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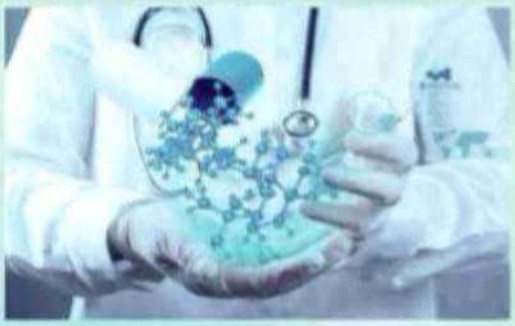

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ANALYSIS AND MODIFICATION OF METABOLIC AND HEMODYNAMIC RISK FACTORS FOR THE PROGRESSION OF CKD IN PATIENTS WITH TYPE 2 DM

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✓ ***Resume***

Type 2 diabetes mellitus (T2DM) remains the leading cause of chronic kidney disease (CKD) worldwide and one of the main determinants of cardiovascular mortality. Up to one-third of patients with type 2 diabetes develop diabetic kidney disease throughout their life, and the combination of decreased glomerular filtration rate (GFR) and albuminuria significantly increases the risk of terminal renal failure, cardiovascular events, and premature death. A particular problem is the "silent" nature of the early stages of CKD and the high proportion of patients with residual risk of progression even against the background of standard therapy.

Keywords: type 2 diabetes mellitus, diabetic nephropathy, chronic kidney disease, metabolic factors, hemodynamic disorders, albuminuria, glomerular filtration rate, renin-angiotensin system

2-TUR QD BILAN KASALLANGAN BEMORLARDA SBK RIVOJLANISHINING METABOLIK VA GEMODINAMIK XAVF OMILLARINI TAHLIL QILISH VA MODIFIKATSIYALASH

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✓ ***Rezyume***

2-tur qandli diabet (QD 2) butun dunyoda surunkali buyrak kasalligining (SBK) yetakchi sababi va yurak-qon tomir o‘limining asosiy omillaridan biri bo‘lib qolmoqda. QD 2 bilan og‘rigan bemorlarning uchdan bir qismida hayoti davomida diabetik buyrak kasalligi rivojlanadi, koptokchalar filtratsiya tezligining (KFT) pasayishi va albuminuriya birgalikda terminal buyrak yetishmovchiligi, yurak-qon tomir asoratlari va muddatidan oldin o‘lim xavfini bir necha barobar oshiradi. SBK erta bosqichlarining "soqov" tabiati va hatto standart davolash fonida ham kasallik rivojlanishining qoldiq xavfi yuqori bo‘lgan bemorlar ulushining kattaligi alohida muammo hisoblanadi.

Kalit so‘zlar: 2-tur qandli diabet, diabetik nefropatiya, surunkali buyrak kasalligi, metabolik omillar, gemodinamik buzilishlar, albuminuriya, koptokchalar filtratsiya tezligi, renin-angiotenzin tizimi

АНАЛИЗ И МОДИФИКАЦИЯ МЕТАБОЛИЧЕСКИХ И ГЕМОДИНАМИЧЕСКИХ ФАКТОРОВ РИСКА ПРОГРЕССИРОВАНИЯ ХБП У ПАЦИЕНТОВ С СД 2 ТИПА

(Литературный обзор)

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✓ ***Резюме***

Сахарный диабет 2 типа (СД 2) остаётся ведущей причиной хронической болезни почек (ХБП) во всём мире и одной из главных детерминант сердечно-сосудистой смертности. До трети пациентов с СД 2 в течение жизни развивают диабетическую болезнь почек, а сочетание снижения скорости клубочковой фильтрации (СКФ) и альбуминурии многократно повышает риск терминальной почечной недостаточности, сердечно-сосудистых событий и преждевременной смерти. Особую проблему составляет «немой» характер ранних стадий ХБП и высокая доля пациентов с резидуальным риском прогрессирования даже на фоне стандартной терапии.

Ключевые слова: сахарный диабет 2 типа, диабетическая нефропатия, хроническая болезнь почек, метаболические факторы, гемодинамические нарушения, альбуминурия, скорость клубочковой фильтрации, ренин-ангиотензиновая система

Introduction

Chronic kidney disease (CKD) is one of the most significant medical and social problems in modern healthcare, characterized by a steady increase in its prevalence, high frequency of complications, and significant economic costs. According to the Global Burden of Disease Study, CKD ranks 12th among the leading causes of death worldwide, with mortality from this disease increasing by 41.5% over the past two decades [1, 2].

