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Web: http://www.tadqiqot.uz/; Email: info@tadqiqot.uz
Телефон: +998 (94) 404-0000

Editorial staff of the journals of www.tadqiqot.uz
Tadqiqot LLC the city of Tashkent,
Amir Temur Street pr.1, House 2.
Web: http://www.tadqiqot.uz/; Email: info@tadqiqot.uz
Phone: (+998-94) 404-0000

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РЕВМАТОЛОГИЧЕСКИЕ И ИММУНООПОСРЕДОВАННЫЕ ЗАБОЛЕВАНИЯ

Ахмедова Гулчехра Абдуллаевна
Самаркандский государственный медицинский университет
ассистент кафедры внутренних болезней №1
Самарканд, Узбекистан
Хасанов Фаррух Шерали угли
Самаркандский государственный медицинский университет
кафедра внутренних болезней №1
Самарканд, Узбекистан
Эшмуратов Сардор Элдор угли
Самаркандский государственный медицинский университет
кафедра внутренних болезней №1
Самарканд, Узбекистан
Уралов Рустам Шербек угли
Самаркандский государственный медицинский университет
ассистент кафедры внутренних болезней №1
Самарканд, Узбекистан
Хамраев Хамза Хамидуллаевич
Самаркандский государственный медицинский университет
к.м.н., доцент, зав.кафедрой кафедры внутренних болезней №1
Самарканд, Узбекистан

ХРОНИЧЕСКАЯ БОЛЕЗНЬ ПОЧЕК У ПАЦИЕНТОВ С РЕВМАТОИДНЫМ АРТРИТОМ

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АННОТАЦИЯ

В настоящее время, по данным последних исследований, хроническая болезнь почек (ХБП) достоверно чаще встречается у больных РА, чем у больных без РА, и тесно связана с риском сердечно-сосудистых осложнений и высокой смертностью. Помимо влияния общепопуляционных факторов риска ХБП, независимым предиктором снижения скорости клубочковой фильтрации <60 мл/мин/1,73 м2 у больных РА является активность самого заболевания. Рассматриваются также возможные морфологические варианты и механизмы поражения почек. Внедрение в последние годы фармакотерапии базисными противовоспалительными и инновационными генно-инженерными и таргетными препаратами изменило течение и исходы РА, в том числе частоту и структуру почечных проявлений.

Ключевые слова: ревматоидный артрит, хроническая болезнь почек, скорость клубочковой фильтрации, амилоидоз, базисная терапия.

Akhmedova Gulchehra Abdullayevna
Samarkand State Medical University
Assistant of the Department of Internal Diseases No. 1
Samarkand, Uzbekistan
Khasanov Farrukh Sherali ugli
Samarkand State medical university
Department of Internal Diseases No. 1
Samarkand, Uzbekistan

Eshmuratov Sardor Eldor ugli
Samarkand State medical university
Department of Internal Diseases No. 1
Samarkand, Uzbekistan
Uralov Rustam Sherbek ugli
Samarkand State medical university
Assistant of the Department of Internal Diseases No. 1
Samarkand, Uzbekistan
Khamraev Khamza Khamidullaevich
Samarkand State medical university
Candidate of Medical Sciences, Associate Professor,
Head of the Department of Internal Diseases No. 1
Samarkand, Uzbekistan

CHRONIC KIDNEY DISEASE IN PATIENTS WITH RHEUMATOID ARTHRITIS

ANNOTATION

According to recent studies, chronic kidney disease (CKD) is significantly more prevalent in patients with rheumatoid arthritis (RA) than in those without RA, and is closely associated with the risk of cardiovascular complications and high mortality. In addition to the influence of general population risk factors for CKD, the activity of RA itself is an independent predictor of decreased glomerular filtration rate <60 ml/min/1.73 m2 in RA patients. Possible morphological variants and mechanisms of kidney damage are also considered. The introduction of pharmacotherapy with disease-modifying antirheumatic drugs and innovative biologic and targeted therapies in recent years has changed the course and outcomes of RA, including the frequency and pattern of renal manifestations.

