Review Article

Accelerated atherosclerosis and cardiovascular disease in systemic lupus erythematosus

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ABSTRACT

Cardiovascular disease (CVD), particularly coronary heart disease and stroke, is one of the most important causes of morbidity and mortality in patients with systemic lupus erythematosus (SLE). The increased prevalence of CVD and subclinical atherosclerosis, even after adjustment for traditional risk factors, are well established. Several associations with disease-related clinical, genetic and immunological features have been identified. The SLE-specific stratification algorithms with emphasis on composite risk-assessment scores including both traditional risk factors and novel biomarkers is recommended. The clinical complexity of accelerated atherosclerosis will most likely require an integrated approach for the identification, treatment, and intensive study into this aspect of SLE that will ultimately lead to improved cardiovascular outcomes for these patients.

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Atherosclerosis acelerada y enfermedad cardiovascular en el lupus eritematoso sistémico

RESUMEN

La enfermedad cardiovascular (ECV), en particular la enfermedad coronaria y el ictus, es una de las causas más importantes de morbimortalidad en pacientes con lupus eritematoso sistémico (LES). El aumento en la prevalencia de la ECV y de la atherosclerosis subclínica, aun después del ajuste de los factores de riesgo tradicionales, está claramente establecida. Se han identificado diversas asociaciones con características clínicas, genéticas e inmunológicas relacionadas con la enfermedad. Se recomienda el uso de los algoritmos de estratificación específicos para el LES, con énfasis en los puntajes compuestos de evaluación de riesgo, incluyendo tanto los factores de riesgo tradicionales como los nuevos biomarcadores. La

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complexidad clínica de la aterosclerosis acelerada muy probablemente requerirá un abordaje integral para la identificación, el tratamiento y el estudio intensivo de este aspecto del LES, que en última instancia permita obtener mejores desenlaces cardiovasculares en estos pacientes.

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Introduction

Cumulative evidence over the last 30 years strongly supports the active involvement of the immune system in the development of atherosclerotic plaque as well as the interconnection between chronic autoimmune/inflammatory disorders and excessive cardiovascular burden, not easily attributed to traditional cardiovascular risk factors (CVRFs).1-3

In young women with SLE, the risk for myocardial infarction (MI) has been found to be 50 times higher compared to healthy women of similar age distribution.4,5 While traditional risk factors associated with atherosclerosis including smoking, dyslipidemia, diabetes mellitus, hypertension and increased body mass index (BMI) are present in lupus patients, standard Framingham scores do not fully explain the high rates of ischemic events so far reported. It has therefore been proposed that the atherosclerotic process is accelerated in patients with SLE due to a complex interplay of traditional and lupus-specific risk factors.6-8 SLE is known to be an independent risk factor for endothelial dysfunction.9

Epidemiology of CVD in SLE

SLE is a heterogeneous autoimmune disease, affecting women of childbearing age, with substantial morbidity and mortality. The effect of SLE on atherosclerotic disease has been recognized since the 1970s, when Urowitz et al. observed a bimodal mortality peak for lupus patients; the first was attributed to disease activity and infections and the second to CVD.10 Three decades later, progress in disease treatment had resulted in decrease of mortality due to disease activity; however, CVD and infectious complications remain the main causes of death in these patients.11 The prevalence of ischemic heart disease in SLE patients is estimated between 3.8% and 16%,12,13 conferring a 10-fold risk compared to the general population and a 50-fold risk in young women of reproductive age.1,4,14 The risk of stroke in SLE patients was also found to be increased by 2-8-fold in different studies.14,15

About 30-40% of patients with SLE show evidence of subclinical atherosclerotic lesions, depending on the diagnostic methods. The excess of carotid plaque in SLE is particularly striking in those under 55 years old and it has consistently been shown that patients with SLE have significantly higher prevalence of atherosclerotic plaque than healthy controls.16-20

In addition to macrovascular abnormalities in SLE, there is evidence to suggest abnormal coronary microvascular function. When positron emission tomography was used, abnormal coronary flow reserve was seen even in SLE patients with normal coronary arteries.21 Abnormal stress myocardial perfusion imaging (shown by adenosine stress cardiac magnetic resonance imaging) was found in 44% of SLE patients with angina and chest pain in the absence of obstruction. Quantitative myocardial perfusion reserve index was also observed to be lower in patients with SLE as compared with controls, and the presence of SLE was a significant predictor of myocardial perfusion reserve index.22

