



Sociedad Española  
de Reumatología -  
Colegio Mexicano  
de Reumatología

# Reumatología Clínica

[www.reumatologiaclinica.org](http://www.reumatologiaclinica.org)



## Editorial

### The Cardio-Rheumatology Approach to Atherosclerotic Cardiovascular Disease



### El enfoque cardiorreumatológico de la enfermedad cardiovascular aterosclerótica

Ricardo O. Escárcega<sup>a</sup>, Mario García-Carrasco<sup>b</sup>, Claudia Mendoza-Pinto<sup>b,\*</sup>

<sup>a</sup> Heart and Vascular Institute, Lee Health System and Florida Heart Associates, Fort Myers, FL, USA

<sup>b</sup> Systemic Autoimmune Diseases Research Unit and Rheumatology/Immunology Department, BUAP School of Medicine, Puebla, Mexico

Cardiovascular disease (CVD) remains the leading cause of death in developed countries.<sup>1</sup> Mounting evidence from a growing body of epidemiological studies shows that patients with systemic autoimmune rheumatic diseases (ARDs) are at increased risk of premature CVD, with atherosclerosis being the most common cardiac abnormality.<sup>2</sup>

ARDs are also associated with higher rates of CVD morbidity and mortality, primarily secondary to accelerated atherosclerosis. This may be attributed to traditional risk factors for atherosclerosis and the use of specific drugs, such as corticosteroids, but might also be the result of other inflammatory mechanisms that are aggravated in autoimmune diseases.<sup>3</sup> The current viewpoint is aimed at providing an overview of how ARDs increase cardiovascular risk, and preventive and therapeutic measures based mainly on evidence from cardiology and rheumatology, and consideration of the relatively new field of cardio-rheumatology.

The basic understanding of atherosclerosis begins with its biology. The defining characteristic of the fatty streak, the first visible lesion of atherosclerosis, both in animals and in humans is the “foam cell.” This cell, loaded with droplets rich in cholesteryl esters, is derived mainly from arterial wall macrophages, which originate in circulating monocytes that penetrate the subendothelial space. Smooth muscle cells and endothelial cells in lesions also accumulate lipid droplets, but monocyte-derived macrophage foam cells predominate.<sup>4</sup>

The concept that oxidative stress and the oxidation of low-density lipoprotein (LDL) might play a role in atherosclerosis originated decades ago,<sup>5</sup> based on the simple observation that in vitro incubation of macrophages with oxidized LDL, and not with native LDL, led to the accumulation of cholesterol ester. The oxidation of LDL is a complex process during which both the protein and the lipids undergo oxidative changes and form a complex product.<sup>6</sup> Human macrophages avidly phagocytize cholesterol crystals and store the ingested cholesterol as cholesteryl esters. The cholesterol

crystals induce dose-dependent secretion of mature IL-1 $\beta$  from human monocytes and macrophages. A key finding was that cholesterol appeared to increase IL-1 $\beta$  via an inflammasome-mediated pathway. Silencing of the nucleotide-binding domain leucine-rich repeat pyrin domain containing the 3 (NLRP3) receptor, the crucial component in the NLRP3 inflammasome, completely abolished cholesterol crystal-induced IL-1 $\beta$  secretion, thus identifying the NLRP3 inflammasome as the cholesterol crystal-responsive element in macrophages. Since IL-1 $\beta$  production leads to increased levels of IL-6 and C-reactive protein, these data provide a mechanistic link between the early deposition of cholesterol crystals within the vessel wall and the macrophage–monocyte interactions that initiate fatty streaks and promote local atherosclerotic progression.<sup>7,8</sup> Therefore, LDL cholesterol modification and inflammation are likely not independent but rather co-dependent.

The lipid hypothesis, which postulates that lowering serum cholesterol saves lives and prevents CVD, has been supported by a prodigious volume of evidence over the past 30 years. Lowering LDL has become the foundation of CVD prevention guidelines.<sup>9</sup> Recently, PCSK9 inhibitors, fully human monoclonal antibodies that bind PCSK9, were found to reduce LDL cholesterol (LDL-C) by approximately 60% and the risk of myocardial infarction (MI) and stroke by approximately 20% after over two years of treatment.<sup>10</sup> The inflammatory hypothesis, which postulates that lowering systemic inflammation reduces the risk of cardiovascular morbidity and mortality, has been tested in a large and adequately powered randomized clinical trial, the CANTOS trial,<sup>11</sup> in which patients were randomized to placebo or canakinumab. There was a significant decrease in the risk of the primary endpoint (MI, stroke and death) favoring canakinumab, a reduction in the rates of MI, and a significant reduction in the rate of hospitalization for unstable angina leading to urgent revascularization. Therefore, the data clearly suggests that targeting LDL-C and inflammation seems to reduce cardiovascular risk in selected populations. How can this data be extrapolated to patients with ARDs?

