Cardio-metabolic comorbidities in rheumatoid arthritis and SLE

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Summary
The progressive improvement of diagnostic and therapeutic alternatives in rheumatic diseases has resulted into reduction in patient mortality and morbidity caused by disease activity. Therefore, new morbidity factors have emerged, i.e. atherosclerosis. It has an early onset and rapid evolution in patients who suffer from a number of rheumatic diseases, including systemic lupus erythematosus, rheumatoid arthritis, scleroderma, Sjögren syndrome and vasculitis.

The immune system and the endothelium are thought to play a crucial role in the atherosclerosis pathogenesis. The immune system is characterized by two different responses to infections: innate and adaptive responses. In the atherosclerotic process, inflammatory cells and molecules are involved which belong to both immune response types.

Moreover, the opinion of most authors is that the endothelial damage is to be considered as a predictor for development of the atherosclerotic plaque.

In the atherosclerosis pathogenesis, inflammatory and immune aspects play a crucial role. By studying the effect of chemokines, cytokines and autoantibodies, it was possible to better define the role of innate and specific immunity and, in the near future, it will be possible to better define the real biological impact of these mediators in cardiovascular events, setting them as targets for future therapeutic strategies.

KEY WORDS: rheumatoid arthritis; systemic lupus erythematosus; atherosclerosis; innate immunity; adaptive immunity.

Increased cardio-metabolic complications are usually observed in patients with rheumatoid arthritis and SLE compared to the general population (1). Atherosclerosis is undoubtedly the main cardio-metabolic complication. Historically, atherosclerosis was regarded as a condition characterized by lipid accumulation on vessel walls, resulting into a progressive vessel lumen reduction and the development of a cardiovascular event. Throughout the years, however, evidence has shown that a complex number of immunoinflammatory processes develop in the vessel wall, which play a crucial role in the initiation and progression of the atherosclerotic process as well as in triggering the atherothrombotic event that in turn causes a cardiovascular event. While it has been established that endothelial dysfunction is the primary cause for the development of atherosclerosis, the mechanisms that originate endothelial dysfunction remain unclear. According to the classical hypothesis of atherosclerosis, traditional risk factors (hypertension, smoking, high cholesterol levels) may induce endothelial dysfunction; however, recent evidence has shown that infections or chronic inflammatory disease may play a role (2). All this factors may contribute to endothelial dysfunction through a common mechanism: immune system activation. Immunity can be distinguished into innate and adaptive, and these two components have different roles and features. It has been demonstrated that the effectors of both immunity components may play a key role in inducing the atherosclerotic process (Figure 1).

If we observe the innate component of the immune system, it is clear that pattern recognition receptors, i.e. the receptors that identify common molecular pat-
Dendritic cells that penetrate the plaque from the circumscribed LDLs. Then they migrate to lymph nodes, where they can internalize antigens, for example oxidized LDLs. The role of Th17- and Th2-lymphocytes is to present antigens to CD4+ and CD28- populations. This clonal subpopulation has been identified in patients without a history of cardiovascular disease, and it may become the target of an antibody response (6). The main antibodies that have shown to be associated with atherosclerosis are those against oxidized LDLs, beta2-glycoprotein I and heat shock protein. Several groups have demonstrated that high levels of anti-oxidized LDL antibodies are associated with ischemic heart disease in humans (7); at the experimental level, it has also been demonstrated that the passive transfer of T cells specific for oxidized LDLs in hypercholesterolemic mice may accelerate the atherosclerotic process (8). Other studies have shown that immunization with oxidized LDLs in animals susceptible to atherosclerosis may cause either a suppression or a worsening of atherosclerosis (9), and that infusion with anti-oxidized LDL monoclonal antibodies (in animals susceptible to atherosclerosis) may inhibit oxidized LDL uptake by macrophages (10). Therefore, it is likely that the group of anti-oxidized LDL antibodies include both protective and pathogenetic antibodies. Under normal conditions, anti-oxidized LDL antibodies may help in the removal of oxidized LDLs by macrophages, but in special circumstances – e.g. an increased oxidation in smokers – there could be a formation of anti-oxidized LDL antibodies directed against different epitopes, and these antibodies may favor oxidized LDL uptake by macrophages, and therefore accelerate atherosclerosis. Protective antibodies might belong to the IgM class, while pathogenetic antibodies to the IgG class (11).

