Editorial

Atherosclerosis and Lupus: What We Know and What We Should Know

Whether atherosclerosis is accelerated in patients with systemic lupus erythematosus (SLE) is not a matter of debate any more. Since Urowitz, *et al*'s first study[1], myocardial infarction (MI) has been recognized as one of the leading causes of death in patients with SLE, particularly in those with long-lasting disease. The frequency of MI as a cause of death in SLE patients has also proportionately increased in the last few decades due to the decrease in deaths directly related to SLE, a consequence of improvement in SLE treatments and the longer survival of patients[2].

Interestingly, in post mortem studies, significant atherosclerosis was observed in more than 50% of patients regardless of the cause of death[3]. In addition, clinical and epidemiologic studies have thoroughly documented the higher prevalence of coronary artery disease (CAD) in patients with SLE compared with the general population, which ranges between 6% and 10%[4]. These findings were expanded in studies using diagnostic methodologies such as scintigraphy with thallium-201, single photon-emission computed tomography dual-isotope myocardial perfusion imaging, electron-beam computed tomography, and carotid B-mode ultrasound (US): prevalence of subclinical atherosclerosis was shown to be even higher than that of clinical atherosclerosis, with values ranging between 10% and 40%[4].

It is still unknown, however, whether cardiac perfusion abnormalities, carotid plaques, or calcifications in coronary arteries in patients with SLE are as predictive of cardiovascular (CV) events as in the general population.

Studies using either clinical or subclinical outcomes clearly showed that excess atherosclerosis in SLE patients cannot be attributed to "classic" Framingham risk factors, but derives from a complex interaction between traditional and nontraditional predictors[5]. Notably, in SLE a great variability in the predictors of clinical and subclinical atherosclerosis was observed. This variability seems to be primarily dependent on the characteristics of patient cohorts and outcomes considered in different studies.

SLE is an extremely heterogeneous disease; as a consequence, cohorts of patients varied from study to study not only according to age, female to male ratio, disease duration, ethnicity, and prevalence of any single traditional risk factor, but also according to the prevalence of SLE manifestations, disease activity, and treatment. Atherosclerotic outcomes are also extremely variable. Apart from the obvious difference between clinical and subclinical outcomes, it is worth noting that the different techniques used to assess subclinical lesions investigate different stages or different aspects of the atherosclerotic process, leading to the identification of different atherosclerotic predictors.

In addition, if we look at the studies using carotid US, the most common method for detection of subclinical atherosclerosis, we can see that many of them considered the value of intima-media thickness (IMT), and not the presence of plaque, as an outcome measure. However, in the majority of cases the IMT mean values observed in these studies were similar, ranging between 0.50 and 0.90 mm. It is notable that these IMT values are within what is considered the normal range of IMT measurement.

Interestingly, in Roman, *et al*'s study[6] mean IMT was significantly lower in SLE patients compared with healthy subjects, whereas the prevalence of plaque was significantly increased in the former versus the latter. This means that in SLE the arterial tree is not as extensively altered as in subjects with diabetes or hypertension, but it is affected by the presence of plaques. Apart from the number, both composition and stability of plaques are also relevant but poorly investigated aspects in lupus.

In a post mortem study Aubry, *et al*[7] showed that extent of atherosclerosis in coronary arteries as well as grade of stenosis were lower in rheumatoid arthritis (RA) patients with CV disease versus controls with CV disease, which appears to be in contrast to several vascular imaging studies suggesting increased CAD in RA patients. However, in Aubry, *et al*'s study[7], the percentage of vulnerable plaques [defined as lesions with a fibrous cap < 65 μm thick con-

See Risk factors for development of CAD in women with SLE, *page 2454*

taining > 25 inflammatory cells per high-power (×40) field] was higher in RA patients than in controls.

As an explanation of CV events in SLE, an alternative mechanism to the rupture of a vulnerable plaque could be the development of a superficial erosion of the endothelial cells, possibly caused by endothelial apoptosis or desquamation, that could lead to a coronary thrombus formation[8] in patients with high thrombotic risk profile.

