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# ТЕОРИЯ НАСЛЕДСТВЕННОЙ ПРЕДРАСПОЛОЖЕННОСТИ И ПРОБЛЕМА КОМОРБИДНОСТИ РЕВМАТОИДНОГО АРТРИТА У БОЛЬНЫХ С СЕРДЕЧНО –СОСУДИСТЫМИ ЗАБОЛЕВАНИЯМИ

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**АННОТАЦИЯ**

Проблема коморбидности широко обсуждается в современной медицинской литературе. Особенно интересна ее роль при ревматических заболеваниях в связи с их многофакторностью и вовлечением обширного спектра патогенетических механизмов. Многие годы исследователи по всему миру отмечают корреляции между наличием активных аутоиммунных нарушений и осложненным течением сердечно-сосудистых заболеваний. Более глубокое понимание патогенетических механизмов на современном этапе развития ревматологии позволяет по-новому взглянуть на связь между атеросклерозом и ревматоидным артритом. Разработанное в последние годы определение мультиморбидности и результаты недавних научных исследований могут способствовать более корректному выбору тактики ведения пациентов при сочетании этих двух заболеваний.

**Ключевые слова:** коморбидность; мультиморбидность; ревматоидный артрит; сердечно-сосудистые заболевания; атеросклероз, аутоиммунитет, аутовоспаление.

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# HEREDITARY PREDISPOSITION THEORY AND THE PROBLEM OF RHEUMATOID ARTHRITIS COMORBIDITY IN PATIENTS WITH CARDIOVASCULAR DISEASE

**ANNOTATION**

The problem of comorbidity is widely discussed in the current medical literature. Its role in rheumatic diseases is particularly interesting because of its multifactorial nature and the involvement of a wide range of pathogenetic mechanisms. For many years, researchers around the world have noted correlations between the presence of active autoimmune disorders and the complicated course of cardiovascular diseases. A better understanding of the pathogenetic mechanisms at the current stage of rheumatology allows a new perspective on the relationship between atherosclerosis and rheumatoid arthritis. The definition of multimorbidity developed in recent years and the results of recent scientific research can contribute to a more correct choice of management tactics for patients with a combination of these two diseases.

**Keywords:** comorbidity; multimorbidity; rheumatoid arthritis; cardiovascular disease; atherosclerosis, autoimmunity, autoinflammation

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# YURAK-QON TOMIR KASALLIKLARI BO'LGAN BEMORLARDA REVMATOID ARTRITNING IRSIY MOYILLIGI NAZARIYASI VA KOMORBIDLIGI MUAMMOSI

**ANNOTATSIYA**

Komorbidlik muammosi zamonaviy tibbiy adabiyotlarda keng muhokama qilinmoqda. Revmatoid kasalliklarda uning roli, ayniqsa, ularning multifaktorialligi va patogenetik mexanizmlarning keng doirasini jalb qilish bilan bog'liq. Ko'p yillar davomida butun dunyo bo'ylab tadqiqotchilar faol autoimmün kasalliklar mavjudligi va yurak-qon tomir kasalliklarining murakkab kechishi o'rtasidagi bog'liqliklar qayd etildi. Revmatologiya rivojlanishining hozirgi bosqichida patogenetik mexanizmlarni chuqurroq tushunish ateroskleroz va revmatoid artrit o'rtasidagi bog'liqlik haqida yangi tushunchalar o’rganilmoqda. So'nggi yillarda ishlab chiqilgan multimorbidlik ta'rifi va so'nggi ilmiy tadqiqotlar natijalari ushbu ikki kasallikning kombinatsiyasi bilan bemorlarni boshqarish taktikasini yanada to'g'ri tanlashga yordam berishi mumkin.

**Kalit so'zlar:** komorbidlik; multimorbidlik; Romatoid artrit; yurak-qon tomir kasalliklari; ateroskleroz, otoimmunitet, avtoyallig'lanish.