Type 2 diabetes mellitus (T2DM) is the leading cause of CKD development in developed countries, accounting for 30-50% of all cases of terminal chronic renal failure requiring replacement renal therapy [3, 4]. Diabetic kidney disease (DKD) develops in 20-40% of patients with type 2 diabetes and is characterized by progressive decrease in glomerular filtration rate (GFR) and/or the appearance of albuminuria [5]. The fact that the prevalence of type 2 diabetes mellitus continues to steadily increase worldwide is of particular concern, which is predicted to increase the number of patients with DIP in the coming decades.

The pathogenesis of the progression of CKD in type 2 diabetes mellitus is multifactorial and includes a complex interaction of metabolic and hemodynamic disorders. Key metabolic risk factors include chronic hyperglycemia, dyslipidemia, obesity, insulin resistance, and systemic inflammation. Hemodynamic factors include arterial hypertension, intraglomerular hypertension, impaired renal blood flow autoregulation, and the activation of the renin-angiotensin-aldosterone system (RAAS) [6, 7].

Chronic hyperglycemia triggers a cascade of pathological processes, including non-enzymatic glycation of proteins, activation of the polyolic pathway of glucose metabolism, formation of glycation end products (AGEs), oxidative stress, and activation of pro-inflammatory signaling pathways. These mechanisms lead to structural and functional changes in the kidneys: thickening of the glomerular basement membrane, mesangial expansion, glomerulosclerosis, and tubulointerstitial fibrosis [8]. Arterial hypertension, present in 70-90% of patients with type 2 diabetes and CKD, is not only a risk factor for the development of diabetic nephropathy but also significantly accelerates the progression of renal dysfunction. Elevated systemic arterial pressure is transmitted to glomerular capillaries, causing intraglomerular hypertension, which leads to hyperfiltration, proteinuria, and ultimately glomerular sclerosis [9]. Dyslipidemia, characteristic of patients with type 2 diabetes mellitus, also plays an important role in the progression of CKD. Elevated levels of low-density lipoprotein cholesterol (LDL cholesterol), triglycerides, and decreased levels of high-density lipoprotein cholesterol (HDL cholesterol) contribute to the development of renal atherosclerosis, inflammation, and fibrosis of the kidney tissue [10].

Obesity, often associated with type 2 diabetes mellitus, is an independent risk factor for the development and progression of CKD through several mechanisms: increased intraglomerular pressure due to hemodynamic changes, activation of RAAS, insulin resistance, chronic inflammation, and oxidative stress [11].

Modern approaches to slowing down the progression of CKD in patients with type 2 diabetes are based on a comprehensive correction of the identified risk factors. Strict glycemic control with individualized target values of HbA1c, optimal blood pressure regulation with preferential use of ACE inhibitors or angiotensin II receptor blockers, correction of dyslipidemia with statins, body weight control, and the use of new generation nephroprotective drugs (SGLT2 inhibitors, GLP-1 receptor

agonists) demonstrated effectiveness in slowing the rate of GFR decrease and reducing the risk of cardiovascular complications [12, 13].

However, despite the successes achieved in understanding the pathogenesis and improving therapeutic approaches, the problem of the progression of CKD in patients with type 2 diabetes remains relevant. The issues of optimal choice and combination of therapeutic interventions, individualization of approaches depending on the patient's phenotype, temporal aspects of the intervention, and long-term outcomes remain insufficiently studied. In addition, the relative contribution of various metabolic and hemodynamic factors to the progression of CKD in different categories of patients requires further research.

