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Sarcoidosis as a disease associated with metabolic syndrome

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ABSTRACT

The review summarizes and analyzes the results of domestic and major foreign studies of recent years concerning the prevalence of metabolic syndrome components and the explanation of their role in the mechanisms of sarcoidosis development. A deep understanding of the pathogenesis of metabolic syndrome (MS) in terms of the role in it of risk factors for a severe course and complications of most socially sensitive noncommunicable diseases clustered within MS can underly the development of effective pathogen-specific approaches to MS treatment.

Keywords: sarcoidosis, metabolic syndrome, obesity, atherosclerosis, diabetes mellitus, dyslipidemia

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Саркоидоз как ассоциированное с метаболическим синдромом заболевание

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РЕЗЮМЕ

В обзоре обобщены и проанализированы результаты отечественных и крупных зарубежных исследований последних лет, касающихся изучения распространенности компонентов метаболического синдрома (МС)

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и объяснения их роли в механизмах развития саркоидоза. Глубокое понимание патогенеза данного заболевания с позиций участия в нем кластера факторов риска тяжелого течения и осложнений большинства социально значимых неинфекционных заболеваний, объединенных рамками МС, может лечь в основу разработки эффективных патогенетических подходов к лечению.

Ключевые слова: саркоидоз, метаболический синдром, ожирение, атеросклероз, сахарный диабет, дислипидемия

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии финансирования при проведении исследования.

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INTRODUCTION

The growth of interest of fundamental and applied sciences in the problem of metabolic syndrome (MS) is explained both by the drastically growing prevalence of its components (visceral obesity, hyperglycemia, dyslipidemia, arterial hypertension, hyperuricemia, etc.) and by their proven involvement in the pathogenesis of adverse outcomes in a range of noncommunicable diseases, determining high level of morbidity, disability, and mortality and a significant decrease in the quality of life of the population at the present time [1–3]. Currently, the list of diseases clustered within MS is not limited to coronary heart disease and type 2 diabetes mellitus. This group of pathologies includes all diseases caused by atherosclerosis, cancers of different localization, metabolic diseases (gout, urolithiasis and cholelithiasis, fatty liver disease), and connective tissue diseases, etc. [4–11]. In this regard, the need to consider sarcoidosis as a disease associated with MS seems to be quite reasonable.

Timely diagnosis and effective treatment of sarcoidosis continue to be among the most relevant issues for the medical community. The attention of clinicians and researchers to this pathology is due to a number of reasons. Sarcoidosis is a multisystem inflammatory disease of unknown etiology, manifested by the formation of specific granulomas in the affected tissues. The socio-medical significance of this pathology is explained both by a recent increase in its incidence, a trend toward a progressive course, high level of disability in the able-bodied population and by complicated diagnosis and monitoring of the disease course due to variability of its manifestations and the lack of etiotropic therapy. The variety of clinical manifestations of sarcoidosis is determined not only by the target organ affected by granulomas, but also by the influence of comorbid pathology, which also complicates the diagnosis of the disease and the strategy of managing patients [12–14].

The epidemiology of sarcoidosis is characterized by an increase in the incidence and disability of the population in different countries, including Russia and the CIS countries [15]. The prevalence, incidence rate, and clinical characteristics of sarcoidosis are determined by geographic, ethnic, social, and even professional affiliation, as well as by gender, age, and premorbid history [16, 17]. The most reasonable explanation for the recent increase in the incidence of sarcoidosis may be the widespread epidemic level of the prevalence of MS components [15, 18–20]. At the same time, it is important to take into account that MS and its individual components can be considered both as risk factors for the development of sarcoidosis and as a consequence of corticosteroid therapy, which also characterizes the relevance of research in this area.

