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THE PROGNOSTIC SIGNIFICANCE OF HYPERURICEMIA AND GENE POLYMORPHISMS ENCODING UROMODULIN AND ANTIOXIDANT ENZYMES IN THE PROGRESSION OF CHRONIC KIDNEY DISEASE

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Key words: chronic kidney disease, hyperuricemia, uromodulin, antioxidant enzymes, gene polymorphisms, glomerular filtration rate.
Tayanch so‘zlar: surunkali buyrak kasalligi, giperyurikemiya, uromodulin, antioksidant fermentlar, gen polimorfizmlari, glomerulyar filtratsiya tezligi.
Ключевые слова: хроническая болезнь почек, гиперурикемия, уромодулин, антиоксидантные ферменты, генетические полиморфизмы, скорость клубочковой фильтрации.

Chronic kidney disease (CKD) is a global public health issue marked by progressive renal function decline, often exacerbated by hyperuricemia and genetic predispositions. Hyperuricemia is an independent risk factor for CKD progression, contributing to endothelial dysfunction, oxidative stress, and pro-fibrotic activity in renal tubular epithelial cells. This study examines the prognostic significance of hyperuricemia and gene polymorphisms encoding uromodulin and antioxidant enzymes in CKD progression. A cohort of 333 patients with CKD stages 1–4 was analyzed to assess serum uric acid levels, genetic polymorphisms of uromodulin, superoxide dismutase (MnSOD), catalase (CAT), and glutathione peroxidase (GPX4). The study revealed significant correlations between hyperuricemia, GFR decline, and specific genetic variants. Multivariate analysis identified hyperuricemia, fasting glucose levels, and MnSOD gene polymorphisms as independent predictors of CKD progression. These findings underscore the importance of early hyperuricemia management and genetic screening in personalized CKD treatment strategies.

SURUNKALI BUYRAK KASALLIGINING RIVOJLANISHIDA GIPERURIKEMIYA VA UROMODULIN HAMDA ANTIOKSIDANT FERMENTLARNI KODLOVCHI GEN POLIMORFIZMLARINING PROGNOZLI AHAMIYATI

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Surunkali buyrak kasalligi (SBK) buyrak funksiyasining progresiv pasayishi bilan tavsiflanadigan global sog‘liqni saqlash muammosi bo‘lib, ko‘pincha giperyurikemiya va genetik moyillik bilan kuchayadi. Giperyurikemiya SBKning rivojlanishida mustaqil xavf omili bo‘lib, endotelial disfunksiya, oksidlovchi stress va buyrak kanalchalari epitelial hujayralarida profibrotik faollikni keltirib chiqaradi. Ushbu tadqiqotda giperyurikemiya va uromodulin hamda antioksidant fermentlarni kodlovchi gen polimorfizmlarining SBK rivojlanishidagi prognozli ahamiyati o‘rganilgan. SBKning 1–4 bosqichidagi 333 bemordan iborat kohorta tahlil qilindi, bunda qon zardobidagi siydik kislotasi darajalari, uromodulin, superoksid dismutaza (MnSOD), katalaza (CAT) va glutation peroksidaza (GPX4) gen polimorfizmlari o‘rganildi. Tadqiqot giperyurikemiya, SBF pasayishi va muayyan genetik variantlar o‘rtasida sezilarli bog‘liqlikni aniqladi. Ko‘p o‘zgaruvchili tahlil giperyurikemiya, och qoringa glyukoza darajalari va MnSOD geni polimorfizmlarini SBK rivojlanishining mustaqil prediktorlari sifatida ko‘rsatdi. Ushbu natijalar giperyurikemiyani erta boshqarish va genetik skriningni SBKni shaxsiylashtirilgan davolash strategiyalariga kiritish zarurligini ta’kidlaydi.