Patients with ARDs have an increased risk for CVD. For example, the association of SLE with atherosclerosis suggests a common pathogenic mechanism. In SLE patients, the mean number of

\* Corresponding author.

E-mail address: [cmp.26@yahoo.com.mx](mailto:cmp.26@yahoo.com.mx) (C. Mendoza-Pinto).

modifiable traditional risk factors for atherosclerosis is higher than that expected in an age-,sex-, and race-matched normal population.<sup>12</sup> Coronary disease has been described in SLE patients, with a prevalence ranging from 6% to 10%, and the risk of coronary disease is up to 8 times higher than normal,<sup>13</sup> while acute myocardial infarction is the cause of death in 3–25% of SLE patients according to historical data.<sup>14</sup> We have previously reported that SLE patients without traditional factors for coronary disease and low disease activity (reflected by a low SLEDAI index) were not shown to have a positive stress test in the first 10 years of the disease, regardless of the corticosteroid dose.<sup>15</sup> This could suggest that managing the traditional risk factors for coronary disease along with strict disease control is mandatory in all patients to reduce early cardiovascular morbidity.

Generally, cardiologists treat older patients with CVD, which is the consequence of a complex interplay between traditional risk factors, genetics and lifestyle. Patients with autoimmune diseases are a special group: they tend to be younger, some lack traditional risk factors for heart disease and are usually evaluated only by rheumatologists. In the general population, cardiovascular risk reduction is generally accomplished by targeting risk factors with lifestyle modification and medications. Aspirin and statins have been the cornerstone for primary prevention. Older data suggested the absolute reduction in nonfatal MI was twice as large as the absolute increase in nonfatal gastrointestinal bleeding in a primary prevention population, irrespective of age, sex, and baseline cardiovascular risk.<sup>16</sup> However, recently, aspirin for primary prevention has become controversial due to trials showing no favorable risk-benefit ratio. There is a lack of long-term randomized data in patients with ARDs and the use of aspirin for primary prevention. Statins, on the other hand, remain the main pharmacologic therapy for primary prevention. In ARD patients, statins have led to an improvement in disease activity scores in rheumatoid arthritis patients; a reduction in pro-thrombotic factors in anti-phospholipid syndrome patients; changes in vasculature, proteinuria, and cardiac events in systemic lupus erythematosus patients; changes in vasculature and proteinuria in patients with vasculitis; disease activity scores in ankylosing spondylitis; and vascular changes in patients with systemic sclerosis.<sup>17</sup>

In recent years, team-based approaches have replaced isolated specialty evaluations. For example, the heart team, where cardiac surgeons and interventional cardiologists work together to define the optimal treatment. Oncologists and cardiologists have formed the so-called cardio-oncology teams to treat the consequences of chemotherapy and radiation. Patients with ARDs are living longer and better due to improvements in therapies. A team-based approach may be best way to reduce cardiovascular risk in all patients with autoimmune diseases.

CVD risk calculators developed for use in the general population inaccurately predict CVD in patients with ARDs, but the addition of disease-specific risk factors does not improve CVD risk prediction (mainly due to the difficulty of estimating the cumulative burden of high-grade inflammation). Owing to large geographical differences in CVD risk, clinicians are recommended to use a CVD risk algorithm that has been developed for their specific population. Additionally, non-invasive imaging, such as the calcium score, derived from non-contrast gated computer tomography, can be used for risk stratification, due to its high negative predictive value in excluding significant coronary disease.<sup>18</sup> Although the supplemental value of adding carotid intima-media thickness or carotid plaque measurements to the CVD risk prediction model is still unclear, patients with carotid plaque identified by ultrasonography should be considered to be very high-risk individuals for whom lipid-lowering treatment is recommended.<sup>19</sup>

Equally important, a thorough rheumatology evaluation and treatment to reduce inflammation is essential. However, targeting

solely inflammation to reduce the cardiovascular risk is still in its infancy, and its value may increase in the future. We have reported a proposed algorithm to evaluate patients with ARDs in which the focus is on identifying and treating traditional risk factors for coronary artery disease and early identification of atherosclerosis with the calcium score.<sup>20</sup>

There is room for improvement in the management of patients with ARD. Accelerated atherosclerosis must be prevented and treated early, and thus a team-based approach, including rheumatologists and cardiologists interested in the inflammatory component of atherosclerosis is likely to narrow this gap, as shown by recent novel efforts in Norway. However, we hope that, in the future, more cardio-rheumatology team-based approaches will become as frequent as heart teams and cardio-oncology teams.