Traditional CVD risk factors in SLE

Metabolic syndrome

Metabolic syndrome (MetS) is a constellation of central obesity, insulin resistance, dyslipidemia and hypertension, that was found to be prevalent in lupus patients compared to age matched controls at a rate ranging from 15.8 to 32.4% vs. 4.2% to 10.9%, depending on the mean age of the study subjects and the definitions used.23,24 In lupus patients the presence of MetS has been associated with racial/ethnic background (Hispanic or Black African), increasing age and disease-related characteristics such as baseline renal disease, Systemic Lupus International Collaborative Clinics damage index (SDI) >1 and higher disease activity, as well as coronary atherosclerosis, arterial stiffness and inflammatory biomarkers.1

Increased waist-to-hip ratio, sedentary lifestyle and obesity are more prevalent in SLE patients compared to controls.25,26 Interestingly, increased BMI levels were found to be significantly associated with subclinical atherosclerosis in both adult and pediatric lupus populations.27

Insulin resistance is also more frequent in lupus patients compared to controls (44.1 vs. 24.8%) in association with high BMI, waist circumference, hypertension, corticosteroid treatment and SDI.28

Hypertension

The prevalence of arterial hypertension in lupus patients ranges from 33% to 74%29,30 and is a recognized risk factor for the development of CVD in SLE patients,31 in addition to its contribution to both plaque formation and arterial stiffening.32,33 A longitudinal study, explored the determinants of atherosclerosis progression in 187 SLE patients, identifying age and hypertension as independently associated factors with the progression of carotid intima-media thickness (IMT) and plaque formation.34 Another study, identified that renal disease, insulin levels and SLE disease activity index (SLEDAI) were independent predictors of
hypertension in SLE.29 Notably, non-obesity-related insulin levels was the main predictor of hypertension in the younger age subset (<40 years), while age and obesity were the predictors among the older group (≥40 years). In a subsequent study, examining the patterns of night-time blood pressure in female lupus patients, an adverse night-time blood pressure pattern (steady, non-dipping hypertension or nocturnal hypertension/reverse dipping) was more frequent in SLE; these patterns were independently associated with increased carotid-femoral pulse wave velocity.35

Dyslipidemia

The association of increased levels of total cholesterol, low density lipoprotein (LDL) and decreased levels of high-density lipoprotein (HDL) cholesterol with increased risk for CVD in the general population is well established and acknowledged for many years.36,37 Reported rates of dyslipidemia in SLE patients range from 36% at diagnosis, to more than 60% within a three year follow-up.38 The classical pattern, is characterized by elevated levels of very-low-density lipoprotein cholesterol (VLDL), triglycerides and low levels of HDL which can be aggravated by disease activity.39 In addition, SLE patients tend to have a more atherogenic LDL phenotype characterized by small dense LDL molecules.40 Likewise, circulating lipoprotein remnant particles and the intermediate density lipoprotein (IDL) fraction have also been strongly associated with IMT values in lupus patients, while small HDL particles have been associated with activation of the complement system, also shown to be linked to higher IMT values.1 A newly recognized proinflammatory HDL subtype (piHDLs), is also present in a high proportion of SLE patients and is associated with carotid artery plaque and clinical CVD.41 Furthermore, levels of apolipoprotein A-I (apoA-I) are reduced in SLE patients with IgG anticardiolipin antibodies.42

Smoking

Smoking has been associated with CVD, cerebrovascular and peripheral vascular events as well as with markers of subclinical atherosclerosis. Smoking has also been identified as a risk factor for progression of coronary artery calcification after adjusting for age, gender and ethnicity.34

Hyperhomocysteinemia

Elevated homocysteine is a prothrombotic coagulation factor with toxic effects on the endothelium, increased collagen production and decreased nitric oxide availability.1 Hyperhomocysteinemia is a recognized risk factor for premature atherosclerosis and thrombotic risk in the general population because of its adverse effects on the endothelium, inhibition of nitric oxide synthesis, proliferation of smooth muscle cells and platelet activation.44,45 The increase of homocysteine levels in lupus patients compared to healthy controls ranges from 11.6 to 81.2% vs. 0.8 to 20%.36,47 Elevated homocysteine was found to be associated with subsequent development of coronary artery disease, thrombotic events and markers of subclinical atherosclerosis.13,48

