Antibodies to high-density lipoproteins are associated with inflammation and cardiovascular disease in rheumatoid arthritis patients

JAVIER RODRÍGUEZ-CARRIO, MERCEDES ALPERI-LÓPEZ, PATRICIA LÓPEZ, FRANCISCO J. BALLINA-GARCÍA, FRANCISCO ABAL, and ANA SUÁREZ

ASTURIAS AND POLA DE SIERO, SPAIN

Several lines of evidence suggest that chronic inflammation and immune dysregulation are related to altered lipid profiles in rheumatoid arthritis (RA), but the actual mechanisms are still unclear. We wondered whether the development of antibodies against high-density lipoprotein (HDL) can be found in RA patients linked to clinical and cardiovascular (CV) risk factors. To this end, immunoglobulin G (IgG) anti-HDL antibodies and total IgG serum levels were quantified in 212 RA patients, 131 sex- and age-matched healthy controls (HC), and 52 subjects with traditional CV risk factors (tCVRs). A subgroup of 13 RA patients was prospectively followed on TNFα-blockade. TNFα, interferon (IFN)α, MIP1α, IFNγ, IL-8, VEGF, GM-CSF, IL-17, MCP-1, SDF-1α, resistin, and leptin serum levels were quantified by immunoassays. IgG anti-HDL levels were higher in RA patients compared with HC ($P < 0.0001$) and tCVR subjects ($P = 0.015$). Differences with HC remained after correction for total IgG levels ($P < 0.003$). Anti-HDL/IgG were negatively associated with HDL levels in RA (−1.182 (−1.823 to −0.541), $P = 0.0003$) after adjusting for demographical, clinical, inflammatory parameters, and treatments. RA patients with high levels of anti-HDL/IgG (n = 40, 18.8%) were more likely to have experienced a CV event ($P < 0.0001$) and exhibited increased levels of several proinflammatory mediators (C-reactive protein, IFNα, MIP1α, IFNγ, IL-8, GM-CSF, IL-17 and MCP-1). Finally, change in anti-HDL antibodies on TNFα-blockade was independently associated with increasing HDL levels. Overall, IgG anti-HDL antibodies are increased in RA independently of tCVRs and associated with a proinflammatory milieu and impaired lipid blood profile, which may contribute to the increased rate of CV events in these patients. (Translational Research 2015;166:529–539)

Abbreviations: Apo A1 = Apolipoprotein A1; CVD = cardiovascular disease; DAS28 = disease activity score 28-joints; ELISA = enzyme-linked immunosorbent assay; HDL = high-density lipoprotein; IgG = immunoglobulin G; RA = rheumatoid arthritis; tCVR = traditional cardiovascular risk factors

Javier Rodríguez-Carrio, PhD, *is a postdoctoral fellow is the Department of Functional Biology at the University of Oviedo in Spain. Dr. Rodríguez-Carrio's research interests are the identification of new biomarkers of cardiovascular risk that can be easily integrated into the clinical setting for the personalized care of patients.*

From the Area of Immunology, Department of Functional Biology, University of Oviedo, Oviedo, Asturias, Spain; Department of Rheumatology, Hospital Universitario Central de Asturias, Oviedo, Spain; Centro de Salud Sariego, Servicio de Salud del Principado de Asturias, Pola de Siero, Spain.

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Reprint requests: Dr. Ana Suárez, Area of Immunology, Department of Functional Biology, Faculty of Medicine, University of Oviedo, Campus El Cristo, C/ Julián Clavería s/n, 33006 Oviedo, Spain; e-mail: anasua@uniovi.es.

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AT A GLANCE COMMENTARY

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Background

Because new biomarkers of cardiovascular (CV) risk are needed for CV risk stratification in rheumatoid arthritis patients and high-density lipoprotein (HDL) dysfunction seems to be an emerging concept in the field, we evaluate the presence of immunoglobulin G (IgG) anti-HDL antibodies using enzyme-linked immunosorbent assay (ELISA) techniques. Our findings revealed that these autoantibodies are increased in rheumatoid arthritis patients and they could be the missing link between lipid abnormalities, inflammation, and CV disease. Decreasing anti-HDL levels could mediate the beneficial effect of TNFα blockade on lipid profile.

