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RISK FACTORS FOR KIDNEY DAMAGE IN RHEUMATOID ARTHRITIS

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ABSTRACT

Recent studies have demonstrated a high risk of kidney damage and associated cardiovascular complications in patients with rheumatoid arthritis (RA), which generally determines the prognosis of these patients. However, the frequency of chronic kidney disease (CKD) in RA in the Uzbekistan cohort of patients has not been precisely established. The unfavorable prognostic significance of kidney damage in rheumatoid arthritis (RA) has been actively attracting the attention of researchers in recent years. Certain clinical variants of involvement of the kidneys in the pathological process in rheumatoid arthritis are noted in most patients. Various variants of kidney damage in rheumatoid arthritis are described, in particular, glomerulonephritis, amyloidosis, vasculitis, as well as iatrogenic forms (analgesic tubulopathy, membranous nephropathy, etc.). It is noteworthy that in real clinical conditions, morphological verification of renal pathology may not be performed for a long time in such patients for a number of objective reasons. Early manifestations of functional renal disorders, especially with their moderate severity, do not always attract the attention of clinicians, while the progression of chronic kidney disease (CKD) in RA can be rapid, especially in old age, as well as in association with cardiovascular pathology. The formation of nephropathy in RA has a complex multifactorial character and manifests itself in various clinical and morphological variants. Thus, various clinical forms of kidney damage in RA are known (amyloidosis, glomerulonephritis, less often rheumatoid granulomatosis and rheumatoid renal vasculitis), as well as iatrogenic, due to ongoing treatment (medicinal tubulointerstitial nephritis, membranous nephropathy, mesangioproliferative glomerulonephritis). At the same time, in real clinical practice, the nosological diagnosis of kidney disease in RA is usually established when clinical and laboratory criteria appear, the most important of which is proteinuria, at the same time, it has recently been established that with a low-symptomatic course, renal dysfunction can develop without the presence of proteinuria. It is noteworthy that rheumatologists do not always pay attention to the early manifestations of functional renal disorders, especially with moderate severity of proteinuria, although the rate of decline in kidney

function in RA can be quite fast, especially in old age and in association with cardiovascular pathology.

Keywords: rheumatoid arthritis, kidney damage, chronic kidney disease, genetically engineered drugs

INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune disease characterized by the development of chronic destructive polyarthritis with frequent involvement of other systems in the pathological process. Extra-articular systemic lesions in RA can have a serious impact on the prognosis of the disease. Major studies conducted in recent years have demonstrated the association RA at high risk of chronic kidney disease (CKD) and cardiovascular complications, which is associated with an increase in mortality in this category of patients. In the Russian population, studies devoted to this problem are still few. The spectrum of renal pathology underlying CKD in RA is quite wide. Secondary amyloidosis for many years occupied the main position among the variants of nephropathy in RA patients. According to some studies, there is a tendency to change the structure of kidney damage in RA, taking into account the use of highly effective therapy regimens, including genetically engineered drugs, which serves as an additional prerequisite for studying this category of patients. It is very important that according to modern concepts, functional renal disorders lasting more than three months (so-called chronic kidney disease), including without a definite nosological diagnosis, are considered as the most important prognostic factor requiring correction of therapeutic tactics both in the general population and, possibly, in RA. According to some researchers, the development of chronic kidney disease in RA may be associated with cardiovascular pathology, while renal pathology itself is a risk factor for damage to the cardiovascular system. At the same time, no large-scale epidemiological studies have been conducted on the prevalence of chronic kidney disease in RA and risk factors associated with its development, and the available data are scattered and contradictory. Thus, the assessment of functional renal disorders and associated factors in RA is relevant for clinical medical practice, approaches to early detection of renal pathology and assessment of the risk of its progression in RA are insufficiently developed.