A number of scientific articles provide data on the influence of MS components on the prevalence of sarcoidosis and vice versa. Thus, South Korean researchers conducted an epidemiological study that showed that in patients with metabolic disorders, the incidence of sarcoidosis, calculated per 100,000 population, was significantly higher than in patients without metabolic disorders: in patients with diabetes mellitus (DM) – 2.40 versus 0 .76, in patients with arterial hypertension – 1.81 versus 0.74, in patients with dyslipidemia – 2.60 versus 0.74. It was also

shown that these categories of patients not only have a higher risk of developing sarcoidosis but also a significantly higher risk of death [21].

Colleagues from the Istanbul University of Medical Sciences conducted a study of 47 patients with sarcoidosis and 45 apparently healthy individuals. MS was diagnosed according to the NCEP-ATP III criteria; the level of insulin resistance was also assessed by calculating the HOMA-IR index. The groups did not differ significantly in gender and age. The comparative analysis of body mass index (BMI), waist circumference (WC), triglycerides, and blood glucose levels showed significantly higher values of these parameters in patients with sarcoidosis than in the control group. 80% were diagnosed with stage 2 sarcoidosis, and almost half of the patients in the main group received steroids. The relative risk of developing MS in patients with sarcoidosis was 7.66, while the relative risk of developing insulin resistance was 5.48 [22].

Another group of Turkish scientists conducted a study that included 133 patients with newly diagnosed sarcoidosis, 133 age- and sex-matched controls, and 51 patients with rheumatoid arthritis (RA); all patients were investigated before receiving pathogen-specific therapy. A comparative analysis of the frequency of occurrence of MS and its individual components was carried out in accordance with the NCEP-ATP III criteria. It was found that MS was significantly more common in the sarcoidosis group than in the control group. These results were comparable with the data in the group of patients with RA. An important conclusion of this study, as the authors emphasize, is the evidence that MS components are associated with sarcoidosis and can be regarded as risk factors for its development, independent of the effects of corticosteroid therapy [23].

Sarcoidosis is a multisystem disease that is characterized by lesions of not only respiratory organs but other body systems. Extrapulmonary manifestations of sarcoidosis include damage to the eyes, nervous system, heart, kidneys, etc., which can aggravate the prognosis [24].

Some studies have shown an association between the course of sarcoidosis and a number of MS-associated diseases. In particular, a mutual aggravating effect of sarcoidosis and coronary heart disease has been established. In the presence of postinfarction cardiosclerosis and circulatory failure, a decrease in forced vital capacity (FVC) was explained by a decrease in myocardial contractility due to systolic and diastolic dysfunction of the left ventricle. At the same time, a decrease in functional parameters coincided with the timing of cardiac disease [20]. In this regard, it is difficult to differentiate the presence of cardiac sarcoidosis in patients, which also reduces left ventricular contractility and ultimately affects a decrease in the function of the respiratory system [25]. Clinically, symptoms of a heart disease are observed in only 5% of sarcoidosis cases, but in a series of autopsies, it was found that 27% of patients with sarcoidosis had granulomatous infiltration in the heart [26, 27].

Currently, there is no evidence that severe coronary artery stenosis is characteristic of sarcoidosis, but angina-like complaints have been described [28]. At the same time, sarcoidosis, like atherosclerosis, has a chronic inflammatory nature, which underlies microvascular damage and endothelial dysfunction and determines a high cardiovascular risk in patients of this category [29, 30]. Therefore, damage to the cardiovascular system in sarcoidosis can be caused not only by damage to the heart muscle by a specific process, but also by comorbid pathology [31]. In this regard, research can be aimed at establishing common links in the pathogenesis, namely, determining the role of MS components.

Thus, Russian scientists of the Moscow City Scientific and Practical Center for Combating Tuberculosis determined the association of dyslipidemia with the activity of the inflammatory process and insufficient antioxidant defense in sarcoidosis, which increases the cardiovascular risk in patients of this category [32]. These results are consistent with the data presented in a review by Italian authors, who confirmed that the pathogenesis of sarcoidosis is associated with increased oxidative stress (protein carbonylation and lipid peroxidation) and changes in the lipid profile of the circulating blood. Lipid metabolism disorders, including a decrease in high-density lipoprotein cholesterol levels and apolipoprotein A-I concentrations, cause damage to the plasma membrane and bronchial and capillary endothelial cells in patients with sarcoidosis. Foreign researchers also confirm that dyslipidemia is associated with oxidative stress, a decrease in overall antioxidant defense, and, consequently, an increased risk of atherosclerosis [33, 34].