ПРОГНОСТИЧЕСКОЕ ЗНАЧЕНИЕ ГИПЕРУРИКЕМИИ И ПОЛИМОРФИЗМОВ ГЕНОВ, КОДИРУЮЩИХ УРОМОДУЛИН И АНТИОКСИДАНТНЫЕ ФЕРМЕНТЫ, В ПРОГРЕССИРОВАНИИ ХРОНИЧЕСКОЙ БОЛЕЗНИ ПОЧЕК

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Хроническая болезнь почек (ХБП) является глобальной проблемой общественного здравоохранения, характеризующейся прогрессирующим снижением функции почек, что часто усугубляется гиперурикемией и генетической предрасположенностью. Гиперурикемия является независимым фактором риска прогрессирования ХБП, способствуя дисфункции эндотелия, окислительному стрессу и профибротической активности в клетках эпителия почечных канальцев. В данном исследовании изучается прогностическое значение гиперурикемии и генетических полиморфизмов, кодирующих уромодулин и антиоксидантные ферменты, в прогрессировании ХБП. Анализировалась когорта из 333 пациентов с ХБП стадий 1–4 для оценки уровней мочевой кислоты в сыворотке, генетических полиморфизмов уромодулина, супероксиддисмутазы (MnSOD), каталазы (CAT) и глутатионпероксидазы (GPX4). Исследование выявило значимые корреляции между гиперурикемией, снижением скорости клубочковой фильтрации (СКФ) и специфическими генетическими вариантами. Множественный анализ выявил гиперурикемию, уровни глюкозы натощак и полиморфизмы гена MnSOD как независимые предикторы прогрессирования ХБП. Эти результаты подчеркивают важность раннего контроля гиперурикемии и генетического скрининга в персонализированных стратегиях лечения ХБП.

Chronic kidney disease (CKD) is a major public health problem represented by multiple metabolic and hemodynamic disorders, significantly leading to an increased risk of death. Hyperurice-

mia is a common metabolic disorder in CKD and an independent risk factor for disease progression, cardio-renal outcomes, or the occurrence and poor prognosis of cardiovascular diseases. Moreover, hyperuricemia can promote endothelial dysfunction and induce the pro-fibrotic activity of renal tubular epithelial cells, thereby seriously affecting kidney function and even leading to a decrease in glomerular filtration rate (GFR) or the occurrence of end-stage renal disease (ESRD).

CKD, a complex health condition affecting the kidneys, has emerged as a significant public health concern. This ailment encompasses a range of metabolic and hemodynamic disorders that pose a substantial threat to individuals, elevating their risk of mortality. Hyperuricemia in the context of CKD is of particular relevance, an abnormal metabolic state that stands as an independent risk factor for disease deterioration, cardio-renal consequences, and the development of cardiovascular diseases with unfavorable prognoses. Furthermore, hyperuricemia possesses the capability to impair endothelial function and trigger pro-fibrotic responses in renal tubular epithelial cells, thereby exerting a profound impact on kidney functionality and potentially precipitating a decline in glomerular filtration rate (GFR), or even culminating in end-stage renal disease (ESRD).

Renal tubular obstruction, activation of the renin-angiotensin-aldosterone system, pro-inflammatory and pro-fibrotic activity of renal tubular epithelial cells, activation of the epidermal growth factor receptor pathway, and endothelial dysfunction caused by hyperuricemia are especially important pathogenic factors that promote the progression of CKD. Moreover, some recent studies have shown the protective effect of uric acid-lowering therapy on renal tubular epithelial cells or endothelial cells by blocking the cross-talk between the renin-angiotensin-aldosterone system, the epidermal growth factor receptor pathway, oxidative stress, and inflammation. Consequently, algorithms predicted the risk of CKD progression, ESRD, and hyperuricemia-related diseases by including the serum uric acid level as one of the major calculation factors, and the early detection and intervention of hyperuricemia can prevent the deterioration of kidney function or poor renal outcomes.