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease with progressive destruction of the joints and internal organs, caused by a variety of pathophysiological mechanisms involving the innate and acquired immune system. RA is characterized by severe systemic inflammation, which contributes to true comorbid conditions (iatrogenia and secondary amyloidosis), as well as, of course, a more severe course of concomitant pathology. The prevalence of RA varies considerably between geographical areas, with the highest rates occurring in urban populations in developed countries (1). A recent meta-analysis summarising data from 41 countries showed that the overall prevalence of RA between 1986 and 2014 was around 0.46% [2]. From 1990 to 2017, the age-standardised prevalence of RA increased by 7.4% and the incidence increased by 8.2%, resulting in an increase in years lived with RA-related disability from 0.24 to 0.31% of total years lived with disability worldwide [1]. At the same time there has been a decrease in the number of patients with seropositive RA and an increase in the number of patients with seronegative RA. The incidence of RA in Russia for 2015-2016 reached 27.2 cases per 100,000. [3]. It is believed that the development of RA is associated with the presence of a hereditary predisposition, which can manifest when exposed to the relevant environmental factors that induce activation of innate and acquired immunity, which, in turn, leads to the development of chronic autoimmune inflammation. Genetic factors not only determine the predisposition to the disease, but also significantly influence the severity and rate of progression of RA. The alleles most relevant to RA belong to class II of the major histocompatibility complex. A common epitope (DE) associated with the risk of RA is found in the third hypervariable region of the DRβ-chain. DRB*0401, DRB*0404, DRB*0101 and DRB*1402 are considered the most significant risk factors. Over 90% of RA patients are carriers of at least one of these variants [4]. It is likely that these alleles may increase the risk of RA due to interaction with arthritogenic antigens such as citrullinated proteins. Epidemiological studies have shown that smoking can be a pathogenic stimulus triggering the chronic autoimmune process in RA, and the degree of risk is directly related to its duration and the number of cigarettes smoked. The risk increases dramatically when smoking and related genetic factors are combined. Carriage of OE-containing HLA alleles increases the likelihood of RA by a factor of 4-6, and in combination with smoking, by a factor of 20-40 [5]. Apparently, in people with these alleles, the presentation of citrullinated peptides may be more efficient, which favours the production of antibodies to citrullinated proteins (ACBs). Their appearance could be due to the unique properties of the binding site of the RA-associated HLADR alleles and a defect in cellular regulation that contributes to the autoimmune process. It is possible to detect ADCs several years before the onset of clinical symptoms of the disease. Their serum levels increase with time and reach a maximum by the onset of RA. At the same time, there is an increase in pro-inflammatory cytokines and chemokines in the blood, which is considered a sign of the development of a systemic inflammatory process [6]. After the onset of the disease, autoantibodies present in the joint can bind antigen, fix complement and trigger a cascade of changes leading to activation of resident cells, increased migration of innate and acquired immune cells, and stromal cell activation [6]. This, in turn, leads to increased production of cytokines and chemokines with the formation of a self-sustaining autoimmune process. Musculoskeletal damage can cause severe functional impairment and worsen the quality of life of patients. The development of chronic inflammation in RA is also associated with a significant reduction in life expectancy. There are several factors that contribute to the mortality gap between patients with RA and the general population. For example, RA is accompanied by an increased risk of the formation/progression of serious comorbid conditions, which can significantly worsen the prognosis of the underlying disease, and patients with RA often do not receive optimal preventive therapy (both primary and secondary). In addition, RA-associated systemic inflammation and immune system dysfunction can significantly exacerbate the progression of comorbid and comorbid conditions/disorders and lead to increased associated mortality [7]. Between 1990 and 2017, there was a decrease in age-standardised mortality from RA and other musculoskeletal diseases in Western Europe, several countries in