Non-traditional risk factors

Disease related features

Antiphospholipid antibodies (aPLs), impaired renal function as well as low total white blood cell count, lymphopenia and renal disease have all been associated with carotid IMT and arterial stiffness.49,50 Carotid plaque may occur twice as commonly in SLE patients with nephritis compared to age-matched non-nephritis SLE patients and population controls. This excess risk among nephritis individuals was mainly attributed to concomitant hypertension.49 Disease duration, chronic organ damage (reflected by SDI) and disease activity were identified by numerous studies as important factors for CVD development in the setting of lupus.49,50,51 Longer lupus duration has also been independently associated with coronary artery calcification and carotid plaque formation, as well as progression. Similarly, the SDI score was found to be independently associated with increased IMT scores, carotid plaque formation, clinical CVD and arterial stiffness.49,52,53

Treatments

Long-term corticosteroid use has been associated with MI and angina, while higher cumulative doses of steroids are also associated with carotid plaque formation.4,53 Azathioprine and cyclophosphamide use has also been associated with increased rates of clinical CVD, carotid plaque and higher carotid IMT values, in addition to an independent determinant of carotid plaque.1,54 The association with immunsuppression and steroids may partially reflect unaccounted confounders due to the severity of the disease; however there is good evidence that glucocorticoids can exacerbate a number of classic risk factors including hypertension, impaired glucose tolerance and dyslipidemia.

Antimalariales (AM) are commonly used in lupus treatment and are reported to be beneficial against CVD through cholesterol lowering, reduction of thrombotic risk and possibly through dampening of type I interferon (IFN) production.55-57

In addition, AM use has been inversely associated with plaque and carotid/femoral arterial stiffness and was shown to be protective against Mets.55,56,58 Mycophenolate mofetil may also play a potentially beneficial role to prevent atherosclerosis progression.55

Autoantibodies

Anti-endothelial cell antibodies (AECA) and aPLs seem to play a significant role, although the underlying mechanisms are not fully elucidated. AECA can directly activate endothelial cells and are detected in 73% of SLE patients; however, their clinical relevance has not been clearly confirmed.50,61

aPLs have been shown to activate the endothelium and inhibit annexin A5-binding, a protein shown to prevent plaque rupture to the endothelium.62 APLs have also been identified as independent predictors of cerebrovascular or peripheral vascular events and MI.4,63

The presence of anti-oxidized low-density lipoprotein (OxLDL) antibodies has been identified in up to 80% of SLE
inflammatory factors

- Metabolic syndrome
- Hypertension
- Dyslipidemia
- Smoking
- Hyperhomocysteinemia
- Non-traditional risk factors
- Disease related features
- Antiphospholipid antibodies
- Treatment
- Inflammatory cytokines

**Pathogenic mechanisms**

The mechanisms of the increased and accelerated atherosclerotic risk for SLE patients remain to be determined. It is likely that multiple mechanisms are operative, resulting from a complex interplay between traditional cardiac risk factors and SLE-driven inflammation. Atherosclerosis is not just a consequence of passive accumulation of lipids in the vessel wall, but also a result of inflammation. As in the pathogenesis of SLE itself, the interplay of multiple inflammatory mediators, including leukocytes, cytokines, chemokines, adhesion molecules, complement, and antibodies, results in the formation of atherosclerotic plaques. In response to different factors such as hemodynamic stresses or inflammatory mediators, the vascular endothelium undergoes a series of inflammatory changes that may result in AECA formation. Activated endothelial cells up-regulate leukocyte adhesion molecules such as vascular cell adhesion molecule 1 (VCAM-1), intercellular adhesion molecule 1 (ICAM-1), and E-selectin. Chemoattractant cytokines such as monocyte chemoattractant protein1 (MCP-1), interleukin 6 (IL-6) and IL-8 are also expressed, thus inducing a cascade of pro-inflammatory, pro-atherogenic changes in the endothelium that result in

migration of monocytes into the subendothelial space. T-cells are also recruited into the subendothelium by similar mechanisms, although in lower numbers. LDL molecules are transported into the arterial wall where they become trapped and when exposed to reactive oxygen species, become oxLDL. OxLDL can stimulate AECA formation and are also phagocytized by infiltrating monocytes/macrophages where they form foam cells around which atherosclerotic lesions are built. Monocytes and T cells infiltrate the margin of the plaque formed by foam cells. Muscle cells from the media of the artery are stimulated to grow, and ultimately encroach on the vessel lumen.

