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Aletration of Lipid Profile in Rheumatoid Arthritis

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Abstract: ***Rheumatoid arthritis (RA), especially active disease, is associated with considerable changes in body composition, lipids, adipokines and insulin sensitivity. Metabolic changes, such as increased total cholesterol, LDL cholesterol and triglyceride levels, occur even in preclinical RA. Active RA is associated with decreased lipid levels, BMI, fat and muscle mass, as well as altered lipid profiles. Some of these changes are also seen in metabolic syndrome, and could increase cardiovascular mortality. Importantly, the systemic inflammation underlying RA is an independent risk factor for cardiovascular disease. This perspectives article summarizes data on the associations of various components of metabolic syndrome with RA, and discusses the effects of biologic therapy on these factors. The authors propose that components of metabolic syndrome should be monitored in patients with RA throughout the disease course, and argue that optimal disease control using biologic agents might attenuate several adverse effects of metabolic syndrome in these patients.***

Keywords: rheumatoid arthritis, dislipidemia, metabolic syndrome

1. Introduction

Inflammatory rheumatic diseases, including rheumatoid arthritis (RA), are associated with several chronic comorbidities, such as cardiovascular disease (CVD) (1 - 5). A significant proportion of arthritis - related mortality is due to CVD4 and traditional risk factors for CVD, as well as systemic inflammation, are implicated in the accelerated atherogenesis observed in patients with RA (1, 3). Apart from these changes in vascular pathology, RA is also associated with various components of metabolic syndrome, which increase CVD mortality. Obesity and rheumatoid cachexia (a combination that is characteristic of RA), insulin resistance, dyslipidemia and altered adipokine profiles have all been associated with RA (6). However, the metabolic profile observed in patients with RA does not reflect that seen in the general population. A 'lipid paradox' has been described, such that low total cholesterol and LDL cholesterol levels in patients with RA are associated with increased cardiovascular risk (7, 8). In addition, adipokine profiles in RA might differ from those in non - inflammatory states (6, 9) Thus, obesity, lipids, adipokines and insulin sensitivity should be interpreted differently in patients with RA. The recommendations of a EULAR task force state that adequate control of disease activity is necessary to lower CVD risk in patients with RA (5). Numerous publications have suggested that traditional DMARDs, as well as biologic agents, could have significant effects on these patients' metabolic profiles, but much controversy persists regarding the effects of such therapies on lipids, adipokines and insulin resistance (10).

2. Material and methods

This is a systematic review of the literature conducted using PubMed database. In this perspectives article, we summarize data on various components of metabolic syndrome that are associated with RA. We focus on RA- specific changes in lipids, adipokines and body fat composition that give rise to both obesity and rheumatoid cachexia, and discuss the effects of biologic therapy on these components of metabolic syndrome. We propose that optimal disease control might help to attenuate several adverse effects of metabolic syndrome in patients with RA. As dyslipidaemia and the lipid paradox in patients with RA has been comprehensively reviewed elsewhere, these topics will be briefly outlined here in the context of metabolic disease.

3. Results and Discussion

Metabolic syndrome in RA

At least five definitions of metabolic syndrome have been derived from large epidemiologic cohort studies (6, 11). According to a widely used National Cholesterol Education Program (NCEP) definition, the constituents of metabolic syndrome are central obesity, dyslipidaemia, hypertension, hyperglycaemia and insulin resistance, as well as a pro inflammatory and prothrombotic state that leads to atherosclerosis and vasculopathy. Each individual component of metabolic syndrome is an independent risk factor for CVD, but whether metabolic syndrome as a whole is also a risk factor for CVD is less clear (6, 11).

Epidemiologic studies suggest that RA is also an independent risk factor for CVD, and that the level of risk is influenced by the occurrence of metabolic syndrome.6 Indeed, a meta - analysis involving a total of 2, 283 patients with RA and 4, 403 controls without RA confirmed a significant association between RA and metabolic syndrome. In addition, a cross - sectional relationship between the inflammatory activity of RA and metabolic syndrome has been suggested, although no prospective studies have confirmed an increased risk of metabolic syndrome development during the course of RA (6, 12).

