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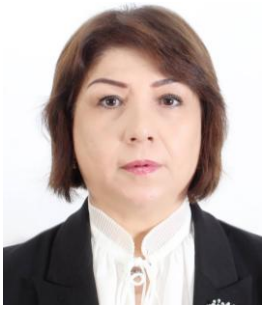
PROGNOSTIC SIGNIFICANCE OF HYPERURECEMIA IN THE DEVELOPMENT OF CHRONIC KIDNEY DISEASE

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СУРУНКАЛИ БУЙРАК КАСАЛЛИГИ РИВОЖЛАНИШИДА ГИПЕРУРЕМИЯНИНГ ПРОГНОСТИК АҲАМИЯТИ

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ПРОГНОСТИЧЕСКОЕ ЗНАЧЕНИЕ ГИПЕРУРЕКЕМИИ В РАЗВИТИИ ХРОНИЧЕСКОЙ БОЛЕЗНИ ПОЧЕК

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Резюме. *Сурункали буйрак касаллиги ривожланишининг хавф омили ва мавжуд буйрак касалликларининг ривожланишидаги омиллардан бири сифатида гиперурикемия ролини таъкидлайдиган адабиётларни кўриб чиқиш тақдим этилади. Гиперурикемия ва буйрак шикастланиши ўртасидаги боғлиқлик ҳақида эпидемиологик маълумотлар келтирилган. Экспериментлар ва клиник шароитларда олинган сийдик кислотасининг буйрак тўқималарига зарарли таъсирининг механизмлари кўриб чиқилади. Гиперурикемияни тузатишнинг асосий йўналишлари ва бу терапиянинг нефропротексиянинг умумий стратегиясида тутган ўрни аниқланган.*

Калит сўзлар: *гиперурикемия, подагра, сурункали буйрак касаллиги, тубулоинтерститиал фиброз.*

Abstract. *A review of the literature is presented highlighting the role of hyperuricemia as a risk factor for the development of chronic kidney disease and one of the factors in the progression of existing kidney disease. Epidemiological information on the relationship between hyperuricemia and kidney damage is provided. The mechanisms of the damaging effect of uric acid on renal tissue, obtained in experiments and clinical conditions, are considered. The main directions of correction of hyperuricemia and the place of this therapy in the general strategy of nephroprotection have been determined.*

Keywords: *hyperuricemia, gout, chronic kidney disease, tubulointerstitial fibrosis.*

Chronic kidney disease (CKD) is a general concept indicating damage to the kidney tissue, regardless of the etiology of the underlying disease. CKD is defined as the presence of any markers of kidney damage that persist for more than 3 months and/or a persistent decrease in glomerular filtration rate (GFR) <60 ml/min/1.73 m2 over the same period. According to statistics, CKD develops in approximately 15% of people in the general population and in every second patient with arterial hypertension (AH) and diabetes mellitus [Association of Nephrologists, 2021].

Approaches to the clinical diagnosis of CKD are based on direct or indirect assessment of the degree of fibrosis and the mass of active nephrons, as well as identification of the etiological factor. Acute processes leading to kidney damage end with one outcome or another within three months: complete recovery with preservation of the cell populations of the organ, recovery from a residual defect (decrease in the cellular mass of an organ) or death of an organ. The same time period from the onset of the damaging factor is necessary and sufficient for the formation of initial fibroplastic changes.

Consequently, signs of kidney damage over a longer period of time from a pathophysiological point of view reliably indicate the chronicity of the process. It is assumed that it is secondary factors, regardless of the form of preexisting kidney disease, that largely determine the rate of progression of CKD. Along with well-known and fairly widely studied progression factors, such as systemic and intrarenal hypertension, glomerular hypertrophy, hyperlipidemia, hemocoagulation disorders, prostaglandin metabolism, etc. [1, 2].

There is increasing interest in studying the role of uric acid (UA) among them [3, 4]. Priority in this matter belongs to the domestic school of nephrologists, the founder of which is E.M. Tareev was one of the first to describe a case of gouty interstitial nephritis in 1929 in the monograph “Anemia of Bright Men”. Discussing the concept of kidney damage during prolonged hyperuricemia (HU) and gout, the author emphasized its secondary nature: “... the

kidneys are damaged in gout secondarily due to the development of hypertension and atherosclerosis" (E.M. Tareev, Internal Diseases, 1951).