In this context, IgG deposition may be proatherogenic by the formation of oxLDL-containing complexes and subsequent activation of macrophages and dendritic cells which can promote atherosclerosis by also inhibiting regulatory T cells (Tregs). In SLE vascular damage is accelerated and vascular repair mechanisms are less effective. SLE patients have high levels of circulating apoptotic endothelial cells, indicating increased vascular damage, and lower levels of circulating endothelial progenitor cells (EPC) that repair damaged arterial tissues. The production of reparative myelomonocytic circulating angiogenic cells (CAC) is also impaired. Secretion of IFNα, stimulated in part by low density granulocytes undergoing neutrophil extracellular traps (NETosis), also increased in SLE patients, induces EPC apoptosis and converts CAC to dendritic cells, thus losing their ability to repair vascular damage to endothelial cells.
Potential biomarkers for atherosclerosis in SLE

Antiphospholipid antibodies

In the LUMINA (Lupus in Minorities: Nature vs. nurture) cohort study, aPLs were an independent risk factor for cardiovascular or cerebrovascular events.43 In the Hopkins Lupus cohort, lupus anticoagulant was the only aPLs associated with MI.43 Several studies using measures of subclinical atherosclerosis failed to identify any significant associations with aPLs after adjustment for confounding factors.5,6,54 although Ahmad et al. did show an association between carotid plaque and APL, as did a follow-up study from the same cohort, suggesting a direct role in atherogenesis, as well as a role in precipitating arterial events.16,50

C-reactive protein

C-reactive protein (CRP) is not only a marker of systemic inflammation, but rather may play a direct role in the pathogenesis of atherosclerosis. In SLE subjects, however, the role of CRP as a predictor of atherosclerosis is less clear. Elevated CRP levels have been associated with cardiovascular events in the LUMINA cohort51 and high-sensitivity CRP (hs-CRP) levels were associated with cardiovascular mortality in a prospective Swedish Lupus Cohort.71 Hs-CRP has also been associated with both cross-sectional22 and longitudinal progression of carotid IMT.36 Several other studies, however, did not find an association between atherosclerosis and CRP in SLE.5,54

Pro-inflammatory HDL (piHDL)

During states of chronic inflammation, HDL can be converted from its anti-inflammatory to pro-inflammatory state.65 HDL function is abnormal in women with SLE; 45% of women with SLE, compared to 20% of rheumatoid arthritis patients and 4% of controls, had piHDL that was unable to prevent oxidation of LDL.65 HDL dysfunction has also been described in primary APS and piHDL is strongly associated with progression of carotid plaque and IMT.55,72

Paraoxonase

Serum paraoxonase 1 (PON1) has been identified as one of the important components of HDL that prevents lipid peroxidation and blocks the pro-inflammatory effects.73 Decreased levels of PON1 activity have also been associated with atherosclerosis in the general population.74 Altered levels of PON1 activity have also been seen in patients with SLE. In one study, PON1 activity was reduced in SLE and APS patients compared to controls, although there was no reduction in the total antioxidant capacity of the plasma.75 In another study of 55 SLE patients, titers of anti-apoA1 antibodies were inversely correlated to PON1 activity, and in vitro studies confirmed that apo-A1 antibodies have a direct inhibitory effect on PON1 activity.76 Decreased PON1 activity has been associated with increased carotid artery IMT and abnormal flow-mediated dilation in patients with primary APS.76

Adipocytokines

Adipokine leptin is an anorectic peptide; patients with MetS have high circulating leptin levels, but they develop leptin resistance similar to insulin resistance in type II diabetes.77 Several small cohort studies have shown elevated leptin levels in adult SLE patients.78,79 Leptin levels were significantly higher in the SLE patients with carotid plaque versus those without plaque, and also weakly correlated with carotid IMT.65 In another cohort, adiponectin levels were significantly and independently associated with carotid plaque in SLE.80