Keywords: rheumatoid arthritis, chronic kidney disease, glomerular filtration rate, amyloidosis, disease-modifying therapy.

Axmedova Gulchehra Abdullayevna
Samarqand davlat tibbiyot universiteti
1-ichki kasalliklar kafedrasi assistenti
Samarqand, O‘zbekiston
Xasanov Farrux Sherali o‘g‘li
Samarqand davlat tibbiyot universiteti
1-son ichki kasalliklar kafedrasi
Samarqand, O‘zbekiston
Eshmuratov Sardor Eldor o‘g‘li
Samarqand davlat tibbiyot universiteti
1-son ichki kasalliklar kafedrasi
Samarqand, O‘zbekiston
Uralov Rustam Sherbek o‘g‘li
Samarqand davlat tibbiyot universiteti
1-ichki kasalliklar kafedrasi assistenti
Samarqand, O‘zbekiston
Xamrayev Xamza Xamidullayevich
Samarqand davlat tibbiyot universiteti
t.f.n., dotsent, 1-son ichki kasalliklar kafedrasi mudiri
Samarqand, O‘zbekiston

REVMATOID ARTRIT BEMORLARDA SURUNKALI BUYRAK KASALLIGI

ANNOTATSIYA

So‘nggi tadqiqotlar natijalariga ko‘ra, hozirgi kunda surunkali buyrak kasalligi (SBK) revmatoid artrit (RA) bilan og‘rigan bemorlarda, RA bo‘lmagan bemorlarga nisbatan ancha ko‘proq uchramoqda va yurak-qon tomir asoratlari xavfi hamda yuqori o‘lim ko‘rsatkichi bilan chambarchas bog‘liq. SBKning umumiy populyatsion xavf omillari ta’siridan tashqari, RA bilan og‘rigan bemorlarda koptokchalar filtratsiya tezligining 60 ml/min/1,73 m² dan pastga tushishining mustaqil bashoratchisi kasallikning faolligi hisoblanadi. Shuningdek, buyrak zararlanishining mumkin bo‘lgan morfologik variantlari va mexanizmlari ham ko‘rib chiqilgan. So‘nggi yillarda yallig‘lanishga qarshi bazis va innovatsion gen-muhandislik hamda maqsadli dori vositalari bilan olib borilayotgan farmakoterapiya RAning kechishi va natijalarini, jumladan, buyrak ko‘rinishlarining chastotasi va tuzilishini o‘zgartirdi.

Kalit so‘zlar: revmatoid artrit, surunkali buyrak kasalligi, koptokchalar filtratsiya tezligi, amiloidoz, bazis terapiya.

Introduction: Rheumatoid arthritis (RA) is a chronic inflammatory joint disease of unknown etiology, which has a diverse clinical course and is characterized by progressive destruction of synovial joints, accompanied by degradation of cartilage and bone, with possible spread outside the musculoskeletal system (cutaneous vasculitis, secondary Sjogren's syndrome, amyloidosis, etc.). The peak incidence of rheumatoid arthritis occurs between 45 and 65 years old. Women

are exposed to this disease 2-3 times more often than men. Despite the appearance of a wide range of innovative medicines that significantly improve the prognosis of the disease, the risk of various complications remains, including kidney damage [1]. The development of chronic kidney disease (CKD) with a decrease in glomerular filtration rate (GFR) <60 ml/min/1.73 m2 in patients with RA is significantly more common than in patients without RA. For example, one study found that the prevalence of CKD among patients with RA is 24.5% [2]. Our data indicate that kidney involvement in RA affects the prognosis of patients, especially given the close association of CKD with a high risk of cardiovascular complications and overall mortality [3]. Thus, the problem of the development of CKD and associated risk factors in RA is of high relevance at the present time and continues to be studied.

