ARTIGO DE REVISÃO

MULTIPLE FACTORS DETERMINE THE INCREASED PREVALENCE OF ATHEROSCLEROSIS IN RHEUMATOID ARTHRITIS

Ivanio Alves Pereira,* Eduardo Ferreira Borba**

Introduction

Recently there has been a great advance in the diagnostic approach of rheumatoid arthritis (RA) after new laboratory tests, such as anti-cyclic citrullinated peptide (anti-CCP) antibodies, together with imaging methods, such as Ultrasound (US) and Magnetic Resonance of the affected joints, have allowed an early diagnosis and a better characterization of the initial clinical forms. These tests can also be predictive of the future severity of the disease.1-10 In addition, there has been a recent paradigm shift in RA therapy, involving the concept of an early and aggressive treatment that has also contributed to a favourable change in the clinical evolution of these patients.11-15 A better understanding of the immune pathogenesis has allowed the creation of new biological agents that act by blocking target

Abstract

Rheumatoid arthritis (RA) is a systemic inflammatory disease that presents not only involvement of joints but also endothelial dysfunction, dyslipidemia, and premature atherosclerosis. The death rate in RA is known to be higher than in the general population and clinical cardiovascular events secondary to atherosclerosis are responsible for the excessive death rate. A better understanding of the mechanisms that take part in the pathogenesis of atherosclerosis in RA patients is needed. Thus, the authors review the role of several factors involved in RA atherosclerosis, including disease activity, new cardiovascular risk factors, dyslipidemia and the association of atherosclerosis with the use of anti-rheumatic drugs, glucocorticoids and anti-tumor necrosis factor (TNF) agents. The role of humoral autoimmunity, namely autoantibodies against heat shock proteins, cardiolipin and beta2-glycoprotein I, and its link with atherosclerosis is also discussed.

It is likely that the elucidation of the key mechanisms of atherosclerosis in RA may determine a positive impact by reducing cardiovascular morbidity and mortality of these patients.

Keywords: Atherosclerosis; Rheumatoid Arthritis; Inflammation; Autoantibodies; Heat Shock Proteins.

Resumo

A Artrite Reumatóide (AR) é uma doença inflamatória sistémica que, para além do envolvimento articular, apresenta também disfunção endotelial, dislipidemia e aterosclerose prematura. A mortalidade na AR é superior à da população em geral e os eventos cardiovasculares secundários à aterosclerose são responsáveis por esse excesso de mortes. É necessário compreender melhor os mecanismos implicados na patogénesis da aterosclerose nos doentes com AR. Os autores fazem uma revisão do papel de vários factores envolvidos nessa aterogénesis, incluindo a actividade da doença, novos factores de risco cardiovascular, a dislipidemia e a associação da aterosclerose com o uso de fármacos anti-reumáticos, glucocorticóides e agentes bloqueadores do factor de necrose tumoral (TNF). Também é discutido o papel da imunidade humoral, nomeadamente dos anticorpos contra proteínas de choque térmico, cardiolipina e beta2-glicoproteína I, e a sua ligação à aterosclerose. É provável que a elucidação de mecanismos chave da aterosclerose na AR possa ter um impacto positivo, traduzido na redução da morbidade e mortalidade cardiovascular destes doentes.

Palavras-chave: Aterosclerose; Artrite Reumatóide; Inflamação; Proteínas de Choque Térmico; Auto-anticorpos

*Division of Rheumatology. Federal University of Santa Catarina
**Division of Rheumatology. University of São Paulo
cells and cytokines. Despite these new achievements, RA mortality rate is still higher than that of the general population and life expectancy remains reduced by 3 to 10 years. Considering that cardiovascular problems are responsible for the higher mortality in RA, we reviewed important findings on the pathogenesis of atherosclerosis in this disease.

