hypervitaminosis

May reduce capillary permeability, poor vision, anxiety, distortion of the kidney and pancreas, insomnia, delayed menstrual cycle in women, the emergence of various pathologies during pregnancy and even miscarriage.

In addition, there may be irreversible changes in the heart and adrenal atrophy.

It is proved that even with a slight but regular dosage is exceeded, the human body can be extremely sensitive, which in the future can cause acute avitaminosis C, even with minor shortages.

Antivitamins

Antivitamins - are compounds that partially or completely turn off the vitamins from the metabolic reactions of the body by means of their destruction or inactivation of the obstacles to their assimilation.

The main mechanisms of action antivitamin:

1. The blockade of intracellular metabolism of vitamin;
2. Destruction of vitamins;
3. The modification of the molecule of vitamin;
4. Blockade of receptor cells for vitamins.

The list of antivitamin:

1. For vitamin B1 (thiamine) - thiaminase I and II, pyrithiamine, neopyrithiamine
2. For vitamin B2 (riboflavin) - isoriboflavin, galaktoflavin, toxoflavin, quinacrine, chloramphenicol, terramycin, tetracycline
3. For vitamin B6 (pyridoxine) - isoniazid, cycloserine, toxopirimidin, 4desoxypyridoxine
4. For vitamin B12 (cyanocobalamin) - 2-amino-methylpropanol B12
5. For vitamin PP (nicotinic acid) - isoniazid, 3-acetylpirin
6. For folic acid - aminopterin, ametopterin

7. For vitamin C - askorbinaza , glucoascorbic acid
8. For vitamin H (biotin) - ovidin (protein from bird eggs) , destiobiotin
9. For vitamin K (phyloquinone) - coumarin bishydroxycoumarin (reduces the synthesis of prothrombin liver)
10. For vitamin E (tocopherol) - 3 - phenyl phosphate , 3 - orthocresolphosphate

Questions for self-control of knowledge:

1. What is the role of proteins in the body?
2. In what pathological conditions is violated absorption of amino acids?
3. What are the main causes of protein synthesis in body.
4. What are the reasons for increase protein catabolism in body.
5. Describe the factors affecting nitrogen balance.
6. What mechanisms are in the development of product and retention hyperasotemia?
7. Describe the changes in body, with full and absolute starvation.
8. Which pathophysiological changes in body are causes in protein-energy malnutrition?
9. What are the mechanisms of disturbances of physiological functions and metabolism in body with a deficit of fat-soluble vitamins?
10. What are the mechanisms of disturbances of physiological functions and metabolism in body with water-soluble vitamin deficiency?
11. Give examples antivitamin. What is their role? Describe the mechanisms of action antivitamin.

Tasks for self-managed student work:

1. Immunological disorders in the body with a deficiency of C-reactive protein.
2. Role of antibodies to nucleic acids in pathology.
3. Gout; etiology, pathogenesis, basic manifestations, diagnostic criteria.
4. Hypervitaminosis: causes, mechanisms of violations of physiological functions and metabolism, main manifestations.

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