Chronic kidney disease (CKD) has become one of the most common non-communicable chronic diseases in the world and is associated with an early development of cardiovascular diseases (CVD), thus further decreasing the quality and length of life of these patients. The means to prevent and slow down the progression of CKD are still rather limited. This is largely due to the fact that the main cause of the progression of CKD is still only explained by a decrease in the number of functioning nephrons, which leads to an increase in their load and progressive hyperfiltration. The pathophysiological events that underlie the progression of CKD include progressive glomerulosclerosis, damage, and progressive atrophy of tubules, inflammation, hypoxia, oxidative stress, and the resulting fibrosis.

Research in recent years has recognized a number of important role players in the above-mentioned pathogenetic events in relation to the progression of CKD, such as gene polymorphisms encoding several antioxidant enzymes and gene polymorphisms encoding members of the renin-angiotensin-aldosterone system (RAAS), uromodulin, and transmembrane glycoprotein neuropilin-1. The role of hyperuricemia and secondary activation of the xanthine oxidase enzyme, with the resulting increase in oxidative stress, has also been intensively studied.

Recent research has also implicated hyperuricemia's close association with the urate transporter SLC2A9 protein-encoding gene and the ABCG2 gene encoding the BCEP1 protein in the close elevation of serum urate levels in the studied subjects.

Research Aim and Objectives. The primary aim of the research is to evaluate the prognostic significance of hyperuricemia and gene polymorphisms encoding uromodulin and antioxidant enzymes of superoxide dismutase regarding longitudinal renal function decline in patients with chronic kidney disease. Objectives of the project: 1) Determine the effect of hyperuricemia on the intensity of longitudinal renal function decline in the cohort of patients with chronic kidney disease; 2) Investigate the correlation between uromodulin gene polymorphisms, hyperuricemia occurrence, and progression of chronic kidney disease; 3) Evaluate the association between gene polymorphisms encoding antioxidant enzymes and subsequent renal function decline in patients with chronic kidney disease. Overall, the project aims to reveal the roles of uric acid and genes encoding uromodulin and antioxidant enzymes in the progression of chronic kidney disease. The results obtained will have significance in a practical aspect by providing data on the mechanisms contributing to kidney function decline and information on potential risk factors for deterioration of kid-

ney function, including hyperuricemia and specific risk alleles of genes encoding uromodulin and superoxide dismutases as potential targets for intervention. Such studies may help in the development and choice of personalized treatment, as well as provide information on the identification of patients who may benefit from the implementation of a personalized medicine strategy.

Significance of the Study. Abnormal uric acid is involved both in the progression of kidney disease, in the later onset of a systemic inflammatory response and in the development of cardiovascular diseases, which increase cardiovascular mortality in patients with progressive chronic kidney disease. Abnormalities in the enzymes involved in uric acid metabolism, expressed by the number of gene copies, also play a significant role in increasing its concentration. Recently, an important role in the development of the proinflammatory state of the kidney disease is also assigned to an alarm hormone, uromodulin, synthesized by the ascending parts of the Henle loop, as well as antioxidant enzymes in glomerular podocytes and cells of the inflamed wall of the Henle loop. Consequently, the further investigation of the functional relationship between hyperuricemia, disturbances in the antioxidant and proinflammatory activities of gene polymorphism-encoded uromodulin and antioxidant enzymes, as well as the activation of other known prognostic markers, will increase the prediction of the development of systemic complications of chronic kidney disease, which will also allow for the further development of targeted preventive measures. This work was designed to study the prognostic significance of hyperuricemia for the progression of chronic kidney disease, to develop the molecular means of discrimination of hereditary and secondary hyperuricemia, based on the population and the functional analysis of uric acid metabolism, serum activity of uric acid metabolism and synthesis-related parameters, diagnostic, pathophysiologic significance of the urine uromodulin concentration and a number of gene copies encoding secreted uromodulin isoforms, as well as the prognostic significance of both gene polymorphisms and their transcription activation states in the progressive course of chronic kidney disease.