the Asia-Pacific region and southern Latin America [8]. In contrast, the opposite trend was seen in Central Asia, Eastern Europe and tropical Latin America. However, despite a significant decrease in the mortality rate of RA patients, such an important index as the "gap between the rates" of total and "cardiac" mortality in RA and in the general population remained virtually unchanged, since both indices decreased in both populations in parallel and at the same rate [9-11]. The prognosis in RA is not so much determined by chronic arthritis as by comorbidities, among which renal and cardiovascular disease associated with atherosclerosis occupy a special place. A meta-analysis of prospective studies has shown that the risk of cardiovascular mortality in RA patients is 48% higher than in the general population [12]. High mortality from cardiovascular complications (CVD) in RA is not least caused by accelerated progression of atherosclerosis, the development of chronic cardiovascular failure and the formation of the so-called renocardial continuum [13]. N. Gorbunova et al. [14], who analyzed cardiovascular risk in patients observed in FSBSI "Research Institute of Rheumatology named after A.A. Nasonova". V.A. Nasonova Scientific Research Institute, reported that cardiac pathology was the main cause of mortality in 40% of RA patients. An assessment of musculoskeletal system disease (MSD) mortality in the Tula region by original and multiple causes showed that the most frequent original cause of death from MSD was osteoporosis, with inflammatory joint diseases (25 of 29 cases - RA) coming in second and systemic connective tissue lesions in third place. Among the competing causes of death, respiratory diseases, intoxications, and diseases of the circulatory system ranked first, second, and third, respectively, in terms of frequency [15]. In an analysis of the causes of death identified at autopsy (2008-2016), case histories (1995-1999), and databases (2001-2016) of RA patients, it was found that the leading cause of death was chronic renal failure, in other words, chronic kidney disease (CKD) not related to RA-specific or amyloid kidney damage. Ischaemic (atherosclerotic) nephropathy was the most common finding (15). A feature of atherosclerosis developing in RA is multiple coronary artery lesions, early recurrence of acute coronary syndrome, increased mortality after the first myocardial infarction (MI), and a high incidence of asymptomatic MI [16, 17]. RA is characterized by a significant incidence of marked signs of vascular wall inflammation and unstable plaques, which may serve as a substrate for subclinical multiple cholesterol atheroembolism syndrome. The prevalence of subclinical atherosclerotic vascular changes (increased thickness of intima-media complex of carotid arteries, coronary artery calcinosis) in RA patients reaches 25-45% [9]. Even before the development or at early stages of RA, 35-50% of cases reveal markers of cardiovascular lesions: endothelial dysfunction, decreased elasticity of small and large vessels, diastolic myocardial dysfunction, which increase in severity with the duration of the disease [8]. Moreover, the second peak of RA onset occurs at the age of 64-65 years, when the risk of cardiovascular pathology is increased. The accelerated progression of atherosclerosis in RA patients may be partly due to similar pathogenetic mechanisms of the two diseases. To some extent, atherosclerosis is regarded as a chronic inflammatory vascular disease characterized by lipid deposition, leukocytic infiltration and proliferation of vascular smooth muscle cells [3]. Activation of innate and acquired immunity plays a fundamental role in the pathogenesis of atherosclerosis, like RA. In one third of patients it leads to the development of chronic subclinical inflammation, which drives the progression of the atherosclerotic process at all its stages: endothelial dysfunction, low-density lipoprotein (LDL) modification, formation of "foamy" cells, endothelial cell apoptosis, atherosclerotic plaque rupture, cholesterol atheroembolism, atherothrombosis, etc. The inflammatory process in atherosclerosis is accompanied by inflammatory cellular (predominantly macrophage) infiltration of the atherosclerotic plaque, and its severity correlates with the severity of atherosclerosis. There is also an increase in the production of several proinflammatory cytokines and chemokines, as well as serum concentrations of CRP and interleukin (IL)6. These changes correlate with the progression of atherosclerotic vascular disease and the development of CVCs, independent of serum lipid concentrations [4]. Several factors that may contribute to the increase in the frequency and severity of CVCs in RA