Homocysteine

Homocysteine is another predictor of atherosclerosis in the general population.81 Homocysteine may play a direct role in the pathogenesis of SLE through its toxic effects on the endothelium.82 Hyperhomocysteinemia can result from advanced age, renal insufficiency, medications such as methotrexate, genetic, and/or dietary factors.65

In one cohort study of 337 SLE patients, hyperhomocysteinemia was an independent predictor of stroke and cardiovascular events.13 In several other studies, elevated levels of homocysteine in SLE correlated with progression of subclinical atherosclerosis in SLE.34,54,83,84

Vitamin D levels

Recently, low vitamin D has emerged as a potential biomarker of CVD. Patients with low vitamin D levels or with a vitamin D deficiency were found to have a high prevalence of CVRFs including dyslipidemia, hypertension, MetS, aPLs and increased hs-CRP level.85 In a prospective study of 890 patients with SLE in a large international inception cohort, multiple logistic regression analyses revealed that patients in the highest quartiles of 25-hydroxyvitamin D (25-(OH) D) were less likely to present CVRFs, including hypertension and hyperlipidemia, while a non-significant trend of a decreasing hazard ratio of cardiovascular events was noted across successively higher quartiles of 25-(OH) D levels.86 A few studies have addressed the potential relationship between hypovitaminosis D and the unfavorable alterations of these biophysical cardiovascular risk markers. A study showed that patients with arterial stiffness exhibited higher levels of serum vitamin D and most of them were on vitamin D–Ca supplements. Prospective studies with a larger number of patients and follow-up are needed.87 The potential biomarkers for CVD in SLE are depicted in Table 1.

Table 1 – Potential biomarkers for cardiovascular disease in SLE.

<table>
<thead>
<tr>
<th>Biomarker Category</th>
<th>Biomarker</th>
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</thead>
<tbody>
<tr>
<td>Antiphospholipid antibodies</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>Cardiac markers</td>
<td>Pro-inflammatory HDL</td>
</tr>
<tr>
<td>Paraoxonase</td>
<td>Homocysteine</td>
</tr>
<tr>
<td>Adipocytokines</td>
<td>Vitamin D levels</td>
</tr>
</tbody>
</table>

Note: The table lists potential biomarkers for cardiovascular disease in SLE.
Subclinical measures of atherosclerosis

It has been argued that the identification asymptomatic patients with significant subclinical disease is the key for targeted primary prevention of symptomatic CVD. Based on this premise, risk stratification algorithms have been developed and refined in an attempt to estimate the future risk of cardiovascular events with the highest possible predictive value. For the general population, most risk stratification tools are based on levels of well-established CVRFs such as the Framingham risk score. Other examples are the Reynolds score which includes high-sensitivity CRP, the Sheffield table system, and the SCORE system in Europe. These different methods are similar in their overall low sensitivity and specificity for development of CVD as they exclude various emerging, genetic and otherwise unknown risk factors. The majority of these indices fail to take into account the presence of autoimmune diseases. Indeed, several studies have shown that such population risk score systems systematically underestimate the risk of future CVD in SLE and hence should not be used for risk stratification in SLE.

The use of SLE-specific stratification algorithms has been suggested, with particular emphasis on composite risk-assessment scores, including both traditional risk factors and novel biomarkers. The Predictors of Risk for Elevated Flares, Damage Progression, and Increased Cardiovascular disease in Patients with SLE (PREDICTS) score was proposed on the basis of the presence of at least three positive biomarkers or a combination of diabetes plus at least one of the biomarkers considered. The QRISK3 risk score included clinical variables such as chronic kidney disease, migraine, corticosteroids and SLE. The QRISK3 score has been shown to identify a much higher proportion of SLE patients as having a >10% 10-year risk of CVD.

The European League Against Rheumatism (EULAR) recommendation was the calculation of the 10-year CVD risk using the Systematic Coronary Risk Evaluation (SCORE) although the actual risk is underestimated in patients with SLE.

Other modalities have also been used to screen for subclinical atherosclerosis in SLE patients such as ultrasound assessment of the carotid that allows for the assessment of arterial wall thickness and degree of plaque. Patients with higher cumulative damage measured by the modified SDI damage score were more likely to have plaque.