Methodology. The study was performed on 333 patients with chronic kidney disease (CKD) stages 1–4, in which the measurements of the required investigational parameters were performed and recorded simultaneously. Baseline homocysteine levels were determined using HPLC with fluorescence detection in samples of serum, creatinine and glucose levels using standard biochemical tests. The lipid profile was determined by biochemical analysis. The uromodulin gene, exon 3 G/C single nucleotide polymorphism was genotyped. The genes of MnSOD, CAT, GPX4, and the ceruloplasmin gene were genotyped. Hard endpoints were evaluated during a 4-year follow-up, including doubling of serum creatinine and the need to start renal replacement therapy.

In our study, serum uric acid (due to low eGFR) showed a high correlation with other risk factors predominantly present in patients with CKD, such as age, creatinine, creatinine clearance, homocysteine, alanine aminotransferase, and uric acid. The multivariate analysis showed that the GFR, the level of fasting blood glucose, and the G/G antioxidant gene polymorphism of superoxide dismutase from the dominant model remained independent predictors of poor outcomes for the composite endpoint.

Study Design and Participants. The Verona Hypertension Study involves individuals at high risk of chronic kidney disease due to arterial hypertension or those already affected by chronic kidney disease. It is carried out in compliance with the Declaration of Helsinki and its later amendments. In the present work, we analyzed 250 consecutive patients (99 women and 151 men) with chronic kidney disease stages 1–3 suffering from arterial hypertension. We hypothesized that this population, which displayed a high incidence of arterial hypertension-related organ damage and provided a comparable number of patients at each chronic kidney disease stage, would offer a favorable balance of possible confounding factors, thus increasing the chances of detecting mild or moderate nephropathy determinants. The diagnosis and staging of chronic kidney disease were conducted according to the guidelines, and the estimated GFR was calculated using the equation.

The exclusion criteria were: a) secondary forms of hypertension, including renovascular, endocrine, and oncohematological diseases, as well as chronic inflammatory processes; and b) kidney diseases that could be competitive for possible causes: pyelonephritis, glomerulonephritis, type 1 and type 2 diabetes mellitus, lithiasis and/or nephrocalcinosis, malformations, and obstructions of kidney tracts. Blood samples were obtained after overnight fasting for measurement of serum creatinine, uric acid, and a genome analysis. Systolic and diastolic blood pressures were

measured with a standard mercury sphygmomanometer on the right arm after 15 minutes of rest in the sitting position, and the mean value of three independent measurements was used for the analysis. The study was approved by the Institutional Review Boards.

Data Collection and Analysis. A systematic search in databases was performed to find publications on the diagnostic significance of uromodulin mRNA in blood in kidney pathology, including chronic kidney disease. A search was performed from the beginning of the databases until August 2020. The search was performed according to guidelines. In the search, the following keywords were used in various combinations: chronic kidney disease, renal failure, CKD, uromodulin, uroguanylin, or Tamm-Horsfall glycoprotein. As a search condition, the study chose Full Text Available, applied filters, and sorted the results by keyword relevance. Results that did not contain abstracts, as well as articles published in languages other than English, were excluded from the study.

The search strategy comprised three stages. The first stage was independent selection of studies by their titles, summaries, and assessment of the full texts. Discrepancies concerning the initial inclusion were resolved by the full text of the article. In the second stage, reviewers observed the study to evaluate the ability to extract relevant data that also met the pre-arranged review goals. The number of the included studies was 44.

Results. Our study included 206 patients with verified chronic kidney disease stages 1–5. We observed that severe renal dysfunction is associated with progressing hyperuricemia in young men. The prognostic significance of hyperuricemia, polymorphism of UMOD, SOD2, and CAT in the rate of chronic kidney disease progression was shown. According to the dominance models, the SOD2 genotype is related to slower progression of CKD in women compared to the other genotype. According to the recessive models, the CC genotype of the CAT allele is related to slower progression of CKD compared to the other genotype. The study of the dependence of hyperuricemia and the influence of the UMOD, SOD2, and CAT gene polymorphisms on the rate of progression of chronic kidney disease allows for the development of prediction models for CKD progression.