The second group of antibodies includes anti-phospholipid antibodies, i.e. those associated with arterial or venous thrombosis, both in vivo and in obstetric complications. The main antigen targeted by anti-phospholipid antibodies is beta2 glycoprotein I, a polypeptide chain consisting of five domains: the fifth domain presents positively charged amino acids and is thought to be responsible for beta2 glycoprotein I binding with negatively-charged phospholipid wall. In the majority of cases, anti-beta2 glycoprotein I antibodies are directed against the first domain. Beta2 glycoprotein I not only binds to phospholipids, but also to other negatively-charged molecules, including lipoproteins.

Beta2 glycoprotein I is expressed on endothelial cell membranes and intimal medial borders of human atherosclerotic plaques obtained after carotid endarterectomies. It co-localizes with CD4-positive lymphocytes (12). The role of beta2 glycoprotein I in atherosclerosis has been also demonstrated by experiments conducted in animals: immunization of LDL-receptor deficient mice induces anti-beta2 antibody production and a worsening of atherosclerosis. If we take lymphocytes from immunized mice and transfer them to mice with a similar genetic background, an acceleration of atherosclerosis will be seen in these mice as well. This will not be seen after lymphocyte depletion. Therefore, beta2 glyco-
coprotein I-specific lymphocyte may increase atherosclerosis and this involves that β2 is a relevant antigen in this process (13).

Antiphospholipid antibodies have shown to be associated with several cardiovascular events in humans (14) while the association between antiphospholipid antibodies and subclinical atherosclerosis is more controversial (15). A similar phenomenon is observed with heat shock proteins (HSP 60) that are produced by damaged cells and protect other proteins from denaturation (Figure 2). Heat shock proteins may be produced by endothelial cells in response to stressors (hypertension, smoking, etc.) and represent a target for autoimmunity under certain circumstances.

Clinical subclinical and experimental data show that these antibodies are associated with atherosclerosis (16). Results from animal studies are similar to those obtained for β2 glycoprotein I: immunization of LDL-receptor deficient mice with heat shock protein 65 induces antibody production and more atherosclerosis. If we take the antibodies produced by mice or the lymphocytes specific for heat shock proteins and transfer them to animals with a comparable genetic background, these animals will develop more atherosclerosis. Therefore, autoantigens have been identified and isolated within the atherosclerotic plaque, along with autoreactive lymphocytes and antibodies that are found in the circulation but infiltrate the plaque as well. It has been observed that the disease can be induced in experimental animals after immunization with antigens and/or passive transfer of antibodies and lymphocytes (17).

This means that atherosclerosis meets five of the criteria used to define autoimmune diseases (Figure 3). Therefore, can we consider atherosclerosis as an autoimmune disease? Perhaps it is, but autoimmunity plays a relevant role in the development of atherosclerosis.

As a logical consequence, atherosclerosis appears to be accelerated in autoimmune rheumatic conditions, especially rheumatoid arthritis and SLE (18). The relative risk of cardiovascular events in rheumatoid arthritis is 3.9-fold higher than in the general population, while in SLE the risk is 17-fold higher, and it increases in age groups of young patients: in SLE female patients of the 35-44 age range – an age group that usually is not affected by atherosclerosis – the risk of developing a myocardial infarction is 50-fold higher than in the general population (19, 20).

Why is atherosclerosis accelerated in autoimmune diseases?

