METABOLIC SYNDROME IN RHEUMATOID ARTHRITIS

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ABSTRACT

Introduction. Rheumatoid arthritis and metabolic syndrome have common pathogenic mechanisms, thereby potentiating each other together, forming a high risk of cardiovascular diseases.

The aim of the study was to study the effect of metabolic syndrome on the course of rheumatoid arthritis and the formation of cardiovascular risk.

Material and methods. During the study, a clinical evaluation of 100 patients with rheumatoid arthritis, average age 55±12.4 years. The patients were divided into 2 groups depending on the presence of metabolic syndrome: Group 1 – persons with metabolic syndrome (59 people, 59%) and group 2 - persons without metabolic syndrome (41 patients, 41%). The data obtained were processed using the STATISTICA 10 program. Differences in indicators were considered statistically significant at $p<0.05$. Results and their discussion. In group 1, the activity of rheumatoid arthritis was higher (DAS-28 index was 5.58±0.9) than in group 2 (DAS-28 index was 5.23±0.85) ($p=0.02$). The daily dose of glucocorticosteroids was higher in the group with metabolic syndrome: in terms of prednisone 7.5 [5; 10] mg versus 5 [5; 10] mg in the group without metabolic syndrome ($p=0.013$). Verified arterial hypertension was 3.8 times more common in the presence of metabolic syndrome. Left ventricular myocardial hypertrophy was 1.5 times more common in patients in the group with metabolic syndrome (35.9%), and it was noted both in combination with arterial hypertension and without it. In group 1, hypertrophy left ventricular myocardium, unrelated to arterial hypertension, was found in 9 people (9.78%). In group 2, myocardial hypertrophy was associated with arterial hypertension in all patients.

Conclusions. The presence of metabolic syndrome in rheumatoid arthritis is associated with a higher activity of rheumatic disease. In patients with rheumatoid arthritis, it contributes to an increase in cardiovascular risk, characterized by a higher incidence of arterial hypertension (3.8 times), an increase in the level of total cholesterol and an increase in the mass of the myocardium of the left ventricle. In patients with a combination of rheumatoid arthritis and metabolic syndrome, myocardial hypertrophy was detected even in the absence of arterial hypertension, which dictates the need for echocardiography in this group of patients.

Keywords: rheumatoid arthritis, metabolic syndrome, cardiovascular risk

INTRODUCTION

Over the past 20-30 years, the life expectancy of patients with rheumatoid arthritis (RA) has decreased by an average of 10 years compared to that of the general population. Risk factors are not completely clear, there are various opinions that RA is caused by a combination of genetics and lifestyle, viruses or bacteria, some studies associate it with lesions of the endocrine system. Patients with chronic inflammatory arthritis, such as RA, are prone to accelerated development of cardiovascular pathology. There are studies confirming the high prevalence of cardiovascular pathology in patients with systemic rheumatic diseases. Over the past decades, a link has been established between RA and lipid profile disorders. Currently, cardiovascular diseases are the main cause of death in patients with RA, in particular, myocardial infarction is registered in these patients four times more often than in patients without RA.

In recent years, the interest of many scientific fields and clinical studies from around the world to the problem of metabolic syndrome has also been growing. Metabolic syndrome (MS) is a symptom complex characterized by an increase in visceral fat mass, decreased sensitivity of peripheral tissues to insulin and hyperinsulinemia, which cause the development of disorders of carbohydrate, lipid, purine metabolism and arterial hypertension. The share of MS among the general population is growing every year, reaching 10-40% of the population according to various sources. At the same time, as is known, MS significantly increases the risk of cardiovascular complications, promotes the development of endothelial dysfunction and has pro-inflammatory activity, therefore, it can also influence the course of RA. The prevalence of MS among patients with RA is up to 32%. RA and MS have common pathogenic mechanisms, for example, an increase in free radicals, a deficiency of antioxidant systems, an increase in pro-inflammatory cytokines, endothelial damage, as well as the formation and destabilization of atherosclerotic plaques. They potentiate each other together, forming a higher risk of cardiovascular diseases than the sum of individual factors. In the pathogenesis of the development of RA, the role of pro-inflammatory cytokines in the formation of endothelial dysfunction in patients with RA (tumor necrosis factor (TNF)-α, interleukin (IL)-6, IL-8, IL-17 and IL-18) is noted. Excessive synthesis of TNF-α in the early stages induces the development of endothelial dysfunction, and IL-6 increases it as inflammation progresses. In RA, an imbalance of the immune system develops with a significant increase in cytotoxic CD4+ lymphocytes against the background of a decrease in CD3+ T-lymphocytes and with an increase in the level of immunoglobulin G. As the activity of RA increases, IL-1ß and monocytic chemotactic factor-1 (MCP-1) become the main predictors of

autoimmune inflammation, determining the chronization of the process. In turn, MS is a prothrombotic and proinflammatory condition characterized by increased activity of inflammatory components, among which the main role belongs to leptin, C–reactive protein and cytokines - TNF-a, IL-1, IL-6. One of the components of MS is abdominal type of obesity. Currently, adipose tissue is considered as a highly active endocrine organ, which by itself produces a huge number of different pro- and anti-inflammatory cytokines and more than 50 hormonal factors. Thus, altered patterns of secretion of proinflammatory cytokines in MS and RA may aggravate the development and be considered as a link in the development of cardiovascular complications. Considering the above, we have shown interest in studying the relationship between metabolic syndrome and rheumatoid arthritis.