In severe RA, the increased mortality rate is comparable to that found in patients with lymphoma and triple vessel coronary artery disease. The accelerated atherosclerosis determines a greater incidence of coronary artery disease in RA patients, which is responsible for the higher mortality rate when compared with the normal population. There are countless studies on RA that confirm a higher frequency of carotid atherosclerosis, cerebrovascular ischemic events and coronary disease through several diagnostic methods such as carotid US, myocardium perfusion scintilography, and coronary artery angiography. Atherosclerosis in the general population has been related to systemic inflammatory markers such as fibrinogen and, mainly, C reactive protein (CRP), which is consistent with the fact that atherosclerosis results from an inflammatory process in the artery and has even led some authors to suggest changing the nomenclature of atherosclerosis to atheroscleritis.

Currently, there are several studies in the population with coronary disease that search for new independent risk factors that could be predictive of atherosclerosis with the objective of increasing the early recognition of subclinical atherosclerosis, in an attempt to establish general preventive measures or even earlier therapeutic measures.

### Classical risk factors for atherosclerosis

In RA patients, the higher incidence of cardiovascular disease and the higher death rate result from the involvement of multiple pathogenic factors that contribute for the atherosclerotic lesion. Some studies have depicted the occurrence of endothelial dysfunction, which is secondary to the diffuse vascular inflammation resulting from the disease activity. Other studies have shown that RA patients present changes in the levels of lipoproteins with reduced levels of HDL cholesterol and high levels of total cholesterol, which are influenced by the disease activity and RA treatment. The control of RA activity can improve this abnormal lipid profile and it was demonstrated that the use of non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids and gold salts over a 9-month period increased significantly the HDL levels. Moreover, the use of antimalarial agents has beneficial effects on the lipoprotein profile, with a reduction of the LDL cholesterol levels and an increase in the HDL cholesterol levels.

Interestingly, the prevalence of the metabolic syndrome in Brazilian RA patients is 24%, and this finding is not significantly different from the general population. In this study, there was no correlation between lipoprotein levels, glucose levels, hypertension, waist circumference, or body mass index (BMI) and disease activity parameters, functional capacity or response to therapy.

Obesity is a classic risk factor for coronary atherosclerotic disease, however, a recent study in RA patients correlated BMI with cardiovascular mortality and showed that a low BMI (less than 20 kg/m²), usually associated with active RA, was in fact predictive of cardiovascular mortality, contrary to what is observed in the general population.

There are few studies that define the role of other classic risk factors for cardiovascular disease in RA. The prevalence of diabetes mellitus (DM) is not higher in RA patients, although there is a greater prevalence of insulin resistance, similar to what occurs in other systemic inflammatory conditions. In fact, it is known that insulin resistance in RA is associated with disease activity and can improve with the use of glucocorticoids due to its anti-inflammatory effect, contrary to the findings found with this drug in non-RA patients. On the other hand, smoking is an important risk factor for atherosclerosis in the general population, and tobacco has also been described as a major risk factor for RA onset. The association between tobacco and RA is dose-dependent, that is to say, there is a correlation between tobacco consumption and disease severity and with the presence of rheumatoid factor (RF).

However, so far, published studies have not shown that tobacco is an independent risk factor for RA cardiovascular mortality. Thus classic risk factors for cardiovascular disease do not justify the greater incidence of accelerated atherosclerosis in RA patients.

The role of some new risk factors for atherosclerosis, such as homocysteine and lipoprotein (a), have not been defined in RA, although preliminary results have already shown higher levels in these patients.
The role of therapy and inflammation

RA severity markers have been associated with a greater global mortality, but no particular clinical parameters have been specifically related to cardiovascular mortality. On the other hand, the relationship between atherosclerosis and RA treatment has also been analyzed and it was shown that the use of glucocorticoids and DMARDs in RA does not increase the incidence of cardiovascular disease, and some studies with methotrexate have even shown a reduction in cardiovascular mortality. Most studies on the use of TNF blockers in RA patients have suggested beneficial effects on the endothelial function, although Van Doornum et al described different results. Besides that, TNF blockers lead to improvement in insulin resistance and reduce the risk of death and hospitalization secondary to cardiovascular disease.