Translational Significance

Anti-HDL antibodies may be considered as promising biomarkers with potential use in the clinical setting for CV risk stratification and early treatment consideration.

INTRODUCTION

Rheumatoid arthritis (RA) is associated with greater rates of cardiovascular disease (CVD) morbidity than the general population. This greater risk cannot be explained only by traditional cardiovascular (CV) risk factors,[1] and different nontraditional factors, such as genetic background, chronic inflammation, or exposure to treatments, seem to be involved.[2]

Serum lipids and lipoproteins are pivotal players in the field of CVD. Raised low-density lipoproteins (LDL)–cholesterol level and reduced high-density lipoprotein (HDL)–cholesterol level are well-established risk factors in the general population. In RA, however, the association between serum lipids and CVD seems to be more complex. Active RA patients tend to exhibit lower levels of lipids than the general population but an excess of CV risk. Control of the disease using different disease-modifying antirheumatic drugs is usually accompanied by increasing lipid levels, mainly in HDL cholesterol, to variable degrees.[3,4] The phenomenon that a condition associated with increased CVD morbidity was associated with reduced lipid levels was termed as "lipid paradox,"[4,5] and several lines of evidence point toward a role of chronic inflammation as the underlying factor. However, the mechanisms that potentially drive the interactions between inflammation and lipid metabolism are not entirely understood.

HDLs are important in preventing the development of atherosclerotic lesions and endothelial homeostasis,[6] and chronic inflammation has been described to be able not only to decrease HDL levels[4] but also to impair their protective functions,[7] by modification of its composition.[8] Moreover, effective disease activity control leads to normalization of HDL levels in some studies,[9,10] but not in others,[11] whereas other authors found that a good clinical outcome may induce restoration of HDL functions rather than changes in levels.[12] Consequently, some gaps remain in the understanding of changes in lipids in RA, and this warrants further studies on the potential contribution of emergent players.

Recently, the hypothesis that certain autoantibodies may have a role in CVD development in chronic autoimmune diseases has emerged.[13] The presence of anti-HDL IgG antibodies has been reported in systemic lupus erythematosus patients,[14,15] associated with severe disease and inflammatory burden. Interestingly, anti-HDL antibodies can interfere with the anti-inflammatory and antioxidant intrinsic functions of HDL.[16] However, the presence and possible clinical role of anti-HDL IgG antibodies in RA patients remains unknown.

Therefore, the main aims of this study were (1) to investigate whether anti-HDL IgG are present in RA patients; (2) whether they could be related to the altered lipid profile, clinical characteristics, and traditional CV risk factors (tCVRs); and (3) to analyze if these antibodies might be associated with lipid changes on anti-TNFα treatment.

MATERIAL AND METHODS

Patients and controls. This was a cross-sectional case-control study with 3 different groups of individuals enrolled (Table I). Our study involved 212 RA patients recruited from the Department of Rheumatology at Hospital Universitario Central de Asturias. All of them fulfilled the 2010 American College of Rheumatology classification criteria for RA. A complete clinical examination, including Disease Activity Score 28 joints (DAS28) calculation, was performed on each patient on the day of their clinic appointment, and a blood sample was drawn by venipuncture. Also, clinical records were retrospectively revised so as to register tCVRs and the history of CV events. A CV event was considered to be present if the patient had ischemic heart disease, heart failure, cerebrovascular accident, or peripheral arteriopathy since RA diagnosis, as previously established.[17] In addition, a subgroup of 13 RA patients (12 women; median age, 43 years (range: 30–65 years); DAS28, 5.08 (1.93); 38.5% rheumatoid factor (RF)+; 46.1% anticyclic citrullinated peptide antibody [anti-CCP]+), candidates for TNFα blockers, was