One of the most common factors in the development of CKD in RA is drug nephrotoxicity due to the widespread use of nonsteroidal anti-inflammatory drugs (NSAIDs), as well as some basic anti-inflammatory drugs (HDL) [4]. At the same time, an important aspect of the possible progression of CKD in RA is the inadequate correction of the dose of HDL, which is excreted through the kidneys. Thus, according to the data of the MATRIX retrospective study on the effect of various drugs on the risk of CKD in RA patients, an increase in serum creatinine levels was found in 19% of 129 examined patients. Among them, 20 and 15% of patients were diagnosed with stage II and III CKD, respectively. At the same time, the majority (90%) of patients with GFR <60 ml/min/1.73 m2 received at least one drug requiring dose adjustment, and 70% of patients received a potentially nephrotoxic drug. At the same time, half of the patients treated with methotrexate did not have the necessary dose adjustment in accordance with the level of glomerular filtration [5]. In addition to drug nephrotoxicity, CKD is predicted by general population risk factors such as concomitant cardiovascular diseases, dyslipidemia, and carbohydrate metabolism disorders [6]. In particular, the factors provoking the development of acute renal damage when using NSAIDs, in addition to previous CKD, include hypertension, hypovolemia and chronic heart failure, as well as the concomitant use of certain medications [diuretics, angiotensin converting enzyme inhibitors, aminoglycosides] [7].

The work of prominent authors has also established the effect of arterial hypertension along with hyperglycemia and elevated serum cholesterol in RA patients with CKD [8]. Severe arterial hypertension, smoking, and alcohol abuse are considered as independent risk factors for the development of CKD in RA patients and in the general population. According to some authors, men suffering from RA are more predisposed to developing CKD than women, which may be due to the higher prevalence of these risk factors among men. In addition to general population risk factors, the activity of chronic inflammation makes an equally significant contribution to the development of CKD in RA, and the relationship between the activity of the disease and the degree of decrease in GFR has been revealed [9]. In addition, early markers of renal damage, albumin and β2-microglobulin, are detected in urine in patients with higher disease activity and systemic manifestations of RA [10].

The most common clinical manifestation of kidney damage in RA is proteinuria, which indicates the development of amyloidosis or glomerulonephritis, however, a decrease in GFR can develop in the absence of urinary syndrome [11].

Various mechanisms of CKD progression have been discussed in patients with high levels of CRP. In particular, an increase in the C-reactive protein CRP may be associated with other risk factors for CKD – increased blood pressure, high levels of glucose and lipids, and obesity. On the other hand, it has been shown that CRP can be deposited in the glomerular endothelium and tubular epithelium, causing various mechanisms of CKD progression in patients with high levels of CRP. In particular, an increase in C-reactive protein (CRP) may be associated with other risk factors for CKD, such as high blood pressure, high glucose and lipid levels, and obesity. On the other hand, it has been shown that CRP can be deposited in the glomerular endothelium and tubular epithelium, causing severe inflammation with increased infiltration of tubulointerstitium by T lymphocytes and macrophages with increased production of proinflammatory cytokines, chemokines, and adhesive molecules [12]. An increase in CRP levels in the blood serum of RA patients may enhance the mechanisms of endothelial dysfunction, which contributes to damage to afferent arterioles and is accompanied by intraclubular hypertension [13].

The spectrum of renal pathology underlying CKD in RA is quite wide, which is associated with the possibility of damage to various structures of the kidneys, in particular the renal glomeruli, vessels, tubules and renal interstitium (see table). At the same time, the nature and severity of the urinary syndrome, as well as the clinical manifestations of nephropathy, do not always clearly correlate with a specific morphological variant of kidney damage, which in most cases requires a kidney biopsy and morphological verification of the diagnosis. The most common morphological forms of kidney damage in RA are amyloidosis, mesangioproliferative glomerulonephritis, membranous nephropathy, minimal changes, and interstitial nephritis, including those caused by NSAID use [14].