The aim of the study was to study the effect of metabolic syndrome on the course of rheumatoid arthritis and on the formation of cardiovascular risk.

MATERIALS AND METHODS

100 patients with reliable RA were examined (according to the criteria of EULAR, ACR 2010), of which 93 women (93%) and 7 men (7%), aged 21 to 81 years (average age 55±12.4 years). The patients were on outpatient treatment in a multi-profile hospital of the SamMU clinic. He conducted a standard examination for joint syndrome with the determination of the severity of joint pain on a visual-analog scale, with the calculation of the number of painful and swollen joints, and the assessment of RA activity on the DAS-28 scale (Disease Activity Score). The laboratory study included the determination of the level of antibodies to cyclic citrullinated peptide, C-reactive protein (CRP), rheumatoid factor, circulating immune complexes, erythrocyte sedimentation rate, fasting blood glucose, creatinine, total cholesterol, alkaline phosphatase. All patients were calculated body mass index (BMI), as well as standard instrumental studies, including echocardiography, taking into account such indicators as ejection fraction, thickness of the posterior wall of the left ventricle, thickness of the interventricular septum, diastolic size of the left ventricle, E/A mitral and E/A tricuspid valves (blood flow ratio in the phase of early diastole to the phase of atrial systole for the mitral and tricuspid valves, respectively), left ventricular myocardial mass, left ventricular myocardial mass index, the presence of diastolic dysfunction. Joint radiography was performed to determine the radiological stage of rheumatoid arthritis according to Kellgren.

Statistical processing of the material was carried out using the STATISTICA 10.0 program (StatSoft, USA). The results for descriptive characteristics are presented as median and percentiles of 25 and 75% (Me [Q1; Q3]) or M±σ for continuous values, where M is the arithmetic mean, σ is the standard deviation. When comparing two independent groups on a quantitative basis, the Mann-Whitney criterion was used. The correlation analysis was carried out using Spearman's rank correlation method with the

determination of the correlation coefficient r. To compare the qualitative characteristics in different groups, the criterion $\chi 2$ was used. The reliability of the obtained results was assessed by the level of $p<0.05$.

The study did not involve patients with severe organic pathology: moderate and severe valvular heart defects, angina pectoris of 3-4 FC, cardiomyopathy, oncological diseases in the active stage, chronic heart failure in the decompensation stage.

The research protocol was approved by the local ethics committee of the center. Written informed consent was received from each participant to participate in the study.

RESULTS AND THEIR DISCUSSION

Evaluation of RA activity using the DAS-28 index showed that low activity was observed in 2 patients (2%), moderate – in 30 (30%), high – in 68 people (68%). Seropositivity for rheumatoid factor was detected in 85 patients (85%), and for the presence of antibodies to cyclic citrullinated peptide – in 62 people (62%). Among the studied individuals, the 2nd X-ray stage (according to Kellgren) was observed in 27 people (27%), the 3rd - in 33 (33%), the 4th – in 40 (40%) patients. There were no persons with the first radiological stage of RA in the study, since patients more often seek help at a later stage.

The body mass index of the subjects varied from 14.8 to 46.5 kg/m2 (average 26.8±5.86 kg/m2). Metabolic syndrome according to the criteria of the National Recommendations of the VNOK for the diagnosis and Treatment of metabolic syndrome, 2007 was detected in 59 patients (59%), which allowed us to distinguish 2 groups: group 1 - persons with RA and metabolic syndrome, MS+ (59 people, 59%) and group 2 – persons with RA and without metabolic syndrome, MS- (41 patients, 41%). The groups were comparable in age and gender. The presence of arterial hypertension, as well as the average values of body mass index, total cholesterol and glucose, depending on the presence of metabolic syndrome in patients with RA are presented below (Table 1).

Nonsteroidal anti-inflammatory drugs were taken by 71 patients (71%). As a basic anti–inflammatory therapy, 79 people (79%) received methotrexate, and 3 patients (3%) received leflunomide. Glucocorticosteroids (GCS) were taken by 59 people (59%). Therapy with genetically engineered biological drugs was carried out in 16 patients (16%): 13 (13%) rituximab was received, 1 (1%) – golimumab, 2 (2%) – tocilizumab.

Table 1.