## References

- Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, et al. Heart disease and stroke statistics-2019 update: a report from the American Heart Association. *Circulation*. 2019;139:e56–28.
- Liu Y, Kaplan MJ. Cardiovascular disease in systemic lupus erythematosus: an update. *Curr Opin Rheumatol*. 2018;30:441–8.
- Escárcega RO, García-Carrasco M, Jara LJ, Cervera R. Accelerated atherosclerosis in systemic lupus erythematosus: perspectives towards decreasing cardiovascular morbidity and mortality. Vol. 18, *Lupus*. England; 2009. p. 383–6.
- Rahman MS, Murphy AJ, Woollard KJ. Effects of dyslipidaemia on monocyte production and function in cardiovascular disease. *Nat Rev Cardiol*. 2017;14:387–400.
- Steinbrecher UP, Parthasarathy S, Leake DS, Witztum JL, Steinberg D. Modification of low density lipoprotein by endothelial cells involves lipid peroxidation and degradation of low density lipoprotein phospholipids. *Proc Natl Acad Sci USA*. 1984;81:3883–7.
- Parthasarathy S, Raghavamenon A, Garelnabi MO, Santanam N. Oxidized low-density lipoprotein. *Methods Mol Biol*. 2010;610:403–17.
- Ridker PM, Lüscher TF. Anti-inflammatory therapies for cardiovascular disease. *Eur Heart J*. 2014;35:1782–91.
- Rajamäki K, Lappalainen J, Oörni K, Välimäki E, Matikainen S, Kovanen PT, et al. Cholesterol crystals activate the NLRP3 inflammasome in human macrophages: a novel link between cholesterol metabolism and inflammation. *PLoS One*. 2010;5:e11765.
- DuBroff R. A reappraisal of the lipid hypothesis. *Am J Med U S*. 2018;131:993–7.
- Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med*. 2017;376:1713–22.
- Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med*. 2017;377:1119–31.
- Escárcega RO, García-Carrasco M, Fuentes-Alexandro S, Jara LJ, Rojas-Rodríguez J, Escobar-Linares LE, et al. Insulin resistance, chronic inflammatory state and the link with systemic lupus erythematosus-related coronary disease. *Autoimmun Rev*. 2006;6:48–53.
- Manzi S, Meilahn EN, Rairie JE, Conte CG, Medsger TAJ, Jansen-McWilliams L, et al. Age-specific incidence rates of myocardial infarction and angina in women with systemic lupus erythematosus: comparison with the Framingham Study. *Am J Epidemiol*. 1997;145:408–15.
- Cervera R, Khamashta MA, Font J, Sebastiani GD, Gil A, Lavilla P, et al. Morbidity and mortality in systemic lupus erythematosus during a 5-year period. A multicenter prospective study of 1,000 patients. *European Working Party on Systemic Lupus Erythematosus. Medicine (Baltimore)*. 1999;78:167–75.
- García-Carrasco M, Escárcega RO, Pérez-Terrón J, Ramírez A, Muñoz-Guarneros M, Beltrán A, et al. Lack of subclinical myocardial ischaemia in Mexican patients with systemic lupus erythematosus without traditional risk factors for coronary artery disease. *Lupus*. 2007;16:298–301.
- Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, Peto R, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet (London, England)*. 2009;373:1849–60.
- Khattari S, Zandman-Goddard G. Statins and autoimmunity. *Immunol Res*. 2013;56:348–57.
- Budoff MJ, Achenbach S, Blumenthal RS, Carr JJ, Goldin JG, Greenland P, et al. Assessment of coronary artery disease by cardiac computed tomography: a scientific statement from the American Heart Association Committee on Cardiovascular Imaging and Intervention, Council on Cardiovascular Radiology and Intervention, and Committee on Cardiac Imaging. *Council on Clinical Cardiology. Circulation*. 2006;114:1761–91.
- Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J*. 2020;41:111–88.
- Escárcega RO, Lipinski MJ, García-Carrasco M, Mendoza-Pinto C, Galvez-Romero JL, Cervera R. Inflammation and atherosclerosis: cardiovascular evaluation in patients with autoimmune diseases. *Autoimmun Rev*. 2018;17.