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The pathogenic relationship between metabolic syndrome and rheumatoid arthritis activity

ABSTRACT

Metabolic syndrome (MetS) and its components often occur in patients with rheumatoid arthritis (RA). Both conditions, RA and MetS, share pro-inflammatory pathogenic mechanisms. The occurrence of MetS in patients with RA seems to be associated with higher disease activity and suboptimal response to treatment. In this review, we have presented the pathogenesis of MetS and its associations with metabolic disorders in RA. Screening for and managing MetS is necessary to reduce cardiovascular risk and improve prognosis in patients with RA.

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KEY WORDS: rheumatoid arthritis; metabolic syndrome; disease activity

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by symmetric joint inflammation leading to irreversible joint damage and disability in patients [1]. The active form of RA may be associated with the involvement of internal organs, metabolic disorders, and premature development of atherosclerosis. Currently, RA is considered an independent risk factor for cardiovascular diseases (CVDs), similar to type 2 diabetes [2]. In patients with RA compared to the general population, the risk of CVD is increased by about 50%, and CVDs are recognized as the leading cause of death [3]. The prevalence of traditional CVD risk factors (central obesity, hypertension, dyslipidemia, insulin resistance) in RA patients is high and may manifest as metabolic syndrome (MetS) [2–4].

The term MetS defines the coexistence of interconnected metabolic disorders that increase the risk of atherosclerosis, CVD, and type 2 diabetes development [4]. Currently, the 2009 criteria, which were developed by several organizations, including the International Diabetes Federation (IDF), American Heart Association (AHA), and the National Heart, Lung, and Blood Institute (NHLBI) (Tab. 1) [5], are applied to diagnose MetS.

Table 1. Definition of metabolic syndrome (MetS) developed by the International Diabetes Federation (IDF), American Heart Association (AHA), and the National Heart, Lung, and Blood Institute (NHLBI) in 2009

Criteria for MetS: 3 out of the following 4 criteria should be fulfilled
Central obesity: waist circumference ≥ 94 cm (men) or waist circumference ≥ 80 cm (women)
Triglyceride level (TG) ≥ 150 mg/dL, or treatment of hypertriglyceridemia
HDL-cholesterol (HDL-C) level < 40 mg/dl (men) or < 50 mg/dL (women) or treatment of low HDL-C level
Blood pressure ≥ 130/85 mm Hg, or treatment of hypertension
Fasting glucose ≥ 100 mg/dL, or type 2 diabetes

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THE PATHOGENESIS OF METABOLIC SYNDROME

The pathogenesis of MetS is still not fully understood. It is widely accepted that both genetic predisposition and environmental factors such as high-calorie diet and low physical activity contribute to the MetS development. It is considered that essential metabolic changes in MetS result from visceral obesity and insulin resistance [6, 7].

The body fat distribution (visceral obesity) is even more important than the total amount of body fat. The Mets may be found in patients with normal body mass index (BMI); however, simultaneously, accumulation of visceral adipose tissue in the upper body is observed [7]. The adipose tissue is regarded not only as an energy storage but also as an essential endocrine and paracrine organ, producing and releasing various cytokines and adipokines. The type and proportion of secreted proteins depend on the location and amount of adipose tissue [8].

An excessive calorie intake results in hypertrophy of adipocytes, the cells which form the adipose tissue. Progressive enlargement of adipocytes is associated with impaired blood flow and, consequently, hypoxia. It has been shown that hypoxia is the leading cause of local inflammation, which stimulates the influx of macrophages, secretion of pro-inflammatory cytokines [tumor necrosis factor (TNF), interleukin 6 (IL-6), IL-1], plasminogen activator inhibitor 1, free fatty acids (FFA) and pro-inflammatory adipokines (leptin, resistin, visfatin, lipocalin 2] [4].

Leptin regulates food intake by inhibiting appetite. It induces hypertension as a result of the sympathetic nervous system activation. Leptin also affects insulin metabolism, leading to insulin resistance. Serum leptin concentrations correlate positively with the adipose tissue mass [4, 8]. Resistin and lipocalin 2 are also involved in the development of insulin resistance. Visfatin inhibits insulin secretion by pancreatic β cells, leading to hyperglycemia [8]. Unlike other adipokines, adiponectin improves the insulin sensitivity of tissues and displays anti-inflammatory effects. Serum adiponectin concentrations are decreased in patients with increased body mass [7, 8].