Prevalence of arterial hypertension, average values of BMI, cholesterol and glucose, depending on the presence of metabolic syndrome in patients with RA

	All studied	Patients MS+	Patients- Significance MS-	level, p
AH, %	47	63	16.3	0.000005
BMI	27,95±5,89	30,58±5,3	23,01±3,14	0,00013
HS, mmol/l	4,86 [4,65; 5,42]	5,1 [4,72; 5,53]	4,68 [4,41; 4,88]	0,035
Glucose, mmol/l	5,1 [4,7; 5,6]	5 [3,68; 5,6]	4,8 [4,58; 4,95]	0,036

Note: AH – arterial hypertension, BMI – body mass index, HC – cholesterol, MS+ – patients with metabolic syndrome, MS- – patients without metabolic syndrome. BMI - body mass index,

RA - rheumatoid arthritis.

In the group of patients with MS, RA activity was higher (DAS-28 was 5.58±0.9) than in the group without MS (DAS-28 was 5.23±0.85) (p=0.02), which is probably related to the role of inflammation in RA and MS. So, there are studies proving that in patients with MS, even with normal values of glycemia, but with reliable changes in carbohydrate, lipid metabolism and anthropometric data, the presence of signs of MS has a negative effect on the course of joint syndrome in RA, causing more frequent joint damage, provoking the development of synovitis, increasing the intensity of inflammation and the severity of pain syndrome among patients.

Given the absence of significant differences between the groups in terms of ESR, C-reactive protein, and the presence of rheumatoid factor, we hypothesized that, in addition to inflammation, the pain syndrome itself in RA, leading to a sedentary lifestyle of patients, psychological problems with a likely tendency to develop depressive states in susceptible individuals, in turn, may aggravate weight gain due to low activity and overeating, forming a vicious circle for this group of patients.

We did not obtain significant differences in the spectrum of therapy received, however, the daily the dose of GCS was higher in the MS+ group: in terms of prednisone 7.5 [5; 10] mg versus 5 [5; 10] mg in the group MS- (p=0.013). Probably in this case it is difficult to establish what is the cause and what is the consequence, since most patients took GCS for quite a long time. Based on this, it can be assumed that such therapy contributes to the maintenance of MS, which, in turn, leads to an increase in pro-inflammatory cytokines and is an aggravating factor for RA.

Verified arterial hypertension was 3.8 times more common in the presence of metabolic disorders and was present in 58 patients (63.04%) of the MS+ group (grade 1 – 2 people (2.17%); Grade 2 – 31 (33.7%); grade 3 – 25 patients (27.17%)). At the same time, arterial hypertension was detected only in 8 patients (16.33%) in the group MS- (1st degree – 1 person (2.04%); 2nd degree – 7 patients (14.29%)). Systolic blood pressure (BP) was also higher in the MS+ group (130.9±15 mmHg) than in MS group- (119.3±11.6 mmHg). A similar situation developed with respect to the level of total cholesterol, which was higher in the MS+ group (5.1 [4.72; 5.53] mmol/l), than in MS- (4.68 [4.41; 4.88] mmol/L). However, we did not find any significant differences in both cases. According to echocardiography, in the MS+ group, the left ventricular myocardial mass was higher than in the MS-group (173 [146.52; 226.15] and 158.22 [120.75; 202.24] g, respectively) (p=0.015), but the value of the left ventricular myocardial mass index did not significantly differ: in the MS+ 105.51 group [82; 120.99] g/m^2, and in the MS group - – 98 [75.09; 114.52] g/m^2. Obesity has a significant impact on the development of cardiovascular diseases in MS. One of the characteristic manifestations of obesity is myocardial hypertrophy of the left ventricle of the heart.

The probability of its development in people with normal body weight is 5.5%, and in obese people – 29.9%. Even a slight increase in blood pressure in obese patients causes severe myocardial hypertrophy left ventricle. High blood pressure increases the afterload on the left ventricle, which leads to an increase in the thickness of its walls and the formation of concentric hypertrophy of the left ventricle.

In our study, left ventricular myocardial hypertrophy was 1.5 times more common in metabolic disorders: in 33 patients in the MS+ group (35.9%) and in 12 in the MS- group (24.49%). At the same time, only in the MS+ group, left ventricular myocardial hypertrophy was observed both in combination with arterial hypertension and without it. Number of patients in The MS+ group with left ventricular myocardial hypertrophy not associated with an increase in blood pressure was 9 people (9.78%). At the same time, in the MS group, myocardial hypertrophy was associated with arterial hypertension in all patients.

CONCLUSIONS

The presence of metabolic syndrome in rheumatoid arthritis is associated with a higher activity of rheumatic disease. In patients with RA, it contributes to an increase in cardiovascular risk, characterized by a higher incidence of hypertension (3.8 times), an increase in total cholesterol and an increase in left ventricular myocardial mass. In patients with a combination of RA and MS, myocardial hypertrophy was detected even in the absence of an increase in blood pressure, which dictates the need for echocardiography in this group of patients.

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