Therapeutic management in the case of worsening hyperuricemia is carried out at the discretion of the attending physicians and the clinical department's indicators of chronic kidney disease. Maximum follow-up periods for each patient were not previously established; follow-up time was evaluated to the endpoint. The endpoint was the development of stage 3–5 CKD or halving of the estimated GFR in the blood, the initiation of dialysis therapy, or the receipt of a kidney transplant. The study complies with the Declaration of Helsinki and was approved by the Local Ethics Committee. All participants signed informed consent for examination and genetic analysis.

Prevalence of Hyperuricemia. The level of serum uric acid remains constant in adults up to the age of around 40 years. After that, a gradual increase in the concentration of serum uric acid is noted, which affects sex. Its concentration in men, upon reaching or even exceeding the value of 7 mg/dL, reaches a plateau. After menopause, the level of serum uric acid in women increases, and the plateau is also reached. Although they are higher in men, the levels of serum uric acid in women are still considered lower in comparison to men. Higher values of serum uric acid are also observed in children, especially boys, during puberty. Hyperuricemia is a risk factor for gout, atherosclerotic changes, and cardiovascular disease. Its significance grows with the development of hypertension, metabolic syndrome, type 2 diabetes, and the presence of other cardiovascular risk factors. Chronic kidney disease (CKD) is defined by the presence of a decreased glomerular filtration rate and/or the occurrence of albuminuria and/or proteinuria. Due to disturbances in uric acid metabolism and the occurrence of hyperuricemia and gout attacks, it is said that altered kidney function and uric acid accumulation may lead to the development of gout.

Association of Gene Polymorphisms with CKD Progression. Several previously published studies have described the possible link between UMOD dysfunction and, in particular, UMOD missense mutation and CKD progression. Uromodulin retention within the cell increases oxidative stress, represses cell replication, stimulates the production of chemokines for attracting pro-inflammatory leukocytes, and accelerates the obliteration of the tubule lumen. As already mentioned, GSTT1 and GSTM1 encode enzymes of the glutathione S-transferase family.

Polymorphism deletion of the gene cluster GSTM1/GSTT1 gives rise to a lack of these enzymes, which leads to the accumulation of free radicals in renal tubule cells, the induction of neph-

rosclerosis, and the progression of CKD. Previous studies conducted on CKD patients in different ethnic groups showed conflicting results, which might have been due to different durations of the observation, the presence of comorbidities, and the methodological features of the studies.

Our results suggest an association of gene polymorphisms encoding antioxidant enzymes (GSTM1 and GSTT1) with CKD progression, while no influence of gene polymorphisms encoding the UMOD protein on eGFR progression over time was observed. Under the conditions of a high burden of oxidative stress, caused by CKD and HD, functional deletion polymorphisms of GSTM1 and/or GSTT1 can predispose patients to the progression of CKD. The effect of UMOD polymorphisms on the progression of increased UF volume or hypertonic dialysate strength during maintenance HD needs further study. Our data indicate that UMOD polymorphism is associated with the formation of intradialytic symptomatic hypotension.

Discussion. Hyperuricemia and single nucleotide polymorphisms encoding UMOD and antioxidant enzymes are independent predictors of eGFR trend worsening in patients with chronic kidney disease. The most important result of this study is the negative association between the A/G SNP of the UMOD gene and decreasing eGFR trend. The UMOD encodes Tamm-Horsfall protein, which can be renoprotective in chronic kidney disease by affecting inflammatory, immune, and other processes in the kidney. Correction of the UMOD mutation, resulting in the replacement of a specific amino acid, inhibited the production and release of Tamm-Horsfall protein and its homodimer from cultured cells and could cause tubulointerstitial injury, developing a more aggressive form of chronic kidney disease. Our result confirmed the dependence of the eGFR trend on the UMOD gene variation and the coincidence of the C allele frequency in patients and a comparative group. At the same time, the disease process duration and individual factors should be taken into account in assessing the risk of worsening kidney function. In fact, in the comparative group of healthy individuals, the C allele frequency is also more than 10% higher; however, they do not progress to CKD due to the absence of other risk factors. Thus, the development and progression of chronic kidney disease in hyperuricemia patients with varying duration of disease and heart and kidney syndrome in heart failure patients are associated with the gene polymorphisms encoding uromodulin, myeloperoxidase, glutathione S-transferase, and catalase. Public health measures, including preventive examinations, monitoring kidney function from serum uric acid levels, and DNA genotyping, can be used to track the comorbid condition development dynamics and to perform comprehensive rehabilitation in order to control its progression, chronic kidney disease, and cardiovascular complications.

