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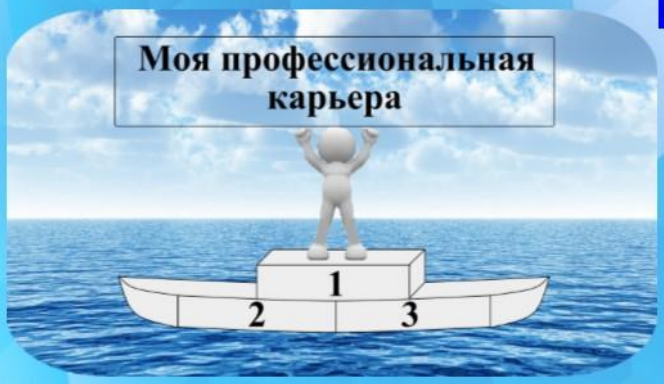

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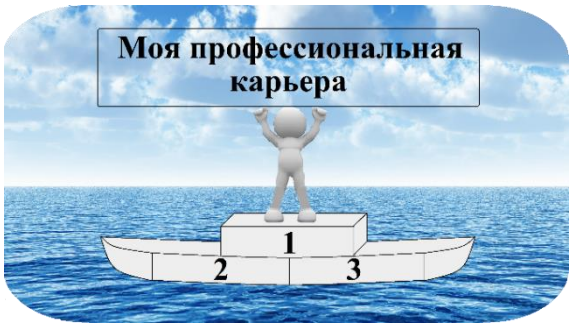

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Международный научно-образовательный электронный журнал «ОБРАЗОВАНИЕ И НАУКА В XXI ВЕКЕ». Выпуск №44-4 (ноябрь, 2023). Дата выхода в свет: 27.11.2023.

Сборник содержит научные статьи отечественных и зарубежных авторов по экономическим, техническим, философским, юридическим и другим наукам.

Миссия научно-образовательного электронного журнала «ОБРАЗОВАНИЕ И НАУКА В XXI ВЕКЕ» состоит в поддержке интереса читателей к оригинальным исследованиям и инновационным подходам в различных тематических направлениях, которые способствуют распространению лучшей отечественной и зарубежной практики в интернет пространстве.

Целевая аудитория журнала охватывает работников сферы образования (воспитателей, педагогов, учителей, руководителей кружков) и школьников, интересующихся вопросами, освещаемыми в журнале.

Материалы публикуются в авторской редакции. За соблюдение законов об интеллектуальной собственности и за содержание статей ответственность несут авторы статей. Мнение редакции может не совпадать с мнением авторов статей. При использовании и заимствовании материалов ссылка на издание обязательна.

РЕДАКЦИОННАЯ КОЛЛЕГИЯ:

СОДЕРЖАНИЕ

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Название публикации: «A LOOK AT THE ETIOPATHOGENETIC MECHANISMS OF THE DEVELOPMENT OF THE GOUT AND HYPERURICEMIA»

Abstract

Today, the symptom of hyperuricemia is detected during the diagnosis of many diseases. But will this symptom be the main one in the validation of gout? Its occurrence occurs by the deposition of uric acid crystals, or urate crystals in the tissues of the joint. A crystal is a foreign body in the body that strengthens the body's defense system to eliminate it and thus a gout attack occurs. Based on etiological data and epidemiological studies, an analysis of the main pathochemical mechanism of gout development is provided. Diagnostic methods for studying biological fluids of the body for the detection of gout are considered.