Improved ultrasound assessment of carotid plaques can be achieved using integrated backscatter analysis of the carotid-intima complex, which appears to correlate with calcium and collagen content of the vascular wall, for a non-invasive evaluation of arterial sclerosis. Some argue that the femoral arteries should also be scanned because in non-SLE patients, femoral plaque is also associated with increased risk of coronary disease without carotid affection. An alternative method to ultrasound is high-resolution computed tomography angiography, which focuses essentially on providing improved accuracy and sensitivity and allows for a ‘virtual’ histology of plaques as it has been shown to correlate with histological findings of atheromatous plaques at the carotid bifurcation. However, none of these imaging techniques are recommended in routine practice for CVD screening.

Management strategies for prevention and treatment of CVD outcomes

Interventions aimed at promoting health include dietary modification, exercise and smoking cessation and are generally recommended as they can contribute to improving long-term patient outcomes. Appropriate disease management focused on the remission of symptoms and signs, prevention of damage accrual and improved quality of life may also contribute to improving CVD risk.

Lipid-lowering therapy

In patients with SLE and hyperlipidemia, mortality was lower in patients taking statin therapy; furthermore, these patients had a lower incidence of myocardial infarction and stroke. Interestingly, several trials have failed to find any significant changes in surrogate markers of atherosclerosis with statin therapy. In a study in adults with SLE without previous cardiovascular events, patients were randomized to atorvastatin 40 mg/day or placebo; there was no statistically significant difference in progression of coronary calcification scores over two years. In contrast, in another study lower coronary calcium deposits measured by computed tomography scan were observed in SLE patients without CVRFs after one year of treatment with 40 mg atorvastatin compared to placebo. In children with SLE, a further study found no benefit in the progression of carotid IMT in those randomized to atorvastatin.

Overall, these trials suggest that statin therapy should not be routinely offered to all SLE patients as standard of care. The ideal approach to targeting SLE patients for lipid-lowering therapies therefore remains unclear, but is likely to be appropriate for patients with elevated LDL and in whom lifestyle changes and non-pharmacological approaches are not successful in achieving an ideal LDL target.

Antiplatelet and anticoagulant agents

Two meta-analyses studied the effect of antithrombotic drugs (antiplatelet agents and anticoagulants) on cardiovascular risk in SLE patients. The main outcome was the efficacy of acetylsalicylic acid for the primary prevention of thrombotic events in patients with SLE and CVRFs. The results from both meta-analyses indicated that acetylsalicylic acid is effective for the primary prevention of thrombosis. Another study did not show any differences in the rate of thrombotic events between patients with ASA alone, or with ASA plus warfarin; however, the rate of thrombotic events in the untreated group was twice the rate in the intervention group. Another study assessed the effectiveness of primary (acetylsalicylic acid) and secondary prevention (acetylsalicylic acid + cumarine) of antithrombotic therapy. Three different groups were analyzed: patients with SLE and positive aPLs, patients with SLE and APS and patients with SLE and negative aPLs. The occurrence of cardiovascular events was lower in all groups.
Acetylsalicylic acid should therefore be considered for all SLE patients, especially those with a significant cardiovascular risk (positive aPLs, hypertension, dyslipidemia), unless contraindicated.102

Specific SLE treatment

Several studies have analyzed the effectiveness of AM on cardiovascular risk in SLE. The use of AM in patients with SLE and CVRFs is useful for the primary prevention of thrombotic events as they have known positive effects on glucose levels, insulin resistance and LDL levels.103–105

The discrepancy among the studies on the effectiveness of AM in CVD prevention may be due to differences in terms of the presence/absence of a control group and disease status, variable definition of clinical outcomes and heterogeneity in the ethnic composition of the study populations and, most importantly, on the different duration of exposure of patients to AM prior to the event.102 Indeed, a time-dependent effect of AM exposure has been suggested by other studies.33,56 Strategies for prevention and treatment of CVD in SLE are depicted in Fig. 2.

Conflict of interest

None.

Appendix A. Supplementary material

The Spanish translation of this article is available as supplementary material at doi:10.1016/j.rcreu.2021.03.002.

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