To assess the prevalence of DM in patients with sarcoidosis and to establish the relationship between these diseases, Egyptian researchers conducted a meta-analysis that included 19 studies (n = 18,686,162). The

mean prevalence of DM in patients with sarcoidosis was 12.7% (95% confidence interval (CI) 10–16.1): the highest prevalence was in North America with 21.3% (13.5–31.8); in Europe, it was 10.4% (7.9–13.7), and in Asia, it was 10% (1.8–39.7). Patients with sarcoidosis had higher rates of DM compared to the control group in all areas (odds ratio (OR) 1.75; 95% CI 1.49–2.05) [35].

This meta-analysis did not look for reasons for high prevalence of DM in patients with sarcoidosis, and the possible impact of corticosteroid therapy was not taken into account. A team of authors from Thailand and Sweden believe that high prevalence of DM in patients with sarcoidosis in North America can be explained both by higher prevalence of obesity in this continent and by the use of higher doses of corticosteroids in the treatment of sarcoidosis, which may potentiate the development of type 2 DM [36]. This statement is supported by a large population-based Swedish cohort study in which patients with sarcoidosis treated with corticosteroids demonstrated a high risk of developing type 2 DM within 2 years after the diagnosis of sarcoidosis compared to patients with untreated sarcoidosis [37].

According to most experts, the main component of MS is abdominal obesity due to the proven role of metabolically and endocrine active visceral adipose tissue in the development of associated pathologies [38, 39]. Obesity exacerbates symptoms of sarcoidosis, and corticosteroid therapy increases BMI. Prospective epidemiological studies conducted to investigate the role of obesity as a potential risk factor for the development of sarcoidosis are worth noting. Three studies in the United States and one study in Denmark demonstrated a higher risk of developing sarcoidosis among obese patients compared to non-obese patients; risk estimates ranged from 1.42 (95% CI 1.07–1.89) to 3.59 (95% CI 2.31–5.57) [40]. A health study of 59,000 African American women [41] found that obesity (BMI $\geq$ 30 kg / m^2) at baseline was associated with a 40% increase in the prevalence of sarcoidosis. Given obesity at the age of eighteen and a subsequent increase in body weight by 30 kg or more, an increase in the incidence of sarcoidosis was noted.

In a prospective health study of 116,430 American women who had been followed up for 14 years, 270 patients developed sarcoidosis, and obesity was associated with a 70% increased risk of developing sarcoidosis [42]. A population study in Olmsted County, Minnesota (USA) [43], which included 345 patients with sarcoidosis and the same number of apparently healthy controls, found a positive correlation between BMI and the risk of developing sarcoidosis. The odds ratio for developing sarcoidosis in people with obesity compared to those with a normal or low BMI was 2.54 (95% CI 1.58–4.06).

Understanding the mechanism of the mutual effect of obesity and sarcoidosis is extremely important in terms of substantiating new areas of prevention and treatment, since excess body weight can be not only a modifiable risk factor for this pathology, but also aggravate its course. Russian researchers indicated obesity as one of the most informative criteria for predicting the recurrent course of respiratory sarcoidosis [44], and BMI was identified as a risk factor for the development of extra-thoracic forms of sarcoidosis [19]. In order to understand the mechanism of the mutual influence of obesity and sarcoidosis, it should be taken into account that obesity, even in the absence of respiratory diseases, can affect many physiological respiratory factors, including static and dynamic spirogram parameters, as well as bronchial hyperreactivity, mechanical function of the upper respiratory tract, neuromuscular strength, and gas exchange [45].