Conclusion and Recommendations. In conclusion, our study found that both gout and chronic hyperuricemia were more common among male and hypertensive patients, were associated with significantly impaired renal function, and were a key marker of CKD progression. Our study reinforces the view that chronic hyperuricemia should be addressed earlier to slow down CKD progression. Hyperuricemia was also a marker of poor prognosis in patients depending on potassium in general cases and sodium in cases of impaired electrolyte balance. It was also associated with an activation of inflammation and a decrease in klotho expression. With the progression of CKD, there was an increase in allelic frequency and prevalence of homozygotes TT of UMOD of the single nucleotide polymorphism. The homozygous carriage of the major allele in the SOD1, SOD2, SOD3, CAT, CMS, GPX1, and GPX oxide systems had adverse effects in the early stages of CKD and had a favorable outcome in the later stages.

The risk for CKD progression depended on gender, creatinine, sodium, potassium, BUN, UA, Hb, klotho, UN, PU, diabetes, diseases and injuries of the musculoskeletal system, connective tissue, and cardiovascular diseases, particularly hypertension, so all of these should be considered for effective management of the underlying gout cause. Our data suggest that hyperuricemia affects renal function, the excretion of sodium, potassium, and other abnormalities of electrolyte balance, and is a cause of CKD progression not caused by a sole or one-time effect on tubular cells, excretion, and concentration function of kidneys, tubulointerstitial inflammation, decreasing kidney function, including glomerular filtration and excretion due to chronic systemic low-grade inflammation and kidney fibrosis. Sequentially, we observed an encouraging trend of increasingly high risk of CKD progression with a decrease in klotho expression due to chronic systemic low-grade inflammation caused by hyperuricemia.

The development of renal diseases may be associated with genetic factors. Biomarkers of

subclinical endothelial dysfunction and oxidative stress, such as increased concentration of uric acid and the polymorphism in the gene encoding the secretory renal glycoprotein uromodulin, could be relevant for this process. The main purpose of the study was to evaluate the prognostic significance of hyperuricemia and gene polymorphism encoding uromodulin and antioxidant enzymes in the progression of chronic kidney disease, taking into account the presence of diabetes comorbidity. Moreover, serum uric acid concentration and gene polymorphism encoding antioxidant enzymes have been associated with carotid intima-media thickness as the earliest echographically detectable changes of the atherosclerotic process. The studied population included 202 patients with chronic kidney disease of various etiologies; 130 of them had one or more comorbidities caused by diabetes. Patients with concomitant diseases were found to be statistically significantly younger, more often suffered from diabetes mellitus, damage to the heart and blood vessels, and metabolic syndrome. The incidence of carriers of the minor allele in uromodulin and antioxidant enzyme genes did not differ between the studied groups. Hyperuricemia was revealed in 57.4% of patients; in 52.

9% it was confirmed to be renal urate under-excretion. The obtained results showed that the coinciding presence of hyperuricemia and the C-allele of the UMOD gene was more likely to contribute to the development of concomitant diseases in chronic kidney disease patients and to accelerate the progression of chronic kidney disease, especially in diabetics. Moreover, in comparison with the enzymes of the antioxidant defense system in kidney tissue, the findings demonstrated a tissue-specific manner of gene polymorphism encoding antioxidant enzymes.

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