Metabolic Syndrome in Rheumatoid Arthritis

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ABSTRACT

Rheumatoid arthritis (RA) generally affects people between the ages of 20 and 50. Patients with RA have a significantly higher prevalence of the metabolic syndrome (MS) compared to the general population. The increased cardiovascular risk (CVR) associated with RA places this disease among the most widely studied. The duration of RA was associated with MS, implicating the role of inflammation in MS development. The presence of MS correlates with increased subclinical atherosclerosis. A positive correlation between prevalence of MS and worsening of functional status was found in patients with RA. Patients with rheumatoid arthritis have an increased risk and a higher mortality from cardiovascular diseases (CVD), the rheumatologist should be aware of those MS risk factors and attempt to modify them. This review summarizes recent advances in the field of MS in RA.

Keywords: rheumatoid arthritis, inflammation, metabolic syndrome, accelerated atherosclerosis

In the past 20 years, the life expectancy of patients with rheumatoid arthritis (RA) has been shown to be reduced by three to ten years as compared to that of the general population. Rheumatoid arthritis is most likely caused by a combination of genetics and lifestyle choices, particularly smoking, or by a virus or bacteria. Some researches show involvement of the endocrine system. Patients with chronic inflammatory arthritis such as RA are prone to accelerated atherosclerosis and its complications. The reasons for the increased prevalence of atherosclerotic risk factors and MS in patients with rheumatic diseases are not totally clear. MS was defined by the updated joint consensus criteria proposed by the Inter-

national Diabetes Federation Task Force on Epidemiology and Prevention, the National Heart, Lung, and Blood Institute, the American Heart Association, the World Heart Federation, the International Atherosclerosis Society, and the International Association for the Study of Obesity, using the Asian criteria for central obesity when ≥3 of the following components were present: 1) increased waist circumference to ≥90 cm in men or ≥80 cm in women, 2) elevated blood pressure to ≥130/85 mm Hg or requiring drug therapy, 3) elevated serum triglycerides level to ≥1.7 mmoles/L, 4) reduced serum HDL cholesterol to ≤1.0 mmoles/L in men and ≤1.3 mmoles/L in women, and 5) elevated fasting glucose level to ≥5.6 mmoles/L. In patients with RA, treatment with biologic agents was associated with a lower prevalence of MS, but the difference was not statistically significant. Dyslipidaemia, particularly low levels of high-density lipoprotein cholesterol (HDL-c), high levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c) and triglycerides (TG) are associated with an increased CVR in the general population. Particularly, the TC/HDL-c ratio is an important prognostic indicator for future CVD. Lifestyle should be considered as a major CVR factor (1,2).

Several groups have documented a high prevalence of MS in patients with systemic rheumatic diseases. A relationship between RA and abnormalities in the lipid profile has been observed for several decades. Currently, CVD is the major cause of death in patients with RA, and acute myocardial infarction can be up to four times more frequent in these patients. These data albeit circumstantial, point out chronic inflammation as one of the key contributors to MS and accelerated atherosclerosis (3,4).

The autoimmune systemic inflammatory response, along with the presence of MS, doubles the risk for fatal or non-fatal CVD and coronary atherosclerosis, regardless of age and sex. Rheumatoid arthritis has been associated with increased prevalence of MS, but its role in the different characteristics of the disease, such as disease duration, activity, and treatment with glucocorticoids, is not well defined. From a clinical point of view, the relevance of the MS derives from its strong association with the occurrence of subclinical atherosclerosis, major adverse CV events and death. Atherosclerosis,

the main determinant of CV morbidity and mortality occurs prematurely in RA. Patients with RA have an increased risk for CVD. MS occurs in up to 45% of RA patients (5,6). Patients with RA were more likely to have low HDL-c compared to controls, elevated levels of inflammatory markers such as C-reactive protein (CRP) associated with MS. Patients with inflammatory arthritis, particularly those with active disease have low HDL-c levels resulting in a higher-that is, unfavourable, TC/HDL-c ratio, and high TG levels (7). Moreover, it appears that these unfavourable lipid changes may already be present at least 10 years before the onset of RA. Hence, an unfavourable lipid profile may contribute to the increased CVR in patients with inflammatory arthritis. The MS, a cluster of classical CVR factors, including hypertension, obesity, glucose intolerance, and dyslipidemia, is highly prevalent in RA (8).

The typical pattern of dyslipidaemia seen in active RA is an increasing in TC and low-density lipoprotein, a reduction HDL-c. Data regarding TG levels in RA are conflicting, with some studies reporting an increase and others a decrease (9,10).

Both dislipidemia and insulin resistance are components of MS frequently found in RA patients. There are some proposals that the inflammation due to RA may result in insulin resistance. Patients with RA, particularly those with active disease, have low HDL-c levels. An adverse lipid profile characterized by low HDL-c, low apolipoprotein A1 and increased atherogenic index (TC to HDL-c ratio) is observed in active RA (11,12).

HDL levels previously suppressed by disease activity will rise, producing a less atherogenic profile. RA patients have lower insulin sensitivity. Insulin resistance correlates with CRP levels and can also be reduced with successful control of RA activity. MS in RA is independent of gender and body mass index (13,14).