These ideas were further developed in numerous clinical and experimental studies carried out in Russia [5-8] and around the world. It has become obvious that primary HU/hyperuricosuria can cause various forms of kidney damage (nephrolithiasis, acute uric acid blockade, tubulointerstitial nephritis). At the same time, disturbances in UA metabolism that occur secondary to CKD and have a damaging effect on the kidneys (the mechanisms of which have been partially deciphered) may be one of the non-immune factors contributing to the progression of CKD of any nature. The prevalence of GU in the population, according to different authors, varies from 5-8% (in Europe) to 25% in certain regions of China and Japan [9]. Among people suffering from CKD, this figure increases significantly (from 24% among patients with stage II-III CKD to 80% among patients after kidney transplantation) [10, 11]. The independent role of uric acid in the development of CKD and associated complications is confirmed by the results of epidemiological studies that revealed an association of urinary tract with cardiovascular diseases, arterial hypertension (AH), diabetes mellitus (DM), and obesity [12].

A number of epidemiological studies have established the importance of HU in the development of CKD also in individuals with initially normal kidney function (without previous kidney disease) [13–15]. The results of 2 cohort studies, totaling 13,388 people followed for 9 years, were analyzed by D. Weiner et al. It was found that every 1 mg/dL increase in serum sUA level was associated with an increase in the risk of developing CKD: odds ratio (OR) 1.07 with 95% confidence interval (CI) from 1.01 to 1.14 and OR 1. 11 with a 95% CI of 1.02 to 1.21 for glomerular filtration rate (GFR) and serum creatinine, respectively [13].

Another study, which included 22,000 healthy individuals, analyzed the development of CKD depending on the presence of moderate and severe HU - 7-8. 9 mg/dL (416-529 mmol/L) and more than 9 mg/dL (more than 535 mmol/L). In a multivariate analysis, the risk of developing CKD was high in both those with moderately elevated levels of UA in the blood and those with severe HU (OR 1.26 with 95% CI 1.02 to 1.55 and OR 1.63 with 95% CI from 1.18 to 2.27, respectively) [14].

In a multivariate risk analysis (age, sex, body weight, levels of sUA, glucose, total cholesterol and triglycerides in the blood, mean arterial pressure and albumin/creatinine ratio in urine) in 900 healthy volunteers, a significant association was revealed between the level of sUA and the risk of a decrease in GFR through 59 months of follow-up (adjusted relative risk - RR 1.28 with 95% CI 1.12 to 1.48 for each 1 mg/dL increase in sUA levels in the blood) [15].

The reasons for this effect of HU may be the development or worsening of hypertension, as well as oxidative stress and, as a consequence, endothelial dysfunction (ED) [26–28]. Analysis of the relationship between the progression of CKD and HU is complicated by a large number of concomitant factors that contribute to the progression of renal failure in patients with CKD. The role of MK as a progression factor is not indisputable. Many researchers assign it only additional importance to the main factors influencing the course of CKD and cardiovascular death - hypertension, insulin resistance, excess body weight, hyperlipidemia [18, 19].

One of the reasons that made it difficult to reliably assess the effect of uric acid levels in the blood on the progression of CKD was the low frequency of morphological confirmation of urate kidney damage due to the lack of clear indications for kidney biopsy in patients with urate dysmetabolism in standard practice. As a result, enthusiasm for the use of allopurinol and the use of other methods for correcting sUA levels in asymptomatic HU has significantly decreased, for example in the USA. At the same time, in Japan, drug reduction of uricemia is included in the standards of treatment for patients with hypertension and concomitant HU, even without clinical manifestations (articular gout, nephrolithiasis, chronic urate tubulointerstitial nephritis) [29].

Meanwhile, studying the morphological changes in the kidney associated with urate dysmetabolism may be of great importance for an in-depth assessment of associated kidney damage and optimization of treatment methods. Despite the fact that an increasing number of studies published in recent years and carried out in accordance with the principles of evidence-based medicine substantiate the connection between HU and CKD, the specific mechanisms of the damaging effects of UA in organs and tissues remain unclear. A sufficient amount of evidence has accumulated that uric acid is an inflammatory factor: monosodium urate crystals cause a cascade of inflammatory reactions in the joints during gout [30] and inflammation in other tissues, primarily in the tubulointerstitium of the kidneys [31, 32]. T-cell and macrophage infiltration makes a decisive contribution to the development and progression of interstitial lesions.

The release of proinflammatory and profibrogenic mediators (chemokines and cytokines) by these immunocompetent cells causes the initiation and maintenance of inflammation and fibrosis, including indirectly through the activation of matrix-producing effector cells, such as tubulocytes and fibroblasts. In rats with experimental HU, MK causes increased expression of fibronectin by tubular cells through activation of the NF-κB signaling system [33, 34]. These results were confirmed by Yang Zhou et al. [32] in a study of kidney tissue in rats with intraperitoneal administration of MK: migration and infiltration of tubulointerstitial tissue by activated T cells and macrophages were accompanied by their release of RANTES (Regulated on activation, normal T-cells expressed and secreted) - a chemoattractant for monocytes and T cells of the phenotype CD4/CD45R0, monocyte chemoattractant protein type 1 (MCP-1), transforming growth factor β-type 1 (TGF-β1). The authors found that the expression of these proinflammatory and profibrogenic cytokines in response to the effects of UA occurs mainly through activation of the intracellular NF-κB signaling system.