In connection with the above, a comprehensive analysis of metabolic and hemodynamic risk factors for the progression of CKD in patients with type 2 diabetes mellitus, as well as the development and assessment of the effectiveness of strategies for their modification, is highly relevant and has important clinical and social significance for improving the prognosis and quality of life of this category of patients. Diabetic nephropathy remains one of the most serious complications of type 2 diabetes mellitus, being the leading cause of chronic kidney disease (CKD) and the terminal stage of renal failure in developed countries. According to international registries, diabetic kidney disease develops in 20-40% of patients with diabetes mellitus, while the risk of progressing to the terminal stage of CKD increases 10-20 times compared to the general population. The pathogenesis of diabetic nephropathy represents a complex interaction of metabolic and hemodynamic factors. Chronic hyperglycemia triggers a cascade of biochemical processes, including non-enzymatic glycation of proteins, activation of the polyolic pathway of glucose metabolism, increased oxidative stress, and inflammatory reactions[1]. Simultaneously, renin-angiotensin system dysfunction leads to hyperfiltration, increased intraglomerular pressure, and progressive sclerosis of the renal tissue.

Modern clinical studies confirm the multifactorial nature of diabetic nephropathy, where, along with glycemic control, the correction of arterial hypertension, dyslipidemia, proteinuria, and other cardiovascular risk factors is of critical importance. The implementation of the concept of comprehensive risk factors management has significantly improved the prognosis for patients with diabetic kidney disease. However, despite the successes achieved in understanding the pathophysiological mechanisms and developing therapeutic strategies, the problem of optimizing early diagnosis, risk stratification, and a personalized approach to treating diabetic nephropathy remains relevant [2]. The need for an integral assessment of metabolic and hemodynamic parameters for predicting the course of CKD and choosing optimal therapeutic tactics determines the clinical and scientific significance of this research direction.

Currently, metabolic syndrome and chronic kidney disease (CKD) are among the most pressing problems in medicine and are of great importance for the global healthcare system in terms of their prevalence and severe complications. According to the World Health Organization, approximately 20-25% of the world's population suffers from metabolic syndrome, which is more than 2 billion people. At the same time, chronic kidney disease occurs in 10-15% of the world's population, and in recent years its prevalence has been steadily increasing[3].

Metabolic syndrome is a complex of a number of pathogenetically interconnected metabolic disorders (abdominal obesity, arterial hypertension, disruption of blood serum lipid levels, insulin resistance) that lead to the development of cardiovascular diseases and chronic kidney disease. According to the results of recent studies, metabolic syndrome increases the risk of developing chronic kidney disease by 2.5-3 times and causes faster deterioration of kidney function [4].

In the Republic of Uzbekistan, the problem of metabolic syndrome and chronic kidney disease is particularly relevant. According to the Ministry of Health of the republic, 18-22% of the population have signs of metabolic syndrome, and 8-10% suffer from chronic kidney disease. The prevalence of these diseases is related to lifestyle, dietary habits, decreased physical activity, and genetic factors[5].

Along with diseases such as chronic kidney disease, diabetes mellitus, and obesity, in terms of the rate of spread, it is a pathology acquiring the character of a non-communicable epidemic. CKD develops among the general population in 13-15% of people, and in risk groups significantly more often - up to 40-50%, these groups include patients with type 2 diabetes [6]. According to the International Diabetes Federation, by 2035, the number of people with diabetes mellitus in the world will reach 587 million, 95% of whom are patients with type 2 diabetes mellitus. The prevalence of DM continues to grow in the

Russian Federation (RF), mainly due to patients with type 2 DM, whose number according to the State Register as of January 1, 2015, reached 4.094 million people, which is 2.8% of the RF population [7]. However, according to the results of studies conducted during active screening of DM, the actual prevalence of the disease is 2 times higher. WHO experts estimate the number of people with diabetes in Russia at approximately 9 million and include our country among the top ten countries in the world with the most common diabetes [8]. The severity of DM is associated with the general damage to the vascular system with the development of multiple microvascular (nephropathy, retinopathy) and macroscopic complications (RHD, coronary and peripheral atherosclerosis). The pathogenesis of kidney damage in type 1 and type 2 diabetes is different. In type 1 diabetes, this is classical DN, the main marker of which is increased protein excretion with urine - microalbuminuria (MAU), and then proteinuria (PU). A clinical feature of type 2 diabetes mellitus is the heterogeneity of renal pathology, which practically does not allow for the differentiation of classical DN based on protein excretion detection, as in type 1 diabetes mellitus [9]. Therefore, unlike type 1 DM, in type 2 DM, it is not advisable to focus solely on the MAU marker. In type 2 diabetes mellitus, CBP, compared to the classical glomerulosclerotic state in type 1 diabetes mellitus, has more significant changes in the parenchyma of kidney structures [10]. In addition to this type of chronic kidney disease, structural changes can be observed in type 2 diabetes mellitus even in the absence of MAU [1]. Therefore, when assessing the functional state of the kidneys in type 2 diabetes mellitus, assessing GFR as the main marker of the pathology is of particular importance. Consequently, in type 2 diabetes mellitus, structural changes can be more pronounced even in the absence of MAU [9]. Therefore, it is important to assess GFR as the main marker of pathology for assessing the functional state of the kidneys in type 2 diabetes mellitus.