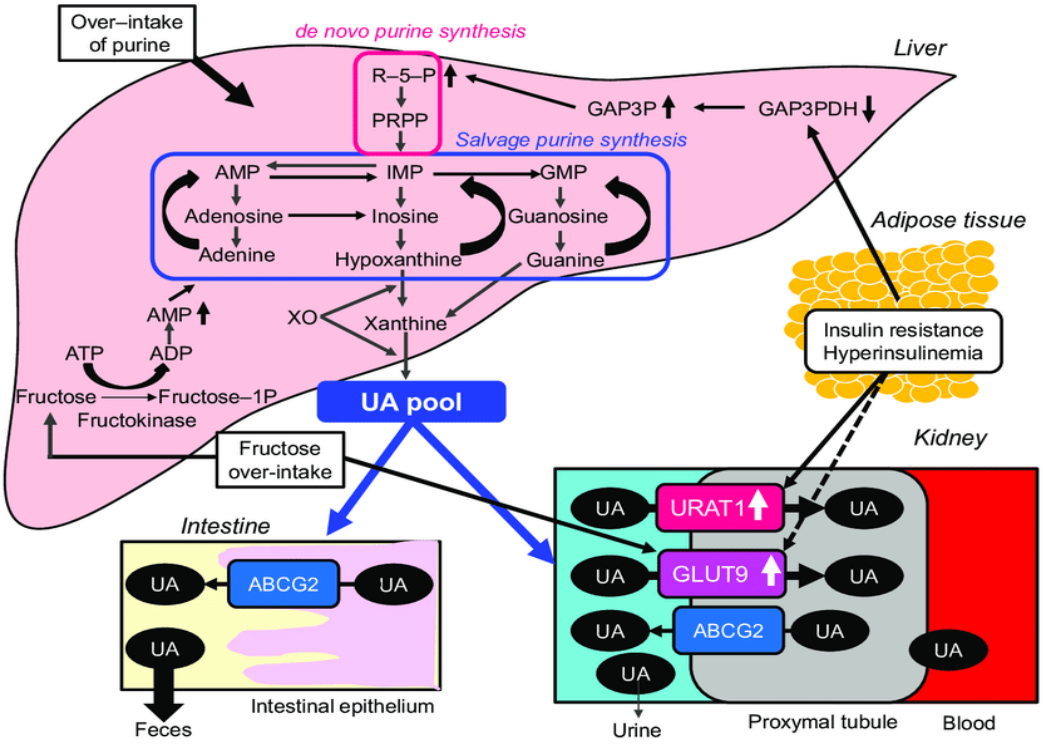
Keywords: *gout, hyperuricemia, uric acid, inflammation, pathogenesis, diagnostics.*

Introduction. In many countries of the world, gout is a significant medical and social problem due to its wide prevalence, affecting mainly middle-aged men. The disease has a progressive course with a correspondingly high complication rate. According to epidemiological studies, there is a true increase in the prevalence of the disease both in countries with a high standard of living, and more recently in regions

where gout was considered a rare disease. Such changes are likely to depend on different values, traditions and patterns of nutrition, which include excessive consumption of meat, fatty foods and the abuse of alcoholic beverages. To date, it is known that the clinical manifestations of gout do not end with an exclusive lesion of the musculoskeletal system and kidneys. The peculiarity of gout lies in the frequent combination with such diseases as arterial hypertension, metabolic syndrome, diabetes mellitus, various renal lesions, which have a high risk of cardiovascular diseases. Gout leads to frequent temporary disability, limitation of professional activity, disability, which makes this disease an urgent health problem and a difficult socio-economic situation for society.

Etiology and mechanisms of development of hyperuricemia At the heart of the development of gout is hyperuricemia. Hyperuricemia is a clinical symptom that is manifested by an increase in the plasma concentration of uric acid in the blood of more than 360 μmol / l, in its excess or metabolic disorder. Most often, hyperuricemia and gout occur due to diseases such as arterial hypertension, heart failure, hypertriglyceridemia, diuretics, alcohol abuse, gene defects [6]. With arterial hypertension, the development process consists in the reabsorption of uric acid in the renal tubules, by increasing the tone of the renal vessels. As a result of vasospasm of the microvasculature, tissue ischemia occurs, which in turn leads to an increase in the formation of uric acid due to increased breakdown of adenosine. At the same time, uric acid secretion occurs in the proximal tubules of the kidneys; uric acid secretion decreases due to a competitive increase in lactate excretion [4]. Insulin resistance can also cause hyperuricemia. Stimulation of insulin reabsorption of sodium in the tubules of the kidneys is associated with the reabsorption of uric acid, due to this, hyperinsulinemia in insulin resistance causes hyperuricemia [2]. The cause of hyperuricemia may be chronic renal failure. Uric acid causes a toxic effect, leading to damage to the renal glomeruli, which is promptly manifested by a decrease in the glomerular filtration rate. Because of this, sodium monourate crystals appear in the renal tissue, forming a latent immune inflammation [11]. The cause of hyperuricemia in heart failure is an increase in xanthine oxidase activity and a decrease in renal blood

flow. The use of loop diuretics in doses that promote natriuresis reduces the volume of circulating blood, which in turn leads to an increase in the reabsorption of urate in the proximal tubules of the nephron. The consequence of this is an increase in the plasma concentration of uric acid up to hyperuricemia [10](pic.1).