patients are distinguished [2,5]: increased production of pro-inflammatory cytokines such as IL1, IL6, tumour necrosis factor , interferon, increased adhesion of activated neutrophils, monocytes and platelets to the vascular endothelium, further activation of platelets by neutrophils and monocytes, activation of the vascular endothelium by PAR1 adhesive neutrophils and macrophages, chronic subclinical inflammation, the effect of neutrophils on activated platelets with intravascular formation of neutrophil extracellular traps (NETs) supporting inflammation. However, the mere presence of chronic autoimmune inflammation is not a sufficient condition for the development of atherosclerosis. Genomic studies have provided evidence for a genetic predisposition to the occurrence of CVCs. Increased cardiovascular risk in RA may be associated with genetic polymorphisms such as rs 1746048 variant CXCLI2 of 10 chromosome 10q 11.21 gene, rs 662 variant of paraoxonase 1 gene, rs1024611 polymorphism 2518A/G promoter of monocyte chemoattractant protein 1 gene, etc. [6,8]. In addition, the IL19 rs17581834(T) gene polymorphism, which increases the risk of CVCs by 3-fold, has been described [2,9]. In addition to chronic inflammatory process and hereditary predisposition, the probability of cardiovascular pathology in RA depends significantly on the presence of traditional cardiovascular risk factors (CVR). In a study of 563 RA patients, it was noted that in the presence of CVD, there was an increase in the frequency of traditional risk factors: arterial hypertension, diabetes mellitus and an increase in body mass index [30]. Increased cardiovascular risk in RA can also be associated with dyslipidemia, smoking, sedentary lifestyle, CVD-associated heredity, and menopause [1]. In addition to these factors, renal pathology (even latent) plays a significant role in the formation of predisposition to CVD, which is one of the key components of cardiorenal continuum, the existence of which has long been convincingly proved in several studies [13]. The close association between chronic arthritis and atherosclerosis is evident not only in the increased incidence of CVD in RA patients, but also in a reduction in its severity under the influence of antirheumatic therapy. Active treatment aimed at achieving remission of RA significantly slows the progression of the atherosclerotic process and reduces the cardiovascular risk [11]. A number of clinical trials have convincingly demonstrated that methotrexate (MT), which is the "gold" standard of basic therapy for RA, reduces not only inflammatory activity, but also the risk of CVC [2, 3]. However, there is also the exact opposite viewpoint. Research evidence of the involvement of inflammation in the progression of atherosclerosis has led to the use of anti-inflammatory drugs in the treatment of this disease. Their efficacy has been studied in two major studies. The randomized, double-blind, placebo-controlled CANTOS trial enrolled patients (n=10,061) who had suffered a MI and had CRP levels ≥2 mg/L [4]. The aim of the study was to test the inflammatory hypothesis of atherosclerosis development by inhibiting IL1-dependent inflammation. The primary endpoints were non-fatal MI, non-fatal stroke and cardiovascular death. Four groups of patients received either placebo or canakinumab at doses of 50, 150 and 300 mg every 3 months. By the end of the study, the rate of reaching the primary endpoint in the placebo group was 4.50 cases per 100 person-years; in the canakinumab 50 mg group, it was 4.11 cases per 100 person-years (relative risk, OR vs placebo, 0.93; p=0.30); in the canakinumab 150 mg group, 3.86 cases per 100 person-years (OR versus placebo, 0.85; p=0.02075); in the canakinumab 300 mg group, 3.90 cases per 100 person-years (OR versus placebo was similar to that in the canakinumab 150 mg group). Cholesterol (CH) levels in the subjects did not change significantly during therapy. These data indicate an important role of IL1-dependent inflammation in the induction and progression of atherosclerosis. It is known that CHC crystals, like sodium monourate crystals, can activate the NLRP3-inflammasome, thereby stimulating IL1 synthesis [3,5]. They also trigger the formation of NETs, which "prepare" macrophages for the synthesis of pro-inflammatory cytokines and activate the Th17-type immune response. NLRP3-inflammasome activation in atherosclerotic lesions most probably occurs via exposure of cholesterol crystals, NETs, tissue hypoxia and locally generated turbulent blood currents [3,9] to LRR-domain of NLR followed by caspase 1 activation and downstream activation of IL1, increased IL6 synthesis in liver and accumulation of SRB. The presence of such changes may confirm the autoinflammatory nature of the