According to modern concepts, MAU is a manifestation of general vascular endothelial dysfunction, which can explain not only kidney pathology but also a certain relationship between kidney diseases and the risk of cardiovascular events. ADVANCE's study showed that MAU and CKF are independent risk factors for cardiovascular pathology and kidney damage, these indicators reflect various structural damage occurring in the kidneys [5].

The introduction of the CBR concept into the practice of diabetic services is an important strategic approach aimed at reducing cardiovascular diseases and overall mortality, as the relationship between kidney dysfunction and changes in the cardiovascular system in patients with diabetes mellitus is based on common population risk factors that determine the commonality of many primary and secondary prevention methods [3].

Monitoring the level of glycemia and blood pressure (BP) in combination with the early use of angiotensin-converting enzyme inhibitors (ACE) and angiotensin receptor blockers (ARB) can slow the development of diabetic kidney damage. However, in some patients with diabetes mellitus (DM), the pathology develops earlier and progresses rapidly despite satisfactory glycemic control. The identification of this category of patients made it possible to assume the presence of genetic factors in the development of diabetic nephropathy (DN) and chronic kidney disease (CKD). A correlation has been shown between proteinuria levels, arterial hypertension (AH) levels, and the severity of glomerular sclerosis [4]. In addition, DN often develops among individuals with a complicated hereditary history of arterial hypertension and cardiovascular diseases. Searching for markers of genetic predisposition to CKD has particular clinical significance from the point of view of reducing the frequency of terminal stages, as it allows predicting the disease and identifying risk groups in the preclinical stage, when the initial structural changes can potentially be reversible. Despite the fact that patients with type 2 diabetes constitute the vast majority (90-95%) of the total number of patients with diabetes, the genetics of CKD were mainly studied on the "pure" model of type 1 diabetes - classical diabetes mellitus [7]. Thus, in the works of domestic scientists conducted among the population living in the territory of the Russian Federation, a strong relationship between DN and the complex of I/D markers of the ACE gene, ecNOS 4a/4b of the NOS3 gene, E2/E3/E4 of the APOE gene, and I/D of the APOB gene in type 1 diabetes mellitus has been shown [8]. The mechanisms of development of chronic kidney disease in patients with metabolic syndrome are complex and multi-component, among which insulin resistance, endothelial dysfunction, chronic inflammation, oxidative stress, and activation of the renin-angiotensin-aldosterone system play an important role. These factors lead to kidney tissue damage, decreased glomerular filtration rate, and the development of chronic renal failure.

Although numerous studies are being conducted to improve the methods of prevention and treatment of chronic kidney disease in patients with metabolic syndrome, there are still unresolved problems in this area. In particular, not all mechanisms of the relationship between metabolic syndrome and chronic kidney disease have been fully studied, criteria for early diagnosis have not been sufficiently developed, and the effectiveness of treatment and prevention methods is low.

Conclusions

Therefore, improving the methods of prevention and treatment of chronic kidney disease in patients with metabolic syndrome, developing algorithms for early diagnosis, effective treatment, and prevention of complications is a pressing scientific and practical task today. This study is aimed precisely at solving these problems and is devoted to developing new approaches that allow for the improvement of methods for early detection, prevention, and treatment of the risk of developing chronic kidney disease in patients with metabolic syndrome. Epidemiological indicators of the prevalence of metabolic syndrome and chronic kidney disease in the world and Uzbekistan Clinical and economic significance of this problem for the healthcare system Pathogenetic mechanisms of the relationship between metabolic syndrome and chronic kidney disease The need to develop a unified methodology for diagnosis, prevention, and treatment.

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