Picture 1. Possible molecular mechanisms for the development of hyperuricemia in metabolic syndrome.

ABCG2, ATP-binding cassette, subfamily G, 2; ADP, adenosine diphosphate; AMP, adenosine monophosphate; ATP, adenosine triphosphate; Fructose-1-P, fructose-1-phosphate; GAP3P, glyceraldehyde-3-phosphate; GA3PDH, glyceraldehyde-3-phosphate dehydrogenase; GMP, guanine monophosphate; GLUT9, glucose transporter 9; IMF, inosine monophosphate; PRPP, phosphorus ribosyl pyrophosphate; PRS, phosphorus-ribosyl pyrophosphate synthetase; R-5-P, ribose-5-phosphate; UA, uric acid; URAT1, urate transporter 1; XO, xanthine oxidase.

Taking thiazide diuretics, causing hypokalemia, creates conditions for reducing the reabsorption of uric acid, thereby ensuring an increase in its concentration in plasma [1].Also, the direct cause of the development of hyperuricemia is alcoholism. The mechanism is manifested by an increase in the transformation of purines due to an

increase in the involvement of xanthine oxidase due to the high content of molybdenum, which is its cofactor. Thus, there is a decrease in uric acid excretion due to temporary lactate acidemia caused by excess alcohol.The mechanism of development of hyperuricemia in hypertriglyceridemia is manifested by selective insulin resistance, a decrease in insulin-mediated uptake of glucose, as well as free fatty acids in the cells of the renal tubules in case of preservation of insulin-mediated reabsorption of uric acid [6]. A defect in the gene responsible for the activity of the enzyme provides an effect on both the production of uric acid (hyperproduction) and its transport in the kidneys (hypoexcretion). In 10% of all situations with increased synthesis of uric acid, it refers to congenital disorders of its metabolism. There are primary and secondary hyperuricemia. Primary hyperuricemia occurs due to a genetically mediated defect in the enzymes that make up the metabolism of uric acid. Secondary hyperuricemia occurs against the background of certain diseases, with the abuse of food rich in purines, with the action of toxins and drugs, etc. [12].The intake of foods rich in purine nucleotides can cause an excess of substrate in the body for the synthesis of uric acid. The breakdown of adenosine triphosphate is significantly increased in glucose-galactose malabsorption and alcohol abuse. Also, an extremely high exchange of nucleotides is manifested in lymphoproliferative diseases. All this leads to an increase in the formation of urates.We can conclude that the main causes of hyperuricemia and gout are uric acid overproduction, hypoexcretion, or a combination of these causes.

Gout (literally “foot in a trap”) is a heterogeneous disease by origin, which in turn is characterized by the deposition of sodium monourate crystals in various tissues and manifests itself as crystal-induced inflammation at the sites of urate fixation (internal organs, joints, etc.) or uric acid. At the center of origin lies the accumulation of uric acid and a decrease in its excretion by the kidneys, which can lead to hyperuricemia. From a clinical point of view, gout is characterized by recurrent acute arthritis and the occurrence of tophi. The most common disease occurs in men, but recently there has been a prevalence among women, with age, the frequency of gout

increases. As a treatment, drugs are used that affect the pathogenetic mechanisms of gout [2].