atherosclerotic process [10]. Parallel to CANTOS, a randomised, double-blind, placebo-controlled CIRT trial was conducted [4,10] in which 4786 participants received tablet MTs 15-20 mg/week in combination with folic acid 1 mg/day or placebo. The primary endpoint (recurrent MI, bypass surgery, stroke or death) was the same as in the CANTOS trial. The study was stopped due to the lack of effect of MT on IL1, IL6 or CRP levels compared to placebo, with the primary endpoint being recorded in 170 patients in the MT group and 167 in the placebo group. As autoimmune inflammation is an important risk factor for the clinical and subclinical manifestations of atherosclerosis, some authors believe that its accelerated progression can be considered as a distinct systemic manifestation of RA [1,2]. However, such an interpretation of the relationship between rheumatoid inflammation and atherosclerosis is, in our opinion, too simplistic. Without denying the pathogenetic proximity of these two diseases and the beneficial effect of anti-rheumatic therapy for RA on cardiovascular risk, we would still like to emphasize that we are talking about two different nosologies, which can develop quite autonomously and in parallel. The results of the CANTOS and CIRT studies suggest significant differences in the inflammatory process in RA and in atherosclerosis, and these differences have a significant impact on the susceptibility of existing pathological changes to therapy. For example, MT, which has been successfully used in RA, has not been able to control both the development of atherosclerosis itself and its cardiac manifestations. Apparently, MT can eliminate the negative effect of RA activity, which accelerates the development of atherosclerosis, but CVD can develop independently of RA. At the same time, canakinumab, which has shown very modest results in RA [2], has provided a significant improvement in atherosclerosis. Of great practical interest is the work of E.V. Udachkina et al. [4,13], who observed patients with early-onset RA who had not previously received basic anti-inflammatory drugs and glucocorticoids. All patients received initial monotherapy with MT. If the effect was insufficient, a genetically engineered biological agent was added to the treatment after 3 months. Initial and after 18 months of therapy, duplex scanning of the carotid arteries was performed. A total of 74 patients with active RA were included in the study, 31 of whom achieved remission after 18 months. At re-examination, the appearance of atherosclerotic plaques was detected in 8 patients without previous signs of atherosclerosis. In addition, an increase in the number of atherosclerotic plaques was detected in 19 patients who had signs of atherosclerosis at the time of inclusion. The development and progression of atherosclerosis occurred despite active modern anti-rheumatic therapy ("Treatment to Achievement"). The onset of remission of RA and the type of therapy had no significant effect on the progression of atherosclerosis. This work clearly demonstrates that active treatment of RA, which is carried out in strict accordance with current recommendations using the most effective drugs, doesn't allow to properly control the progression of atherosclerosis even at the early stage of the disease and even in cases when the set goal of remission or low activity RA is realized. O.A. Fomicheva et al. [12] observed 124 RA patients with suspected coronary heart disease (CHD) for 3 years. At the time of inclusion in the study, atherosclerotic plaques in the carotid arteries were detected in 77% of cases, atherosclerotic lesion of the coronary arteries - in 7%. The progression of coronary and/or carotid atherosclerosis was observed in 23% of patients during the follow-up period. The risk factors were smoking, CVD heredity and the duration of the disease. The levels of proinflammatory cytokines were higher in RA patients with progressing atherosclerosis. At the same time, anti-rheumatic therapy did not significantly affect the progression of atherosclerosis. E.V. Gerasimova et al. [4,5] in 63 RA patients with suspected or verified CHD showed hemodynamically significant coronary artery stenosis in 35% of cases. When performing multiple regression analysis the authors didn't find any correlation between coronary artery stenosis and age, sex, DAS28, sed rate, CRP, CHD, LDL and HDL levels as well as antirheumatic drug use. The above data allow us to state unequivocally that today we cannot regard atherosclerosis as an extra-articular manifestation of RA. Any classification must first and foremost meet the needs of clinical practice and assist the physician in the choice of management of the patient. If we equate atherosclerosis with other manifestations of RA, it will delay