For many years, secondary renal amyloidosis occupied a leading position among all variants of nephropathy in RA patients, which was primarily due to insufficient control of the inflammatory activity of the disease [15]. It has been established that the development of secondary AA-amyloidosis in RA is associated with the hyperproduction of the precursor of amyloid, serum protein of the acute phase of inflammation (serum amyloid A – SAA), which is synthesized in hepatocytes under the influence of proinflammatory cytokines (TNF-α, IL-6, IL-1). The most common clinical manifestations of renal amyloidosis in RA are isolated proteinuria, nephrotic syndrome and, if treatment is ineffective, the formation of renal failure. The development of renal amyloidosis is more often associated with a long-term course of RA (more than 17 years), which distinguishes it from other types of kidney damage, in particular from membranous nephropathy or mesangial forms of nephritis, which develop much earlier. Despite the fact that the frequency of secondary amyloidosis is currently decreasing, patients with long-term chronic inflammation are still at risk of developing amyloidosis. Active therapy aimed at suppressing inflammation can lead to a decrease in amyloid deposition in kidney tissue [16]. Thus, according to the Finnish Registry in the period from 1995 to 2008. In patients suffering from secondary amyloidosis as part of RA, treatment with methotrexate was accompanied by a decrease in the number of end-stage CKD [17]. The expansion of pharmacotherapy possibilities in recent years has led to some changes in the structure of kidney damage in RA. However, according to the results of morphological examination of kidney biopsies, chronic glomerulonephritis is as common as amyloidosis [18].

The rarest morphological variants of renal pathology in CANCER are considered to be the disease of minimal changes, focal segmental glomerulosclerosis and rheumatoid vasculitis of the renal vessels. The latter type of lesion, despite its relative rarity, is prognostically unfavorable, since it is often accompanied by rapidly progressive renal failure, as well as concomitant damage to other organs, in particular the lungs [19].

The widespread introduction of methotrexate and the advent of the era of innovative targeted and genetically engineered biological drugs (GIBPS) in the treatment of RA have dramatically changed the course and outcomes of the disease, as well as the frequency and structure of renal manifestations associated with high inflammatory activity of RA. Several studies, including two meta-analyses, have shown the effect of GIBP (primarily TNF-α inhibitors) and HDL (mainly methotrexate) in RA patients to reduce both cardiovascular risk and CKD risk [20]. The use of TNF-α inhibitors and methotrexate is associated with an increase in the concentration of total cholesterol (cholesterol), low-density lipoprotein cholesterol (LDL) and, to a greater extent, high-density lipoprotein cholesterol (HDL), which improves the ratio of total cholesterol/HDL cholesterol. At the same time, according to Russian authors, against the background of treatment with another GIBP, the IL-6 inhibitor tocilizumab, a decrease in the inflammatory activity of RA is accompanied by an increase in the concentration of cholesterol and LDL cholesterol, an increase in the thickness of the intima—media complex of the carotid arteries and, in some cases, the appearance of atherosclerotic plaques [21].

The beneficial effects of GIBP, including the anti-B-cell drug rituximab, on endothelial function, lipid metabolism and insulin resistance are discussed both through direct action (by interrupting inflammation and endothelial dysfunction) and indirectly (through changes in lipid metabolism, carbohydrates, etc.), which may reduce the risk of CKD in patients with RA [22].

Conclusion: Kidney damage in RA may be associated with the effects of two main factors: the activity of chronic inflammation and nephrotoxicity of drugs used to treat the underlying disease. To date, there is a pathomorphosis of kidney damage in patients with RA with a decrease in the frequency of secondary amyloidosis, which is associated with progress in pharmacotherapy. There seems to be no doubt that the emergence of effective means of influencing the inflammatory activity of RA, in particular methotrexate and GIBP, combined with modern therapeutic strategies, helps to reduce the incidence of CKD in RA patients by better controlling disease activity and reducing the use of nephrotoxic medications. At the same time, cardiovascular and metabolic risk factors remain important in the pathogenesis of CKD in RA, in particular hypertension and lipid disorders, which can contribute to the development of nephrosclerosis through the activation of non-immune mechanisms of CKD progression.

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