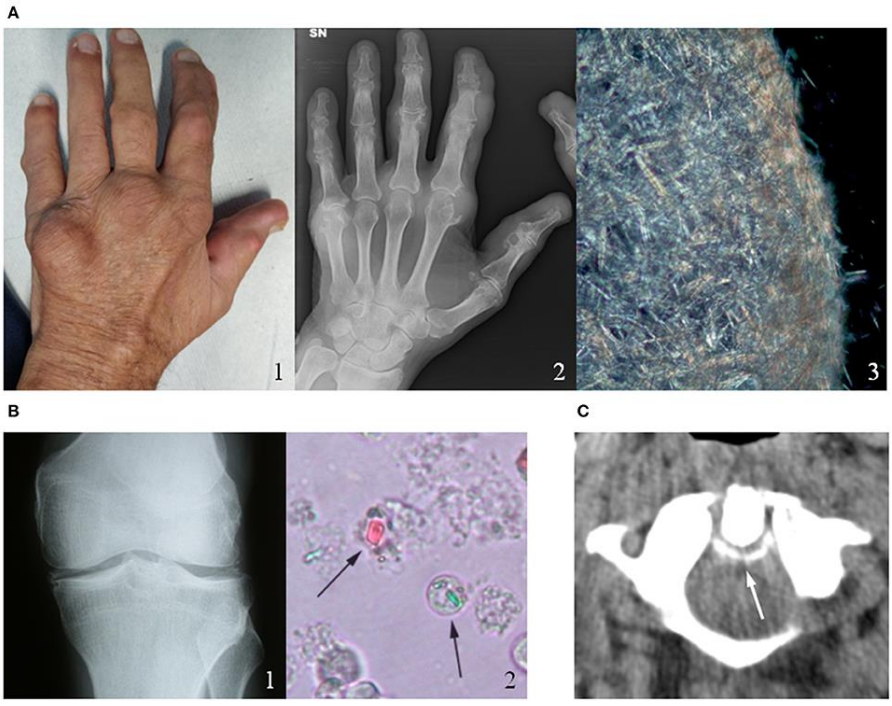
Epidemiology and etiology of gout It is noted that hyperuricemia is established in 4-12% of the population, despite the fact that 0.1% of the population of Russia is susceptible to gout. In Eurasia and America, the incidence of gout is 2% of people; among men over 50–60 years old, 4–6% develop gout [5]. The difference between men and women is from 2:1 to 7:1. The peak incidence in diseased women occurs at the age of 60 years; before menopause, the onset of the disease is very unlikely, because the action of estrogens is directly related to the excretion of uric acid, while in men the peak incidence occurs at 55 years of age [7]. The rate of gouty arthritis in different populations varies and is 5-50 people per 1000 men and 1-9 people per 1000 women; the number of cases per year is 1–3 per 1000 in men and 0.2 per 1000 in women [10]. In adolescents and young adults, an acute attack of gout is rare and is usually caused by a primary or secondary defect in uric acid synthesis.

Risk factors for the development of gout are diverse and include:

1. Numerous defects that are responsible for the activity of enzymes that affect both the synthesis of uric acid (hyperproduction) and its transport in the kidneys (hypoexcretion).
2. Large-scale breakdown of nucleotides from cell nuclei leads to blood diseases, severe psoriasis, sarcoidosis, and other diseases that disrupt renal excretion, that is, storage diseases, preeclampsia, chronic renal failure, cardiovascular diseases, hyperparathyroidism.
3. Use of drugs that cause hyperuricemia. These include anti-tuberculosis drugs (ethambutol) that can induce hyperuricemia and aggravate the course of gout, and increase joint pain. Didanosine has an identical property, which in turn is used in the human immunodeficiency virus. For these drugs, hyperuricemia is considered a prognostic side effect due to competition with urates in the elimination pathway [3].
4. Products rich in purine nucleotides contribute to the development in the body of an excess of the substrate for the synthesis of uric acid.

Link between hyperuricemia and gout Hyperuricemia refers to an increase in the level of uric acid in the blood. Uric acid is a breakdown product of purine within the body. The persistent accumulation of uric acid can lead to gout, a type of arthritis characterized by episodes of painful inflammatory attacks [8].