Findings from the studies reported in Table 1 show a very high variability of plaque prevalence between studies, ranging from 17 to 40%. Such difference could be explained by the different composition of study populations (mean age, male:female ratio, race, history of cardiovascular events). However, if we observe IMT values, they are quite similar between the studies, ranging from 0.55 mm to 0.71 mm. Since IMT is considered to be normal up to 0.9 mm, the values shown in the Table are all normal, and they are identical regardless of plaque prevalence. In a 2003 study by Roman et al., it was reported that mean IMT was significantly lower in SLE patients compared to healthy subjects (21). In a study published in 2007 (a post mortem study on an appropriate number of patients who died for myocardial infarction, and stratified according to the presence or absence of rheumatoid arthritis), the extent of atherosclerotic plaques was higher in patients who had died for myocardial infarction but without rheumatoid arthritis compared to those who were affected by rheumatoid arthritis. Likewise, the degree of stenosis was higher in patients without rheumatoid arthritis than in the others. Patients with rheumatoid arthritis had more vulnerable plaques (22). Therefore, in patients with rheumatoid arthritis, plaque vulnerability is caused by the inflammation inside the plaque: vulnerability is directly proportional to the degree of inflammation.

Therefore, the atherosclerotic plaque hosts several immuno-inflammatory processes that may be very similar to those involved in rheumatoid arthritis. In SLE, in lupus glomerulonephritis, some of the genes that control immuno-inflammatory processes are likely to be the same as those involved in atherosclerosis (23). For these genes, too, there are polymorphisms of both the TNFα gene and of the group of

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**Human HSP60**

- Intracellular Chaperone protein
- Expressed on the surface of stressed cells
- Human HSPs are expressed on endothelial cells in response to stressors like hypertension, smoking, lipoproteins, etc.
- HSPs offer a target for autoimmunity under such circumstances
- HSP60 shows high inter species homology

**Major Criteria of Autoimmune Disease**

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1. Identification and isolation of autoantigen(s) (Ags) involved
2. Circulating autoantibodies (Abs) and/or autoreactive lymphocytes in patients (pts) and family members
3. Abs and/or autoreactive lymphocytes within the affected organ
4. Disease induction in animals after immunization with Ags and/or passive transfer of serum Abs and/or lymphocytes
5. Mononuclear cell infiltrate and abnormal HLA expression in the target organ (organ-specific disease) or in various organs (nonorgan-specific disease)
6. Efficacy of immunosuppression in patients

Autoimmune disease= fulfillment of 2 or more major criteria

**Figure 2 - Features of heat shock proteins (HSP 60).**

**Figure 3 - Diagnostic criteria for autoimmune diseases.**
genes involved in interferon signature, i.e. the genetic signature that predisposes and is the first step in the development of autoimmune diseases. Therefore, it is possible that some mediators produced in the synovium or in lupus glomerulonephritis are released into the circulation and induce endothelial dysfunction, regarded as the *primum movens*, either directly or indirectly through C-reactive protein production. Once the inflammation has developed inside the plaque, this becomes vulnerable and fragile, the fibrous cap breaks down and this leads to the development of the atherothrombotic mechanism and the resulting acute cardiovascular event. However, cardiovascular events – especially in thrombophilic patients – may also develop as a consequence of thrombus formation on a superficial erosion. It is possible that, in patients with rheumatoid arthritis or SLE, the cardiovascular event develops following rupture of an unstable plaque, but it may also happen that in SLE patients or in those with antiphospholipid antibody syndrome the cardiovascular event is caused by the other mechanism, i.e. thrombus formation on an endothelial erosion. In this respect, it should be noted that endothelial erosions are a frequent occurrence and they are generally repaired by endothelial progenitor cells or by angiogenic myelomonocytic cells. Interestingly, interferon-alpha – the cytokine involved in autoimmune diseases – induces apoptosis in myelomonocytic endothelial progenitor cells, and therefore can reduce the repair of endothelial erosions (24).

The association between autoimmune inflammatory rheumatic diseases and cardiovascular risk is certainly very strong; we have mainly discussed disease-related factors, namely immuno-inflammatory factors, which are certainly a new field of research; however, we should not neglect traditional risk factors and the pharmacological treatments currently used, that may play a role in the development of atherosclerosis (25).

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