In recent years, much attention has been paid by researchers to cardiorenal relationships. The results of epidemiological and population studies indicate that even the earliest subclinical renal dysfunction are independent risk factors for cardiovascular events and death. A decrease in glomerular filtration rate (GFR) and

an increase in urinary albumin excretion are currently considered as "renal" markers of an unfavorable prognosis within the cardiorenal continuum. Thus, the attention of clinicians is focused primarily on the defeat of the glomerular apparatus of the kidney. However, in recent years, there has been more and more data on the importance of assessing the condition and tubulointerstitial kidney tissue, which, according to a number of researchers, is involved in the pathological process in cardiovascular diseases often before the glomerular apparatus

The aim of the study was to establish the frequency of kidney damage, as well as clinical and morphological variants and risk factors for the development of secondary nephropathy in RA patients.

MATERIALS AND METHODS

A retrospective analysis of the medical histories of RA patients was carried out. For the diagnosis of RA, the classification criteria ACR/EULAR 2010 (American College of Rheumatology/European League Against Rheumatism Rheumatoid arthritis classification criteria). The following indicators were evaluated in all examined patients: age, gender, duration of the disease, the presence of signs of kidney damage, as well as any other extra-articular manifestations of the disease (lung, skin, blood system damage etc.), serological variant of the disease (seropositive or seronegative), as well as clinical and laboratory indicators of RA activity, in particular ESR, C-reactive protein (CRP), hemoglobin and the DAS28-ESR index. The indicators of lipid and carbohydrate metabolism, body mass index, presence and degree of arterial hypertension (AH) were evaluated from the general population risk factors for CKD. Diagnosis CKD was established in accordance with the KDIGO criteria of 2010:

1) identification of any clinical markers of kidney damage confirmed over a period of at least 3 months;

2) the presence of structural changes in the kidneys revealed during the lifetime morphological examination of the organ;

3) decrease in glomerular filtration rate (GFR)<60 ml/min/1.73 m2, persisting for 3 months or more, regardless of the presence of other signs of kidney damage.

Biopsy material of kidney tissue and rectal mucosa was studied at the light-optical level, and an immunofluorescence study was also conducted. The presence of amyloid in the tissues of the kidney and rectal mucosa was confirmed on the basis of coloring with Congo red dye with microscopy in polarized light. Statistical data analysis was carried out using the software packages Statistica 10.0 and SPSS 22. Median and interquartile range were evaluated. When comparing groups with and without kidney damage, the nonparametric Mann–Whitney criterion was used. Spearman's

nonparametric rank correlation method and multivariate linear regression analysis are used to identify and evaluate the relationships between the studied indicators.

RESULTS AND DISCUSSION

The incidence of CKD in RA patients was 19.7% (41 out of 104) among patients observed in the 1st Clinic of SamMU in the period 2018-2019. Among 90 persons included in the study, 78 (86.7%) were women and 12 (13.3%) were men, the ratio was 7:1. The average age of all patients was 58.3 [50.5; 69.5] years. Various clinical and laboratory variants of kidney damage were observed in 43 out of 90 patients. According to the KDIGO criteria, CKD of stages I–II is noted in 13 (29.1%) out of 43 patients, stage III–IV CKD – in 31 (70.9%) out of 43. To assess the morphological variants of kidney damage in RA, the results of a study of 13 kidney biopsies and 5 biopsies of the rectal mucosa are available, and in 4 the clinical picture of renal damage most corresponded to tubulointerstitial nephritis, therefore, the nosological variant of kidney damage was determined in 23 cases. In 12 (50.0%) of 24 patients, a picture of renal amyloidosis was revealed (in 6 cases – by kidney biopsy, 6 – by biopsy of the rectal mucosa). 7 (30.4%) of 24 patients had chronic glomerulonephritis (CGN), while proliferative forms prevailed: mesangioproliferative glomerulonephritis (GN) – in 3 patients, membranoproliferative GN – in 1 patient. The picture of membranous nephropathy and the disease of minimal changes – in 1 case. Isolated proteinuria was observed in 4 patients, and an isolated decrease in GFR<60 ml/min was observed in 16 (36.0%). Clinical manifestations of nephropathy in patients with morphologically proven amyloidosis and CGN did not significantly differ in the level of proteinuria (1.5 [0.6–3.45] g/day vs 0.71 [0.27–1.46] g/day; p>0.05), the degree of eGFR reduction (61 [32-78] ml/min vs 55 [37-77] ml/min; p>0.05), as well as the severity of nephrotic syndrome (albumin 32.1 [26.2– 39.1] g/l vs 34.5 [28.8–40.9] g/l; p>0.05) in the groups of patients with renal amyloidosis and CGN, there were no significant differences, however, in the group of patients with renal amyloidosis were the duration of the disease and the level of CRP are significantly higher. Among the 90 analyzed patients, 62 received basic therapy with methotrexate or leflunomide, 14 received genetically engineered drugs: rituximab, abatacept, tumor necrosis factor α (TNF–α) inhibitors - infliximab, etanercept, golimumab, certolizumab pegol, adalimumab, interleukin-6 –tocilizumab inhibitors, janus kinase inhibitor - tofacitinib; 13 – various combinations of corticosteroids, sulfasalazine and hydroxychloroquine. We did not note significant differences in the level of proteinuria (0 [0-0.68] g/day vs 0 [0-0.72] g/day; p>0.05) and eGFR (74 [59-87] ml/min vs 59 [47-80] ml/min; p>0.05) in groups of patients receiving treatment with biological