Pathogenetic mechanisms underlying the deposition of urate crystals The basis of the general clinical phenomena of gout is the deposition of sodium monourate crystals in the tissues. This mechanism is poorly understood. A certain influence has a weak vascularization of tissues, which is justified by the frequent deposition of urate crystals in the tendons and bones. The main factors for the formation of crystals are the concentration of urates, local temperature and the presence of complex proteins that retain urates in the liquid - proteoglycans. The occurrence of crystallization is due to an increase in the diffusion of water from the joint. Serum pH plays an important role in the crystallization of uric acid. It has been substantiated that the complete dissolution of uric acid salts is carried out in a concentrated alkali solution with pH = 12.0–13.0, which is impossible in vivo. There is a relationship between ambient temperature and urate solubility: hypothermia of superficial joints has a positive effect on the formation of urate crystals and the occurrence of microtophi [12](pic.2).



Picture 2. Clinical, radiological and microscopic aspects of gout and calcium pyrophosphate (CPP) crystal deposition.

(A) Chronic tophatic gout (1) with severe joint involvement on radiograph (2) in a male patient with long-term polyarticular gout. Analysis of synovial fluid taken from the fifth metacarpophalangeal joint showed an accumulation of needle-like crystals of sodium monourate (3). (B) Deposition of CPP crystals in the knee of a patient with recurrent episodes of pseudogout (1). CPP crystals (arrows) observed in synovial fluid under compensated polarized light (2). (C) Axial computed tomography (CT) of the cervical spine of a male patient at the C1-C2 level, illustrating the "shortening" of the den. The arrow represents CPP deposition. The original drawings were obtained and reproduced with the written informed consent of the patients for publication.

The process of laying uric acid salts in tissues is determined by the clinical manifestations of gout. The most pronounced of them is pronounced gouty arthritis. A specific source of the inflammatory process is the crystallization of uric acid in the joint cavity, which occurs under the influence of provoking factors [5]. The cells of the synovial membrane trigger the process of inflammation, their activation is accompanied by the secretion of cytokines IL-1, IL-6, TNF- and IL-8. It is these cytokines that cause the arrival of neutrophils in the joint cavity. The resulting protein-coated crystals (IgG) promote phagocytosis with the formation of phagolysosomes by reacting with Fc receptors on the cell surface. Phagolisosomal enzymes eliminate IgG from the crystal surface, hydrogen-containing compounds cause membrane lysis. As a result, the release of proteolytic lysosomal enzymes occurs, the secretion of reactive oxygen species, free radicals of prostaglandins, leukotrienes and other inflammatory mediators is initiated. Urate crystals activate the complement system as well as the Hageman factor and trigger the kinin cascade reaction. As a result, the activation of the kallikrein and kinin systems, the increase in the permeability of the vascular wall, the excitation of the complement system, by increasing the chemotaxis of leukocytes to urate crystals, contribute to the inflammatory process. In the focus of inflammation, the pH of the medium decreases, which contributes to even greater crystallization of urates. A pathogenetic vicious circle is created [11]. Independent subsidence of the inflammatory process in the joint with gout is determined by the ability of phagocytes

to digest crystals and secrete a number of anti-inflammatory factors, in particular TGF-beta [6].

Gout diagnostics

The following methods are used to diagnose gout:

1) general blood test;

2) biochemical analysis of blood;

3) general urinalysis;

4) the level of urates in the blood serum;

5) determination of uric acid in daily urine;

6) study of synovial fluid.

A complete blood count is a laboratory study that is carried out for the quantitative and qualitative assessment of key classes of blood cells, includes determining the concentration of the main blood cells (leukocytes, platelets), hematocrit, as well as calculating erythrocyte indices (MCV, RDW, MCH, MCHC). With a gout attack, neutrophilic leukocytosis with a shift to the left is observed, as well as an increase in ESR [3].A biochemical blood test is a laboratory diagnostic method that involves assessing the functioning of internal organs (kidneys, gallbladder, etc.), establishing active inflammatory and rheumatic processes, as well as a violation of water-salt metabolism and an imbalance of microelements.A standard biochemical blood test includes a number of indicators that reflect the state of protein, carbohydrate, lipid and mineral metabolism, as well as the activity of some key blood serum enzymes. In the process of exacerbation of gout, there is an increase in seromucoid, fibrin, haptoglobin, sialic acids, and uric acid [8].A general urinalysis is a comprehensive, diverse testing that is aimed at detecting the general properties of urine, its physicochemical and microscopic examination. Based on this, indicators such as color, transparency, reaction (pH), urine glucose, ketone bodies, bilirubin and its metabolic products are determined. In the urine sediment, the presence of elements of cells, salts and cylinders is observed. This method in a particular case is carried out in order to identify lesions of the urinary system that contribute to the development of gout or are its complication [7].