Reports in the literature point to oxidative stress as a determining factor leading to insulin resistance development, which is associated with positive energy balance. The excess glucose and FFA in adipocytes stimulate the production of acetyl-CoA and nicotinamide adenine dinucleotide phosphate (NADP), resulting in increased synthesis of reactive oxygen species (ROS) [7]. Understanding the protective, antioxidant mechanisms activated in adipose tissue cells is crucial and calls for further research. The increased FFA levels in adipocytes inhibit the insulin-dependent signalling, leading to insulin resistance and reduced glucose uptake. The excessive FFA release from adipose tissue results in increased FFA concentrations in the liver and muscles [7]. The impaired glucose uptake by cells and enhanced glycogenolysis in hepatocytes are both associated with hyperglycaemia and compensatory hyperinsulinemia. The degeneration of overloaded pancreatic β cells is responsible for the development of type 2 diabetes [4]. Both hyperinsulinemia and hyperglycemia are also associated with the development of arterial hypertension as a result of renin-angiotensin system activation, endothelial function impairment, and release of vasoconstrictor agents such as endothelin 1 [7].

In the case of insulin resistance, enhanced synthesis and impaired catabolism of very low-density lipoproteins (VLDL) is observed, and it is associated with increased serum triglycerides (TG) concentration. Hypertriglyceridemia results in the formation of pathological versions of high-density lipoproteins (HDL) and low-density lipoproteins (LDL), respectively small dense HDL and small dense LDL. Small dense HDL do not exhibit anti-atherosclerotic function (reverse cholesterol transport from macrophages in vessel walls) and are removed from circulation. Small, dense LDLs penetrate the blood vessel walls much more easily and form atherosclerotic plaques [4, 7].

The atherogenic dyslipidemia, consisting of increased TG, decreased HDL concentration, and increased small, dense LDL concentrations, is regarded as a component of MetS and an independent risk factor for atherosclerosis development. An association between atherogenic dyslipidemia and insulin resistance has been confirmed [7].

The two factors, central obesity, and insulin resistance are closely related to glucose metabolism, dyslipidemia, increased blood pressure, and systemic inflammatory response. These disorders result in the development of atherosclerosis, type 2 diabetes, and cardiovascular complications [4].

METABOLIC DISORDERS IN RA

It has been reported that components of MetS occur more often in patients with RA than in the general population, which is associated with the effect of pro-inflammatory cytokines (TNF, IL-1, and IL-6) in active RA.

The prevalence of insulin resistance has been observed in 51% of patients with newly diagnosed RA and in 58% of long-standing RA, compared to 19% in the general population [9]. In patients with RA, visceral obesity was most commonly found, followed by arterial hypertension and dyslipidemia [10].

According to data in the literature, the frequency of MetS in RA patients ranged from 14 to 56% [10]. According to a large meta-analysis encompassing 70 studies, the worldwide prevalence of MetS in RA patients was 30,65%, and in the European population, 35,2%, according to IDF criteria [10]. In another study, the prevalence of MetS was 32% in patients with RA and 14% without RA [9]. The risk of MetS was 45% higher in patients with RA than in healthy individuals [10].

However, the impact of MetS on disease activity and treatment response in patients with RA is still not fully understood.

RHEUMATOID CACHEXIA

Chronic inflammatory diseases may be associated with the development of cachexia, characterized by loss of lean body mass while the fat mass is stable or even increased. In the course of RA, the above-mentioned body composition disorders are known as rheumatoid cachexia (RC). The RC may affect up to 1/5 of patients with RA [11].

It has been reported that the development of RC is associated with prolonged, excessive production of pro-inflammatory cytokines, increased protein catabolism, and low physical activity in patients [12]. In patients with RC, the loss of muscle mass is compensated by an increase in fat mass, and as a result, the total body mass is usually not decreased. That is why no changes in BMI are observed in 80% of patients with RC. The excess visceral adipose tissue may lead to the development of insulin resistance and MetS [13].

In RA patients, significant correlations have been reported between RC and the occurrence of MetS, increased waist circumference, arterial hypertension, as well as decreased LDL concentration [14].