genetically engineered drugs and basic therapy with methotrexate or leflunomide, respectively. The number of patients with kidney damage is significantly higher in the seropositive variant of the course of RA – 37 (52.1%) out of 70 than in the seronegative variant of the course – 13 (32.5%) out of 40 ($p<0.05$), as well as in RA with systemic manifestations 31 (60.3%) out of 51 than in RA without systemic manifestations – 12 (31.6%) out of 39 ($p<0.05$). The median duration of RA in the group with kidney damage was 14 [5-20] years, in the group without damage kidneys – 6 [2.5–11] years ($p<0.05$). We found that a longer course of RA (more than 10 years) it is associated with the development of amyloidosis of the kidneys, while CGN developed after a shorter period – on average 5-6 years after the onset of RA ($p<0.05$). In the general group of RA patients, including patients without kidney damage, there was a significant correlation of GFR with age, the presence and degree of hypertension, as well as the level of CRP in blood serum. In the group of patients with stage III–IV CKD, a significant correlation was observed with age, the degree of hypertension, impaired lipid metabolism, as well as the duration of RA and indicators of inflammatory activity of the disease – the values of ESR and the DAS28-ESR index. Among them, according to the results of multivariate regression analysis independent risk factors for CKD in RA patients were age, duration of RA, degree of hypertension and hypercholesterolemia. For the factors included in the multifactor model, relative risk values (RR) with confidence limits are calculated.

The frequency of kidney damage in RA, according to various studies, varies from 5 to 50%, but the true prevalence of CKD remains unknown. In our study, the incidence of kidney damage in RA patients was 19.7%, which exceeds the population level, but is slightly lower than in other samples. According to Japanese researchers, the prevalence of CKD among patients with RA is 24.5%, which is 2 times higher than that in the general population, while 1/4 with dynamic observation shows further progression of CKD. The same frequency (25.1%) was established by American authors over 20 years of observation of RA patients with initially normal GFR. In some patients, kidney damage may occur subclinically. As demonstrated by domestic authors, the appearance of albuminuria in patients with RA without concomitant kidney diseases was noted in 76% of individuals.

Markers of tubular dysfunction – a1 were detected in urine in 82% of patients-microglobulin and enzymes of the brush border of the tubule epithelium g-glutamate transpeptidase. The severity of these disorders is associated not only with the use of nonsteroidal anti-inflammatory drugs, but also with the activity of RA and the presence of systemic manifestations. The majority of patients (44.5%) had changes in urine tests with preserved GFR (stage I CKD), and a decrease in GFR<60 ml/min/1.73