Recent studies have shown that a subgroup of RA patients have a greater number of T CD4+ /CD28- lymphocytes cells, which produce gamma-interferon and induce the activation of Th1 cells with the resulting production of a variety of different proinflammatory cytokines. This observation is also described in atherosclerosis and it has been considered relevant in patients with unstable angina. The T CD4+ CD28- cells, present in greater quantity in RA patients, are probably stimulated by endothelial autoantigens and infiltrate the atherosclerotic plaque, promoting vascular lesion due to their proinflammatory potential. A recent study confirmed the role of T CD4+ CD28- cells in the onset of early atherosclerosis in RA patients. In fact the authors showed that RA patients with a CD4+ CD28- expansion had increased intima-media thickness (IMT) and greater endothelial dysfunction when compared with RA patients without expansion of those cells.

It is considered that the inflammatory process in RA is, at least, partially mediated by T cells which may have as a result, not only joint inflammation but also the induction of inflammation on blood vessel walls. In addition, circulating RF and other immune complexes may also cause direct lesion of endothelial cells. Circulating proinflammatory cytokines released in RA may contribute to the inflammatory process on vessel walls, similar to what occurs in joints. On the other hand, TNFα and IL-6 induce the hepatic synthesis of CRP, which has been shown to be a prognostic factor for the development of cardiovascular disease secondary to atherosclerosis in the normal population. CRP induces the expression of adhesion molecules (ICAM 1, VCAM 1, and E-selectin) in endothelial cells, suggesting a direct pathogenic role for CRP in atherosclerosis. Accordingly, in RA the systemic inflammation results in greater risk of cardiovascular mortality, and CRP levels were correlated with atherosclerosis in carotid arteries. In addition, the increased cardiovascular mortality that occurs in RA patients is more frequent in patients with systemic involvement, such as rheumatoid lung disease and vasculitis, which could suggest the hypothesis of rheumatoid vasculitis as one of the triggering factors for atherosclerosis. However, studies suggest that endothelial dysfunction, more than vasculitis itself is present in RA patients, and this dysfunction is independent of the patient age group, disease duration, disease activity, and RF levels.

Brachial artery studies with high sensitivity US non-invasively assess endothelial function by measuring vasodilatation that occur after occlusion of the blood flow. In RA patients studies with this test have shown less artery vasodilatation and this was associated with disease activity. These findings suggest that chronic inflammation in RA is one of the responsible factors for the initial endothelial dysfunction, which starts the atherosclerotic process. In RA the endothelial dysfunction is more intense in patients carrying the shared epitope.

Coagulation parameters and atherosclerosis in RA

In the general population, studies show that fibrinolysis markers, such as fibrinogen, von Willebrand factor and the plasminogen activator inhibitor (PAI) were predictive of acute myocardial infarction. These observations can be explained by the role of thrombosis caused by the unstable atherosclerotic plaque as an onset factor of acute coronary syndrome. Systemic inflammation may be associated with a state of increased clotting due to thrombocytosis and high levels of fibrinogen, von Willebrand factor and PAI. In RA patients the importance of these prothrombotic elements as predictors of a greater incidence of cardiovascular events secondary to accelerated atherogenesis has not been defined, due not only to the small number of studies, but also to the need of excluding patients with conditions that interfere with the mea-
surement of these parameters, such as DM and hormone replacement therapy. Studies show that high levels of fibrinogen, von Willerbrand factor, tissue plasminogen activator (tPA), fibrin D-dimer, and PAI were predictive of cardiovascular events in RA patients.105-108

Humoral autoimmunity and atherosclerosis of RA

Recent research in the general population suggests the participation of autoimmunity in atherosclerosis, with studies showing the association of atherosclerosis with antibodies against antigens expressed in the atheroma plaque, such as antibodies against oxidized LDL (LDLox), heat shock proteins (Hsp) 60 and Hsp 65, antibodies against membrane phospholipids and against beta2-glycoprotein L109-123 These antibodies are present more frequently in RA patients than in the normal population, but their pathogenic role in RA atherosclerosis requires further clarification.