It is also known that the average respiratory rate in patients with obesity is 30–50% higher than in individuals with normal body weight [46, 47]. Dyspnea on exertion associated with overweight underlies the decline in physical functioning in patients [48]. Indicators characterizing the severity of obesity (WC, waist – hip ratio (WC / HR), and subscapular skinfold thickness) have an inverse correlation with tidal volume, which is explained by the high position of the diaphragmatic dome [45, 49, 50]. The EPIC-Norfolk study of British patients of both sexes found an inverse relationship between WC / HC and FEV_1 and FVC [51]. It is also known that obesity is associated with such respiratory diseases as chronic obstructive pulmonary disease (COPD), bronchial asthma, pneumonia, and obstructive sleep apnea (OSA) [52–54].

The impact of obesity on the development and severity of OSA in patients with sarcoidosis has not been fully studied. Two published studies in Turkey reported that 66 and 52% of patients with sarcoidosis, respectively, had OSA [55, 56]. An earlier study using polysomnography showed that OSA was observed only in patients with a BMI greater than 30 kg / m^2 [57]. The relationship between obesity and sarcoidosis was assessed in terms of the impact of high BMI on symptoms of fatigue, dyspnea, health

status, and spirometry in 184 Serbian patients with sarcoidosis [58]. Compared to healthy controls of the same age and gender, patients with sarcoidosis were more likely to be overweight or obese, have a lower baseline dyspnea index (BDI) and lower FEV_1 values, more pronounced fatigue scores, and reported worse well-being. When the authors examined the independent and combined effects of sarcoidosis and BMI, they found that sarcoidosis itself contributed to aggravation of dyspnea and decreased subjective health scores.

Obesity may be both a consequence of sarcoidosis treatment and a risk factor for the disease, probably due to the metabolic and proinflammatory state of visceral adipose tissue. That is why abdominal obesity is associated with a number of noncommunicable diseases in addition to type 2 DM and atherosclerosis: with obstructive lung diseases (bronchial asthma, COPD), connective tissue diseases (RA, psoriatic arthritis, systemic lupus erythematosus), metabolic diseases (urolithiasis and cholelithiasis, fatty liver disease, gout), etc. [59–63].

According to modern concepts, visceral adipose tissue is classified as an organ of the endocrine and immune systems, which is confirmed by characteristic structural and functional changes. Fundamental studies in recent years have shown that adipose tissue in obesity is infiltrated with mononuclear leukocytes [38, 64, 65] and characterized by a proinflammatory and prooxidant state. This is confirmed by the ability of adipocytes to produce not only adipokines, but also proinflammatory cytokines and reactive oxygen species [38, 39, 64–66]. Biologically active substances synthesized by adipocytes in large quantities have significant systemic effects. The decisive role of chronic low-grade inflammation in the mechanisms of development of MS and its individual components has been proven by a large number of studies that show statistically significant relationships between metabolic parameters (severity of obesity, hyperglycemia, dyslipidemia, hyperuricemia, etc.) not only with the level of acute-phase proteins in blood, but also with the level of proinflammatory cytokines (interleukin (IL)-1β, IL-6, IL-8, TNFα, INFγ, etc.) [38, 39, 64–66]. The proinflammatory background set by MS cannot but affect the course of other diseases, in the pathogenesis of which the inflammatory process plays a leading role. In this regard, it can be assumed that the mechanism of association between sarcoidosis and MS is implemented through the same proinflammatory factors.

CONCLUSION

Thus, the analysis of scientific publications showed that sarcoidosis can be characterized as an MS-associated disease. On the one hand, MS components are modifiable risk factors for the onset and severe course of sarcoidosis, and on the other hand, they are the result of corticosteroid therapy for this disease. A deep understanding of the pathogenesis of the association between these two pathological conditions can form the basis for the prevention of severe sarcoidosis, its control, and effective pathogenetically grounded approaches to treatment.

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