Notably, the strength of the association with metabolic syndrome might differ between long - standing and early RA. In early RA, the prevalence of metabolic syndrome was 16–31% depending on which criteria were used for its assessment. In long - standing RA, the overall risk of develop ing metabolic syndrome was significantly higher in patients with RA than in healthy controls (OR 1.87) (13).

When the specific components of metabolic syndrome were assessed, increased waist circumference, elevated blood pressure and high fasting glucose levels were observed in patients with established RA in comparison with the general population (6, 13). With respect to markers of atherosclerosis in patients with RA, metabolic syndrome was associated with increased carotid intima–media thickness (14). In women with RA, after adjustment for age and physical activity level, high erythrocyte sedimentation rate, 28 - joint disease activity score and health assessment questionnaire score, as well as decreased methotrexate use, were independent predictors of metabolic syndrome development (6, 14).

Obesity and rheumatoid cachexia

The issue of obesity in patients with RA is rather controversial. Although obesity is common in these patients, high - grade inflammation, which is associated with abundant production of TNF, often leads to rheumatoid cachexia (6, 16). Notably, cachexia has been associated with both high levels of RA disease activity and increased mortality from CVD, whereas obesity has been related to decreased CVD mortality in patients with RA (15). Interestingly, the relationship between obesity and RA might depend on geographical location. In a study performed in black patients with RA from South Africa, RA was associated with reduced adiposity, including a markedly reduced BMI as well as decreased abdominal adiposity (17). Unfortunately, all studies showing an inverse relationship between obesity and disease activity have been performed in patients with established RA who have undergone treatment and data in patients with early RA is lacking.

In contrast to classic cachexia, in which both muscle and fat mass are decreased, altered body composition in RA is characterized by increased fat mass and decreased lean mass, resulting in little or no change in BMI. These changes frequently present as abdominal adiposity and are characteristic of RA (18). Increased visceral fat mass in patients with RA has been associated with elevated fasting glucose levels and hypertension, as well as metabolic syndrome (18).

Some controversy is evident about which factors primarily drive RA - associated metabolic syndrome. Obesity seems to be the major determinant, and might be related to environmental factors, such as a high - calorie diet, a lack of physical activity and migration from rural to urban areas. Inflammatory mediators (such as cytokines or autoantibodies) might also be involved in these metabolic changes; however, they are thought to be somewhat less important than environmental and lifestyle - related risk factors (6, 16, 19).

Rheumatoid cachexia is associated with abundant production of proinflammatory cytokines (primarily TNF and IL - 1) as well as anti - citrullinated protein antibody (ACPA) positivity (6, 16, 20). By contrast, obese individuals with RA are commonly ACPA - negative. A few studies also suggest that obesity is associated with reduced radiographic damage and decreased CVD mortality in RA (18, 21). However, the lack of prospective studies limits the interpretation of these data. In summary, patients with RA can have normal or only slightly altered body weight and BMI, and an altered body fat distribution (rather than increased body weight) might account for the possible associations between RA and metabolic syndrome (6, 18). As described below, adipokine levels differ in patients with RA of various body compositions; leptin levels are elevated in obese patients, whereas adiponectin levels tend to be high in lean patients (6, 9). Interestingly, all - cause mortality is elevated in patients with rheumatoid cachexia, whereas overweight patients with RA show decreased mortality despite their increased incidence of comorbid conditions such as hypertension, diabetes mellitus and myocardial infarction (16, 17, 19). The effects of body weight on mortality should, therefore, be considered differently in patients with RA to those in the general population.

Insulin resistance

Increased insulin resistance is associated with RA10–12 and reduced β - cell activity has been linked to increased disease activity (22). In addition, increased insulin resistance has been associated with carotid plaque formation.