THE INFLUENCE OF METABOLIC DISORDERS ON THE ACTIVITY OF RA

The research conducted in recent years in patients with RA suggests a relationship between the central obesity and other features of MetS, and the inflammatory activity of the disease, as well as the response to treatment.

In patients with central obesity, local inflammation in hypertrophic adipose tissue induces influx of macrophages. In the course of MetS, an imbalance between Th1 and Th2 lymphocytes occurs in favour of the former, which results in increased production of pro-inflammatory cytokines by adipose tissue macrophages [8].

Most adipokines secreted by visceral adipose tissue have pro-inflammatory effects and modulate the immune response [15]. The increased levels of adipokines such as leptin, resistin, and visfatin, as well as decreased adiponectin levels, are associated with the production of pro-inflammatory cytokines, lymphocyte activity, and macrophage chemotaxis [16]. The excessive production of pro-inflammatory cytokines, C-Reactive Protein (CRP), intensity of angiogenesis, stimulation of lymphocyte activity, and macrophage chemotaxis, are directly related to RA activity [16].

The relationship between adiponectin level and RA activity is still not fully explained. Higher serum adiponectin levels are reported in patients with RA compared to the general population. The adiponectin concentration in the synovial membrane is higher in patients with RA than with osteoarthritis [16]. Despite the well-known anti-inflammatory and anti-atherosclerotic effects of adiponectin reported in metabolic and cardiovascular diseases, in the course of RA, adiponectin seems to have a paradoxical pro-inflammatory effect in the joints and leads to joint destruction [17]. Adiponectin stimulates synovial fibroblasts to produce TNF and metalloproteinases, contributing to the formation of joint erosions [18]. Central obesity is associated with decreased adiponectin production, which could explain a slower radiographic progression in obese RA patients [17, 19].

RESULTS OF OBSERVATIONAL STUDIES IN PATIENTS WITH RA AND METS

Several studies in the literature demonstrated the significant relationship be-

tween metabolic disorders and RA activity, expressed by different disease activity indices: Disease Activity Score in 28 joints (DAS 28), Simplified Disease Activity Index (SDAI), and Clinical Disease Activity Index (CDAI) [20–22].

A significant relationship was reported between MetS and high disease activity according to DAS 28, SDAI, and CDAI [23]. In the group of newly diagnosed RA patients, higher disease activity according to DAS28 was found in patients with MetS in comparison with those without MetS [24].

The significantly higher Erythrocyte Sedimentation Rate (ESR) values were reported in RA patients with MetS when compared without MetS [23, 25–28]. However, conflicting results regarding CRP levels were presented. Significantly increased CRP concentrations were noticed in large groups of patients with RA and MetS. These observations confirmed an association between components of MetS (central obesity, insulin resistance) and the inflammatory response as a result of high levels of pro-inflammatory adipokines and cytokines (IL-6, TNF) [7, 8]. In contrast, in other studies, no significant correlation was found between CRP levels and the presence of MetS in RA patients. However, a small number of patients were included in those studies [25, 29].

The results of the recent observational study confirmed significant associations between MetS and RA activity. Patients with RA and MetS were characterized by higher disease activity, according to DAS28, SDAI, and CDAI; significantly higher tender and swollen joint counts, and values of ESR, CRP, and ultrasound (US) parameters (grey-scale (GSUS), power Doppler (PDUS)). Significant correlations were found between metabolic parameters (waist circumference, cholesterol, and glucose concentrations) and indices of RA activity [30].

CONCLUSIONS

The occurrence of MetS in patients with RA is associated with higher disease activity, higher inflammatory parameters, functional impairment, and worse quality of life of patients.

The diagnosis of MetS in patients with RA seems to be an additional risk factor of high disease activity, which is why it requires the introduction of therapeutic interventions (both non-pharmacological and pharmacological) in order to eliminate metabolic disorders and improve the prognosis of patients.

AUTHOR CONTRIBUTIONS

K.G.: conception, design, interpretation of the data being published, writing the paper; B.T.-S.: design, interpretation and execution of the data, writing of the final version of the paper.

CONFLICT OF INTERESTS

Authors declare no competing interests.

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