the early detection of cardiovascular abnormalities and the timely prescription of adequate therapy. There is no doubt that the reduction in cardiovascular risk due to anti-rheumatic therapy is an important achievement. But what practical conclusion should we draw from this? That you have to treat RA before you can achieve the goal? Is anyone disputing that? All current guidelines for the treatment of RA contain this statement. The mere presence of RA already serves as an indication for such therapy, and the presence of CVDs would not be a reason to intensify it. But we cannot expect a treatment that provides remission or low activity RA to be as effective for cardiovascular disorders. The current classification of RA considers atherosclerosis as a complication [6]. Such an interpretation may be somewhat more accurate in reflecting the nature of the relationship between the two diseases, but it too cannot be regarded as a good one. A complication is a sign of a late stage of the disease, and cardiovascular abnormalities can often precede the development of RA. It should be considered that the second peak of RA occurs at the age of 65 and such a chronology of these nosologies is at least not uncommon. In determining the management of a patient with RA, the physician must remember that the disease is a serious risk factor for CVDs. Its early detection is as important as the early diagnosis of RA itself. CVDs are often asymptomatic and the first clinical manifestation of RA may be fatal. It is therefore necessary to screen for atherosclerosis early in the course of RA. Furthermore, the choice of therapy should be based on the fact that RA and atherosclerosis, despite their seemingly close relationship and the similarity of a number of pathogenetic mechanisms, are still autonomous diseases and a targeted treatment of one of them does not effectively control the other. Moreover, even the achievement of a sustained drug-induced clinical and laboratory remission of RA (including a rarely achieved immunological remission) does not relieve the patient from the persistent ("smoldering") rheumatoid inflammation. From a practical point of view, the combination of RA and atherosclerosis should be considered within the concept of multimorbidity, according to which the patient's diseases are not divided into "index" and comorbidities, but are considered to be of equal value. Such an approach to the management of patients with a combination of RA and atherosclerosis seems optimal, since these nosologies are comparable in clinical significance and insufficient attention to either of them can lead to severe consequences for the patient. The development of RA is associated with the formation of a complex set of pathological changes: musculoskeletal damage, extra-articular manifestations, disease complications, adverse reactions due to the side effects of drug therapy, as well as increased susceptibility to other diseases, including CVD, contributing to the occurrence of a spectrum of comorbid disorders, the nature of which may vary depending on individual patient characteristics. Atherosclerosis-related cardiovascular pathology occupies a special place in this spectrum. Studies show that the development of inflammatory atherosclerosis in RA patients is not a coincidence. An active inflammatory process in general and rheumatoid in particular may jointly favor the development of atherosclerosis in the presence of an appropriate genetic background. However, we do not yet know whether the genetic factors responsible for the onset of atherosclerosis influence the characteristics of RA itself. There is an opinion that RA is not a single nosology but a syndrome in which similar clinical manifestations may be mediated by different pathogenetic mechanisms [4,7]. Based on the needs of routine clinical practice and scientific research data, it seems reasonable to identify a special variant of RA closely associated with atherosclerosis and, consequently, with its multiple clinical manifestations (multimorbidity). There is a need to develop clinical guidelines for the management of these patients, describing the screening procedure for atherosclerosis, the correction of traditional and inflammatory risk factors, and the specifics of drug therapy for CVD and RA. In addition, it may be of great interest to study the development of RA in these patients, particularly the efficacy of IL1 inhibition in early and refractory RA associated with atherosclerosis. However, the EULAR (European Alliance of Associations for Rheumatology) guidelines [4,9] are already an important step in optimising the screening, assessment and management of cardiovascular risk in patients with RA. At the same time, approaches to risk stratification, correction of modifiable risk factors and selection of optimal immunomodulatory therapy for RA in the context of real control of atherosclerosis progression require further study. In addition, increased collaboration between rheumatologists and primary care physicians, cardiologists and, as is becoming evident, nephrologists is necessary. The basis for this collaboration is the proximity of the mechanisms of onset and progression of RA, atherosclerosis, CVD and CKD: NLRP3,IL1 and IL6 inflammasome activation, clonal hematopoiesis and cellular "aging" represent a significant driving force of systemic inflammation in both CVD and CKD.

**Conclusions:** Establishing a model of cardio-nephro-rheumatology care in which responsibilities are co-ordinated between different specialists will improve compliance with current treatment recommendations for the above conditions. An example of such a successful collaboration is the collaboration between rheumatologists and dermatologists in psoriatic arthritis. Such cooperation can deepen the knowledge of the individual specialties and initiate joint research for the development of modern therapeutic strategies

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