With these caveats on variability of SLE cohorts and atherosclerotic outcomes, there is general agreement that traditional risk factors play a relevant role in accelerated atherosclerosis observed in SLE patients[5]. While older age seems to be the strongest predictor, hypertension, dyslipidemia, sedentary lifestyle, and other traditional risk factors also seem to make a significant contribution[5].

Although the overall role of nontraditional risk factors is unquestioned, the contribution of any single nontraditional predictor is still controversial. Nontraditional predictors have been more extensively evaluated in subclinical than in clinical studies since the number of events are higher in the former compared to the latter.

Apart from immune or inflammatory markers such as C-reactive protein, cytokines, adhesion molecules, and antioxidized low-density lipoprotein, which have been poorly investigated in SLE[9-11], what is not completely clear is the role of some important clinical variables such as disease severity or use of corticosteroids and immunosuppressants[12]. According to some studies[6], but not others[13], patients with mild disease who took less corticosteroid and immunosuppressants have a higher likelihood to develop atherosclerosis. This information is relevant since we need to know which patients require the closest monitoring and the most stringent preventive strategy[14-16]. The effect of treatments on CV risk factors and, in turn, on subclinical and clinical lesions is a key aspect that should be urgently addressed.

It is well known that corticosteroids are a “double-edged sword”: on the one hand they worsen classical CV risk factors by increasing blood pressure, glycemia, cholesterolemia, triglyceridemia, and body mass index; on the other, they have a favorable effect on nontraditional risk factors by reducing inflammation and disease activity. What we should probably focus on is the possibility of identifying a cutoff dosage able to balance favorable and adverse effects.

The use of hydroxychloroquine (HCQ) seems to be associated with lower serum cholesterol and triglyceride levels in SLE patients; moreover, HCQ seems to have an antithrombotic effect and seems to reduce glycemia as well as blood pressure[17]. Despite all these favorable effects, we still do not know whether HCQ can protect SLE patients from atherosclerosis.

Immunosuppressants exert a corticosteroid saving effect; moreover, they do not substantially affect traditional risk factors (with some exceptions: cyclophosphamide induces premature menopause, methotrexate raises serum homocysteine levels, and cyclosporin A increases blood pressure). In contrast, mycophenolate mofetil (MMF) seems to have antiatherogenic properties, including inhibition of inducible nitric oxide synthases, reduction of the expression of adhesion molecules, and, in turn, recruitment of leukocytes, inhibition of T cell and smooth-muscle cell proliferation, induction of apoptosis of T cells and monocytes/macrophages, and inhibition of dendritic cell maturation and T cell activation. However, the real contribution of any single immunosuppressant, including MMF, to atherosclerosis in patients with SLE is still unclear.

Finally, B cell depletion is becoming a popular off-label treatment for refractory manifestations of SLE. Interestingly, serum levels of IgG and IgA as well as of antimicrobial antibodies do not seem to be affected by rituximab treatment, whereas some studies report a decrease in serum IgM levels. Notably, IgM antibodies play a central role in protection against atherosclerosis[18], thus the use of rituximab, particularly in repeated cycles, might potentially increase the atherosclerotic burden in patients with SLE. In contrast, endothelial function improved after rituximab treatment in patients with RA refractory to tumor necrosis factor-α blockers[19]. Thus, the net effect of rituximab on atherosclerosis remains to be elucidated.

In this issue of *The Journal*, Goldberg, *et al*[20] show, in the first prospective controlled study on this topic, that patients with SLE developed significantly more CAD than age-matched controls and that the most important risk factors in multivariate analysis were lupus itself, age, and triglyceride levels. Unfortunately, like many other studies in lupus, the number of patients with CAD was relatively small, leading to an insufficient statistical power of the study to detect the influence of some risk factors. Nevertheless, it represents further evidence of the increased atherosclerotic burden in SLE and the role played by SLE itself.

The time has come to focus our efforts and resources on all the other unresolved issues that need to be urgently addressed.

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