Regarding antibodies against cardiolipin, their prevalence in RA is 15 to 20 percent, without association with any clinical manifestation of thrombosis; the association with clinical atherosclerosis has not been sought.124,125 Additionally, studies have shown the induction of antibodies against phospholipids with the use of TNF blockers in RA patients, although the exact functional meaning of these antibodies in this context has not been clarified.126

In the general population, high levels of anti-LDLox have been associated with atherosclerosis and also with autoimmune rheumatic diseases such as systemic lupus erythematosus (SLE) and RA.127-131 A recent study in RA showed a positive correlation between high levels of IgG autoantibodies against LDLox and carotid atherosclerosis, which suggests that autoimmunity present in RA is also a risk factor for atherosclerosis.132 Finally, studies aiming to clarify the role of the proatherogenic proteins myeloperoxidase and PAPP-A in RA patients have not been carried out and could be important.

Carotid artery ultrasound in RA patients

Performing non-invasive studies such as US of the carotid arteries to recognize the presence of atherosclerosis in the preclinical phase and correlate these findings with clinical parameters is valuable, especially after the recent studies indicating that coronary disease in RA patients is more frequently silent, with a greater incidence of silent myocardial infarction and sudden death from cardiovascular causes.133,134 In a 6.2 years follow up of 4476 non-RA adults who did not present evidence of cardiovascular disease, the increased IMT was associated with a greater incidence of AMI and cerebrovascular accident.135 The presence of atherosclerotic plaques in carotid US predicts a higher risk of cardiovascular disease in the future and is considered an independent risk factor for AMI.136-138 Many investigators have shown that RA patients present a greater mean carotid IMT when compared with the non-RA population.33,34,132,139 The absence of standardized criteria to assess atherosclerosis in RA patients may explain some discordant results.36,140 The increase of IMT in RA patients is correlated with disease duration and with inflammatory parameters such as CRP levels measured at the time of the US.16 Roman et al, showed that the prevalence of subclinical atherosclerosis, defined by the presence of atheroma plaques in carotid artery US, is three times higher in a group of RA patients when compared to a control group paired by age, sex and ethnicity. The presence of plaques in this study did not correlate with the presence of hypertension, smoking, use of glucocorticoids, and low HDL level.141 Two other studies also showed a greater carotid IMT in RA patients, however the presence of atheroma plaques was not increased.32,33 In one of the studies, performed in patients from Korea, the low prevalence of plaques was suggested to be a consequence of the low prevalence of atherosclerosis and cardiac disease in that population.33

Conclusions

In summary, studies show that cardiovascular disease is a leading cause of mortality in RA and many factors contribute to this important clinical problem. Although classical risk factors such as smoking, dyslipidemia and others may be present in RA patients, they do not justify the higher prevalence of atherosclerotic disease. In fact, RA itself is an independent risk factor for coronary and cerebrovascular disease. In addition, the altered cellular immunity leads to endothelial lesions due to infiltration of the same inflammatory cells found in joints. The role of humoral immunity in the pathogene-
sis of atherosclerosis in RA patients is not yet well defined, since the few studies performed did not replicate the association with atherosclerosis that had been depicted in the general population.

It is important to consider that coronary artery disease in RA is often silent, and the extension of the lesions and event related mortality is higher when the diagnosis is only achieved after the clinical events have occurred. Therefore, the use of early atherosclerotic disease diagnostic tests, such as US, should be introduced more precociously in the evaluation of RA patients.

The associations found between disease activity and inflammatory parameters on one hand, and the decrease in mortality with the use of methotrexate and TNF blockers on the other hand, confirm the need for aggressive treatment in this disease, not only to prevent joint deformities but also to reduce cardiovascular events and the overall mortality.

Finally, rheumatoid synovitis shares some aspects with the inflammation that occurs in the atheroma plaque, meaning that RA can be viewed as an in vivo model of the complex inflammatory and autoimmune mechanism that occurs in atherosclerosis. Moreover, the evidence that in RA, intrinsic mechanisms initiate accelerated and early atherosclerosis can be used as a window of opportunity to improve our understanding of the initial mechanisms involved in cardiovascular diseases.

Correspondence to:
Ivanio Alves Pereira
Departamento de Reumatologia
Universidade Federal de Santa Catarina
Florianópolis, Brasil
E-mail: ivaniop@matrix.com.br

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