Serum urate level. An increase in serum urate levels supports the diagnosis of gout, but is neither sensitive nor specific. The level of urate in the blood serum during the acute phase of the disease is normal, this is explained by the uricosuric properties of IL-6. Nevertheless, the initial level of uric acid in the blood serum between exacerbations of the disease shows a single pool of urates in the extracellular fluid. In order to identify the initial level of urate with newly diagnosed gout, it is necessary to measure 2-3 times. Determination of uric acid in daily urine. Uric acid is the end product of the breakdown of purine bases. The content of uric acid in the urine directly depends on the diet (connection in food of carbohydrates, fats), the functioning of the kidneys, and drug therapy. It is performed to diagnose diseases of the urinary system that contribute to the development of gout or are its complication [9].

Diagnosis based on synovial fluid. Synovial fluid is a fairly thick substance that acts as a lubricant for the joints. If gout is suspected, arthrocentesis and synovial fluid analysis should be performed. If repeated attacks occur in patients with proven gout, then this procedure is not needed, but it should be performed if there is a suspicion of the addition of infectious arthritis. Gout is characterized by the presence of needle-shaped urate crystals in the synovial fluid, which are in a free state or phagocytic. Synovial fluid at the time of the attack has signs of inflammation, usually 2000–100,000 leukocytes/mcL and > 80% polymorphonuclear leukocytes. These values are very similar to those of infectious arthritis, which must be ruled out by Gram stain (negative) and culture [3].

Serum uric acid Uric acid is a product of the catabolism of purine bases, which are part of the DNA and RNA of body cells. Purine bases are formed after cell death, a small amount comes from food and liquids. Uric acid is transported by the blood from the liver to the kidneys, where it is partially filtered and excreted in the urine, while the remainder passes into the gastrointestinal tract and is excreted in the stool. A regular increase in the level of uric acid is the cause of gout. An increase in the processes of cell death and a decrease in the rate of excretion of uric acid by the kidneys contributes to hyperuricemia.

Diagnostic markers for gout Diagnostically significant markers of the gouty process in the body are: the presence of microcrystalline urates in the synovial fluid; the presence of tophi with deposition of crystalline urates; more than one acute arthritis attack; pronounced signs of the inflammatory process in the joint in the acute phase; erythema of the skin over the inflamed joint; tophus-like nodules; subcortical cysts without an erosive process, determined by the X-ray method; negative analysis for back culture of joint fluid.

Genetic aspects of gout The risk of developing gout is influenced by genes that determine the concentration of uric acid and the excretion of uric acid by the kidneys and intestines. The concentration of uric acid also depends on the genes associated with glucose metabolism. So far, 38 genetic loci have been identified that may drive the development of hyperuricemia and, apparently, gout. Studies show that certain genetic variants influence the inflammatory response of inflammasomes, the presence of uric acid crystals. Some variants of the SLC2A9 and ABCG2 genes can increase the risk of developing gout by up to 50%. These genes determine the leading position in the regulation of uric acid levels. An increase in the possible risk of developing gout is the carriage of the T allele and the T/T genotype of the MTHFR C677T gene, the G allele and the A/G genotype of the MTR A2756G gene. The allele from the C677T locus of the MTHFR gene, as well as the A allele and the A/A genotype of the MTR A2756G gene, presumably contribute to the improvement of immunity [4].

Conclusion Despite the increased interest in the problem of gout in recent decades, the number of studies aimed at pathochemical processes in gout is not enough. The topic requires further development both from the laboratory diagnostic point of view and pathogenesis. Genetic polymorphism has been proposed to prevent and recognize gout, but predicting gout from genetic variation is still limited due to insufficient knowledge of the relationship between genes and gout. Our assumption is that it is necessary to consider not only the activity and mutation of genes, but also directly consider the very mechanism for the implementation of these genes and its relationship with the systems that regulate it. Consideration of the mechanism of

education gout from this point of view can provide answers to the correlation of the activity of the above genes and the degree of development of gout.

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