CLINICAL AND BIOCHEMICAL CHANGES IN GOUT

Nabieva Dildora Abdumalikovna , Akramova Nigora Turdikulovna , Rakhmonov Doston , Aditya Kush

Tashkent Medical Academy. Department of Faculty and Hospital Therapy No. 1

Gout is one of the most painful and acute disease afflicting humanity and one of the first defined diseases found in historical manuscripts. Over the centuries, gout has attracted the attention of many prominent doctors, including the Egyptian Imhotep (27th century BC) and Hippocrates (460-377 BC) who distinguished gout from other arthritis and called it “the disease of the rich” due to with the fact that it often occurs in people who consume a lot of alcohol and meat products [36]. Although gout is considered one of the most ancient diseases, at present it has not lost its relevance and year after year new features of its course are being determined and the rank of the lesion is expanding day by day. Gout is a systemic, chronic, metabolic joint disease caused by the deposition of uric acid salts into distal joints and peripheral tissues. This is facilitated by an increase in the concentration of uric acid, which leads to the formation of UA crystals and their deposition in various tissues of the body. The connection between gout and uric acid was identified in the 1960s, in the heroic studies of Feres and McCarthy , who both injected 20 mg of UA into their knee joints. Soon both researchers experienced excruciating pain consistent with gouty arthritis and lasted for 4 hours. After the pain passed, they said “we were amazed with the accuracy of Sydenham's (1683) description of classical gout” [37]. Their study showed that uric acid crystals are the primary trigger of gout. A condition in which the concentration of uric acid is higher than normal values is called hyperuricemia . Uric acid is the end product of purine nucleotide metabolism. Humans and great apes, compared to other mammals, have 3 to 10 times higher concentrations of uric acid [3]. With hyperuricemia, the concentration of uric acid in men exceeds 7.0 mg/ Dl (420 μ mol L−1), and in women 6.0 mg/ Dl (350 μ mol L−1) [5, 6]. Deposition of uric acid crystals in joints causes gouty arthritis, in soft tissues leads to the formation of tophi and

tenosynovitis , and in the urinary tract - the formation of urate stones. The disease is 9 times more common in men than in women. The average age of patients is 45 years. The pathogenesis is based on the accumulation of uric acid crystals , due to incomplete excretion or increased synthesis of uric acid.

The development of hyperuricemia (HU) is associated with increased consumption of purine and protein foods, alcohol and sweets [1]. In addition to these, the use of certain medications, such as diuretics, salicylates, can lead to a decrease in the excretion of sUA or an increase in its concentration in the blood. Other risk factors for the development of gout are kidney disease, cardiovascular disease, obesity, diabetes, as well as defects in the functioning of enzymes involved in purine metabolism and genetic factors involved in the transport of UA in the body [2].

Factors that contribute to the development of HU or gout:

- Limitation of UA release

- Kidney failure
- Drugs: diuretics, pyrazinamide , aspirin in small doses
- Lead poisoning
- Hyperparathyroidism
- Myxedema
- Down syndrome
- Lactic acidosis due to: alcohol intake, physical activity, fasting, vomiting, toxicosis of pregnancy, glycogenosis

- increased production of uric acid:

- Increased purine metabolism: chronic myeloproliferative diseases, chronic lymphoproliferative diseases, acute, exfoliative psoriasis
- Enhanced purine synthesis in: deficiency hypoxanthine guanine phosphoribosyl transferase , Hyperactivity of phosphoribosyl 1 phosphate synthetase, Glucose-6 phosphatase deficiency.

The following clinical forms of gout are distinguished:

-acute gouty arthritis

- pseudophlegmonous
- similar to rheumatoid arthritis
- subacute
- similar to infectious-allergic arthritis
- Psoriatic
- asthenic
-abortive
- extra-articular

Periods of the disease: premorbid , intermittent , chronic

By course: light, medium, heavy

Stages: active, remission

Clinical picture. In the gout clinic, there are 4 periods: acute gouty arthritis; interictal period; chronic gouty arthritis; chronic tophaceous gout

A typical acute attack of gout occurs in practically healthy people who have had asymptomatic hyperuricemia for several years. Often the pain occurs at night or early in the morning in the form of very severe and progressive pain, affecting one joint, mainly the first toe of the lower extremities. Elbow and wrist joints are less commonly affected. And the shoulder, sternoclavicular, and hip joints are affected very rarely. In older people, gout attacks occur in a subacute form. Interconnection hyperuricemia with metabolic syndrome [37], chronic kidney disease [38] and cardiovascular diseases has been established by many authors from different fields. A decrease in GFR also contributes to an increase in the concentration of UA, although at the same time its excretion through the gastrointestinal tract is significantly enhanced [4]. Or, conversely, an increase in UA concentration contributes to a decrease in GFR [40]. This is explained by the damaging role of urate crystals in the renal tubules and interstitial spaces [41].