Proinflammatory cytokines are involved in the pathogenesis of atherosclerosis. Tumor necrosis factor (TNF) is a major contributor to the MS. TNF blockers are also associated with a transient increase of TC, mostly accompanied with improvement of the TC/HDL-c ratio, during the first few months of the treatment. TNF-α, interleukin (IL)-1, and interferon (IFN)-γ produced by activated immune cells in the athero-

sclerotic plaque induce the production of substantial amounts of IL-6, which in turn stimulates the hepatic release of acute-phase reactants, including C-reactive protein (CRP), serum amyloid A, and fibrinogen. Persistent elevation of CRP levels as a result of uncontrolled inflammatory arthritis is associated with an increased risk of cardiovascular events. Furthemore, MS was found to be associated with higher CRP levels and higher erythrocyte sedimentation rate. The correlation between RA disease activity and MS is indirect evidence of the role of chronic inflammation in MS and atherosclerosis development. In fact, the risk of having moderate to high RA disease activity was 9 times higher in those patients who also suffered from MS compared to those RA patients who were not burdened by it. A study of RA patients found that MS was associated with disease activity (15).

Finally, patients with severe disease (e.g. those with extra-articular manifestations) have an increased CVR. Therefore, it is recommended that the derived CVR estimate should be multiplied by 1.5 if at least two of the following criteria are present disease duration of more than 10 years, rheumatoid factor (RF) and/or anti-cyclic citrullinated protein antibodies (anti-CCP) positivity, presence of severe extra-articular manifestations (16-18). Modest reduction in weight or improvement in physical activity may significantly reduce CVR. Hence, lifestyle modification should be given to all patients.

In many ways, obesity adversely affects the quality of life of RA patients. Long-term glucocorticoids (GC) exposure does not appear to associate with a higher prevalence of the MS in patients with RA. It is known that patients with active RA have impaired glucose handling and that glucose metabolism may be affected directly or indirectly by inflammatory mediators (17,18).

Glucocorticoids (GC) are known to have beneficial effects in controlling rheumatoid inflammation but their use has been curbed due to their adverse effects. Long-term use of GC is controversial due to an undesirable side effect profile that includes dyslipidemia, hyperglycaemia, insulin resistance, hypertension, and central obesity: these may collectively contribute to the development of the MS and atherosclerosis. GC are commonly used in rheumatic pa-

tients and may influence the CVR in two competing ways. On the one hand, GC could enhance CVR owing to their potentially deleterious effects on lipids, glucose tolerance, insulin production and resistance, blood pressure and obesity. On the other hand, GC may actually decrease the risk of atherosclerosis and CVD by suppressing inflammation, which paradoxically may improve glucose intolerance and dyslipidaemia (19). By contrast, disease-modifying antirheumatic drugs (including initial GC) appear to have beneficial effects on the lipid profile in patients with early active RA. Furthermore, CVR is higher in patients treated with long-term high doses compared with low doses of GC (20-23).

Thereafter the results become divergent and this might be due to differences in disease activity (change of) co-medication, particularly GC, dietary intake and physical activity (24). Hence, future studies should appropriately examine these potential confounders to reach valid conclusions. In the meantime, it appears that the ratio of TC to HDL-c is the most stable marker of lipid-associated risk in RA. Non-steroidal anti-inflammatory drugs, and cyclo-oxygenase-2 inhibitors are associated with an increased CV risk. Studies have shown a positive effect of anti-TNF treatment on insulin resistance (25-27).

A positive correlation between prevalence of MS and worsening of functional status was found in RA patients. Randomised controlled trials are needed to examine this question and some long-term trials are currently being conducted. Additional information is needed about the number needed to harm and the number needed to treat with respect to interaction between lipid-lowering agents and/or antihypertensive agents and antirheumatic treatment in inflammatory arthritis. Etanercept can improve several inflammatory markers in patients with MS. Patients who took etanercept had lower levels of CRP and higher levels of adiponectin (28,29). In RA, many components of the lipid profile are suppressed by the ongoing inflammatory burden, including HDL. Briefly, smoking cessation, weight reduction and exercise are pivotal (evaluating the effect of lifestyle modification on the CVR in inflammatory arthritis should be added to the future research agenda) (30). Therefore, studies evaluating the efficacy and applicability of different

CVR scores are needed in inflammatory arthritis. The molecular mechanisms that account for the interaction between high-grade inflammation and MS feature should contribute to effective drug therapy discovery and development. More aggressive disease activity suppression in patients with persistently active RA and improving adverse lifestyle factors in patients with controlled disease are expected to constitute cornerstones of CVR reduction in RA (31).

The interplay among cytokines, disease activity, atherosclerotic risk factors, and MS in patients with chronic inflammatory arthritis is complex. Elevation of the levels of TNF- and IL-6 as a result of active RA and skin inflammation reduces the activity of insulin and inhibits insulin receptor autophosphorylation and signal transduction, thereby promoting insulin resistance that leads to hyperglycemia, compensatory hyperinsulinemia, and dyslipidemia. The anti-TNF- agents are an effective treatment for inflammatory arthritis. By neutralizing the inflammatory effects of TNF-α, these agents have been shown by controlled trials to reduce levels of biomarkers for CVR in RA (32).

To that end, it is important that more research be conducted in this exciting and evolving field. ❏

CONCLUSION

The above studies represent small, but significant advances in the effort to understand the complex interplay between MS and RA. The prevalence of MS has been reported to be significantly higher in patients with RA as compared to the general population. Patients with RA have an increased risk for CVD. In RA, systemic inflammation, GC use, which are potential determinants of insulin resistance are associated with CVD. The presence of chronic inflammation could explain, in part, the high prevalence of MS among RA patients. RA patients have an increased prevalence of the MS, suggesting a greater need for management to prevent future CV events. MS is not more common in middle and older age RA patients than in non-RA controls, but it tends to correlate with RA disease activity, which adds to the evidence that inflammatory plays a role in the high CVR associated with RA. The presence of the MS in RA appears to be independent of the use of GC. It is possible that the disease process itself is the key contributor. The correlation of RA disease activity with MS suggests that the increased prevalence of coronary heart disease in patients with RA may, at least in part, be attributed to the inflammatory burden of the disease.

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