m2 was observed in 20.3% of patients. Thus, the frequency of kidney damage in RA may be underestimated when using routine examination methods. The results of our study confirm, first of all, the important role of population nonimmune factors – age, hypertension and lipid metabolism disorders in the development of CKD in RA. The data obtained by us are consistent with the results of other studies indicating a possible association of CKD in RA with older age, hypertension, as well as disorders of lipid and carbohydrate metabolism. In addition, according to our data, the most significant independent risk factor was the duration of the disease, the influence of seropositivity for rheumatoid factor, the presence of other systemic manifestations was also noted. RA, high ESR, CRP and the DAS28 index, which indicates a great importance of inflammatory activity RA in the development of CKD. The importance of long-term persistence of chronic inflammation in the development of CKD in RA in recent years has been given much attention in the world literature. So, in the work of M. Kochi et al. Elevated CRP levels for at least 6 months were an independent risk factor for CKD. In population studies It was found that a high level of inflammatory markers interleukin-6 and TNF-α is also a predictor of deterioration of kidney function in RA. Chronic inflammation can directly affect the development of tubulointerstitial fibrosis through the deposit of CRP in the glomerular endothelium and tubular epithelium. An increase in CRP in transgenic mice causes severe inflammation with infiltration of tubulointerstition by T-lymphocytes and macrophages. It was found that an increased level of CRP may be associated with endothelial dysfunction in RA patients, causing damage to afferent arterioles and intraclubular hypertension. So, the vast majority of RA patients (60out of 66) had nephrosclerosis, which the authors associated with hypertension, however, the presence of a correlation between the degree of nephrosclerosis and the duration of RA suggested that the activity of RA can directly affect the development of fibrous changes in the kidney. The diagnosis of nephropathy in RA is most often established on the basis of the appearance of proteinuria, but a decrease in GFR can be detected in the absence of proteinuria. We The high frequency of isolated GFR reduction (36.0%) in RA patients was also confirmed. The decrease in GFR may be due to prolonged use of nonsteroidal anti-inflammatory drugs. So, B. Möller et al. it was established that nonsteroidal anti-inflammatory drugs are an independent factor of progression CKD and GFR reduction<30 ml/min/1.73 m^2.

According to our data, secondary amyloidosis continues to occupy a leading place in the structure of kidney damage in RA (in 50.0%). CGN was detected less frequently (in 30.4%) and tubulointerstitial kidney lesions (in 19.6%). The development of renal amyloidosis, unlike other forms of lesion, is associated with a persistent increase in

CRP (more than 15 mg/l) and RA duration of more than 11 years. CGN developed approximately 5 years after the debut of RA, while there were no direct correlations with the degree of activity of the disease. Among the morphological variants of CGN, proliferative variants of nephritis – IgA-nephropathy and a membranoproliferative variant.

In a retrospective study of another group, membranous nephropathy was predominant in renal biopsies of RA patients (16 out of 31). Amyloidosis was noted only in 6 (19.3%) patients. The remaining morphological variants (proliferative GN, minimal changes, tubulointerstitial nephritis) were found in isolated cases. This frequency of membranous nephropathy seems to be associated with the high prevalence of gold and D-penicillamine therapy.

CONCLUSION

In recent years, the role of genetically engineered biological agents in reducing not only cardiovascular risk, but also the frequency of CKD in RA patients has been discussed. The beneficial effects of biological agents on endothelial function , lipid metabolism and insulin resistance can directly (by interrupting inflammation and endothelial dysfunction) and indirectly (through changes in lipid metabolism, carbohydrates, etc.) affect the risk of developing CKD in this patient population. We also assessed the impact of genetic engineering However, there were no statistically significant differences in patients receiving treatment with traditional basic drugs (methotrexate and/or leflunomide) or genetically engineered drugs in our sample. On the contrary, according to K. Immonen et al., new basic drugs, including biological targeted agents, are more effective in suppressing systemic inflammation, and the use of these drugs reduces the frequency of the development of amyloidosis . Currently, there are several studies that indicate the effectiveness of TNF-α inhibitors in improving kidney function in patients with RA and amyloidosis. K. Sumida et al. in a large number of patients with RA (20,757 patients), it was shown that the administration of biological drugs significantly slows down the development and progression of CKD. The lack of a clear link between CKD and therapy in our study may be due to insufficient follow-up and a small number of patients in the study sample. Prospective studies are needed to assess the degree of decrease in renal function in dynamics during treatment.

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