Recently, the number of patients with hyperuricemia and gout has been increasing, and people suffering from hyperuricemia are very prone to gout [36]. The reason why hyperuricemia is less common among women is explained by the protective role of estrogens and antiandrogen therapy [39]. However, in women after the

menopausal cycle, sUA levels may be elevated. Epidemiological studies (Zahir, 2022) on the distribution of genetic polymorphism of alleles of 11 genes involved in the transport of uric acid showed that among Asians, especially the Japanese, and Chinese, polymorphism of all 11 genes was found, which indicates a 2.7 times higher incidence of gout in representatives of these ethnic groups than Europeans, Caucasians, African Americans and Mexicans. In addition, the number of Asians visiting US medical institutions for gout was 3 times higher than that of Europeans and African Americans, which is due to geno- and phenotypic factors [2].

The study of the relationship between gout or hyperuricemia and other diseases has been a trend since the beginning of the 20th century. A lot of studies have been devoted to studying the relationship between hyperuricemia and cardiovascular diseases, hypertension, diabetes mellitus and metabolic syndrome [16,17], as well as cerebrovascular diseases, vascular uric acid dementia, preeclampsia and kidney diseases [18]. In the early 60s, the relationship between hyperuricemia and hypertension was studied. Prospective studies have shown that 26% of patients with untreated hypertension and preserved renal function had high sUA levels. These numbers increased to 58% in those who received antihypertensives and 70% in patients who received diuretics [6]. In the work of Messerli and Tykarski , A. (1991) employees, a decrease in renal blood flow and a decrease in tubular secretion of uric acid was associated with hyperuricemia in patients with hypertension [7,8]. Uric acid plays a pathogenetic key role in the development of hypertension [9,10,11] through several pathways: inflammation, proliferation of vascular smooth muscle cells in the renal circulation, endothelial dysfunction and activation of the RAAS [12,13]. Studies conducted in animals have shown that a very high concentration of sUA induces a sharp increase in blood pressure, and a chronic high level of sUA leads to a constant increase in blood pressure and stimulates irreversible changes in the vessels and glomeruli, and also leads to saline hypertension (14,15). Research results Rahimi-Sakak , F., Maroofi , M., Rahmani , J., et al . (2019) showed the association of hyperuricemia with an increased risk of CV mortality [19]. With

hyperuricemia , numerous pathophysiological changes occur, such as: increased oxidative stress, multiple proatherogenetic processes, activation of leukocytes, proliferation of vascular smooth muscle cells, initiation of inflammatory reactions, as well as possible prothrombotic changes mediated through increased adhesion and aggregation of platelets and the formation of crystals within the atherosclerotic plaque [20 ,21]. In addition to these studies, Langlois , Kang , Patetsios , Viazzi , F., Zuo , T et al . (2005) it was proven that uric acid is a marker of tissue ischemia and its role in the formation of atherosclerotic plaque was established [22,23,24,25,26].

Hyperuricemia with several inflammatory markers has recently been studied [27]. It is clear that UA is a direct stimulator of inflammatory mediators such as CRP in vascular cells [28]. This means that UA is a direct damaging factor to the endothelium. A number of studies have established the prothrombotic and pro-inflammatory effects of UA, which increases the risk of venous thrombotic embolism several times [29,30,31,32,33].

Studies of the hemostasis system in patients with gout have been carried out since the 50s of the last century. So, already in 1955 Mengghini P and Bellotti R established a direct correlation between thrombophlebitis and increased sUA concentrations [34].

Thus, in a large-scale study (Papavasileiou et al., 2023) , the relationship of UA with: fibrinogen, international normalized ratio (INR), homocysteine , antithrombin 3, D- dimer and plasminogen activator inhibitor-1 (PAI-1) was studied. The results of the study showed a significant correlation between UA and the indicated hemocoagulation factors , which indicates the prothrombotic effect of UA in patients [35].

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