Dyslipidaemia

In RA, high - grade inflammation and associated factors, such as increased levels of C - reactive protein (CRP) and inflammatory cytokines, can influence commonly measured lipid levels, leading to their misinterpretation (7, 8). Other issues can also lead to some confusion when assessing these patients. For example, the atherogenic index is commonly calculated in the general population as the ratio of triglyceride level to HDL cholesterol level. By contrast, rheumatologists calculate the atherogenic index as the ratio of total cholesterol or LDL cholesterol to HDL cholesterol, which demonstrates the relationship between ‘bad’ and ‘good’ cholesterol (23).

In RA, this simplification seems particularly insufficient, as the qualitative changes observed in lipid subfractions under inflammatory conditions are considered at least as important as the absolute lipid values, as discussed in detail below (24).

Quantitative blood lipid changes

Changes in lipid levels observed in early RA might be characterized as the effects of metabolic syndrome and low - grade inflammation. Studies in patients with preclinical RA and early RA demonstrate a lipid profile that is typical of metabolic syndrome: normal or mildly elevated total cholesterol, LDL cholesterol and triglycerides, associated with decreased HDL cholesterol levels (25). By contrast, the development of established RA is associated with long - lasting or relapsing high - grade inflammation that leads to decreases in both muscle mass and subcutaneous white fat, along with an increase in visceral fat. In addition, the relapsing–remitting course of established, progressive RA affects catabolic obesity and lipid levels. This phase of highly active RA is associated with decreased total cholesterol and LDL cholesterol levels. RA therapies also have effects on lipid levels, discussed below.

Qualitative blood lipid changes

In addition to quantitative changes in the lipid levels of patients with RA, important proatherogenic modifications in

lipid subfractions can be observed. Phenotypic modifications to LDL particles, representing proatherogenic dyslipidaemia, have been identified at every stage of RA (26). Lipoprotein (a), an LDL particle bound to apolipoprotein A, is an independent moderate risk factor for CVD. Significantly higher serum levels of lipoprotein (a) have been found in patients with RA than in healthy controls.28 Notably, small dense LDL particles pene trate more easily into the arterial subintimal space, and are highly susceptible to oxidative modifications, which lead to increased binding of these particles to alternative LDL receptors. Elevated levels of (mostly oxidized) LDL and of antibodies to oxidized LDL have been found in the sera and synovial fluids of patients with RA (27).

The unique lipid profile in RA

In general, formation of proinflammatory HDL particles and complex forms of HDL dysfunction, including impaired HDL antioxidant capacity, are associated with RA—especially with active, poorly controlled disease. Increased inflammation - associated oxidation of LDL and a decreased protective capacity of HDL seem to be the cornerstones of the pronounced lipid oxidation observed in RA, and inflammation - induced functional impairment of lipid particles is considered an important contributor to the atherosclerotic process underlying both metabolic syndrome and RA.

4. Conclusion

RA is associated with most components of the metabolic syndrome: body weight changes, quantitative and qualitative dyslipidaemia, a characteristic adipokine profile and insulin resistance. Obesity in patients with RA has been mostly associated with traditional environmental risk factors, such as a high - calorie diet and physical inactivity, whereas rheumatoid cachexia is probably a result of sustained inflammatory activity. In addition, rheumatoid cachexia, rather than obesity, has been associated with increased CVD mortality in RA. During the disease course, active RA with high - grade inflammation is associated with further loss of muscle mass, decreased subcutaneous fat mass and decreased BMI, as well as low serum lipid levels and increased production of proinflammatory HDL and small dense LDL particles. In addition, some adipokines may exert proinflammatory effects in RA. For example, although obesity and high leptin levels have been associated with attenuated joint destruction, high adiponectin and visfatin levels, as well as rheumatoid cachexia, are linked with severe joint damage. Biologic therapies might interfere with these pathological metabolic changes. However, optimal disease control could result in increased lipid levels, particularly in patients with rheumatoid cachexia, owing to the potent opposing effects of biologic therapies on CRP and lipids. Biologic therapies also improve insulin sensitivity and exert variable effects on adipokines. We suggest that further large studies need to be conducted to understand the nature of these RA - related metabolic alterations.

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