The use of allopurinol helped slow the progression of kidney damage, which was expressed in the absence of an increase in albuminuria and a decrease in the activation of TGF-β1 in tubular cells and was accompanied by an increase in the expression of E-catherin by tubulocytes, a decrease in their production of vimentin and smooth muscle α-actin (α-SMA), indicating a slowdown in the transdifferentiation of these cells into myofibroblasts

(MFBs), the main "producers" of fibrosis in kidney tissue. This study made it possible for the first time, using the example of nephropathy caused by type 2 diabetes, to evaluate the effect of therapy that reduces the level of sUA on profibrogenic processes in kidney tissue [35].

Thus, activation of the URAT-1 transport system enhances, and blockade with probenecid inhibits the expression of RANTES, MCP-1, TGF-β1 in response to exposure to MK. However, blockade of URAT-1 does not completely stop the entry of UA into the cell. Apparently, there are other transport systems that ensure the entry of MK into the cell. At the same time, there is no doubt that the state of transport systems, their activation or blockade, including those caused by genetic factors [37], play an important role in the processes of inflammation and damage to the tubular structures of the kidneys in HU. In earlier works devoted to the mechanisms of the damaging effect of MK on the tissue structures of the kidney, the DE induced by it has been studied [38–40]. Experimental data, the results of prospective and placebo-controlled studies have shown that MK has the ability to initiate and maintain DE indirectly through NO synthase [39, 43], as well as stimulate the proliferation of smooth muscle cells both in the systemic vascular bed and in the renal vessels [39].

M. Kanbay et al. [43] found that when using allopurinol at a dose of 300 mg/day for 4 months in patients with HU and hypertension, there is a significant decrease in the manifestations of DE, assessed using the endothelium-dependent vasodilation test (EDVD). The results of multivariate linear regression analysis indicated a significant independent relationship between GU and EVZ both before and after treatment (β=−0.55; p=0.03 and β=−0.40; p=0.024) [42]. The experiment also showed that UA directly stimulates the renin-angiotensin-aldosterone system [39], and through the activation of angiotensin II it can participate in the genesis of renal hypertension, aggravate DE and EndMT and the formation of tubulointerstitial fibrosis in CKD [41]. Currently, the definition of microalbuminuria (MAU) is widely used to assess DE and kidney damage in general [40–41].

MAU was significantly more often detected in patients with HU and correlated with signs of DE [27]. In patients with hypertension associated with HU, a high and significant correlation was revealed between uricemia and the severity of albuminuria (r = 0.898; level of sUA in the blood, in patients with CKD with HU as nephroprotective therapy. These prospects are supported by the emergence of new drugs that disrupt the synthesis of sUA, such as as febucostat, the pharmacokinetics of which differ from those of allopurinol, with preferential elimination through the liver, with a greater degree of safety and a wide "therapeutic corridor." Thanks to these properties, febucostat can become the drug of choice in patients at advanced stages of CKD [27].

The need for an individualized approach to primary and secondary prevention of CKD, taking into account the progression factors in each individual patient, becomes obvious. In this regard, the study of HU as an additional risk factor for the development and progression of CKD is promising and relevant [28]. The emergence of new drugs that reduce the level of uric acid, have a greater degree of safety and broad therapeutic effect [37], as well as the use of previously studied drugs with uricosuric action (in particular, a number of angiotensin II receptor blockers) [36], makes it possible to more actively correct GU in order to slow down progression of CKD and prevention of cardiovascular complications.

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ПРОГНОСТИЧЕСКОЕ ЗНАЧЕНИЕ ГИПЕРУРЕКЕМИИ В РАЗВИТИИ ХРОНИЧЕСКОЙ БОЛЕЗНИ ПОЧЕК

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Резюме. *Представлен обзор литературы, в котором освещена роль гиперурикемии как фактора риска развития хронической болезни почек и одного из факторов прогрессирования имеющейся патологии почек. Представлены эпидемиологические сведения о связи гиперурикемии и поражения почек. Рассмотрены механизмы повреждающего действия мочевой кислоты на ткань почек, полученные в экспериментах и клинических условиях. Определены основные направления коррекции гиперурикемии и место этой терапии в общей стратегии нефропротекции.*

Ключевые слова: *гиперурикемия, подагра, хроническая болезнь почек, тубулоинтерстициальный фиброз.*