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ORIGINAL RESEARCH

Atherosclerotic risk in middle-aged women with rheumatoid arthritis

Riesgo aterosclerótico en mujeres de mediana edad con artritis reumatoide

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Key words: Rheumatoid arthritis, carotid intima media thickness, oxidized LDL, lipid risk quotients.

Palabras clave: *Artritis reumatoide, espesor de la capa íntima-media de la carótida, LDL oxidadas, cocientes de riesgo lipídico.*

ABSTRACT

Background: Rheumatoid arthritis (RA) is a chronic inflammatory disease, with progressive joint destruction, leading to disability. In half of patients, mortality is associated to coronary events, caused by classical risk factors (RF) and/or the inflammatory process. **Objectives:** To explore the relevance of systemic inflammatory milieu in RA without the burden of traditional RF. **Methods:** Women with RA and free of traditional RF (n = 30) were compared against healthy women (n = 31). Body mass index, blood pressure, glycemia, serum creatinine, total cholesterol (TC), high density lipoprotein (HDL-c), low-density lipoprotein cholesterol (LDL-c), triglycerides (TG) and oxidized LDL (oxLDL), erythrocyte sedimentation rate, high-sensitivity C reactive protein (hsCRP), lipid quotients for assessing risk (TC/HDLc, LDLc/HDLc, oxLDL/non HDL cholesterol, TG/HDLc), and ultrasonographic carotid intima media thickness (IMT) were estimated or measured. **Results:** hsCRP and oxLDL were significantly higher in RA patients. IMT values were among normality, but thickness was slightly increased in left carotid, suggesting early atherosclerotic changes. In RA patients inflammation is associated to a higher concentration of oxLDL. No atherosclerosis was proven but a slight greater thickness in left carotid foretells the development of the disease. **Conclusions:** In RA patients without vascular RF, a special follow up must be implemented to halt atherosclerosis development.

RESUMEN

Antecedentes: *La artritis reumatoide (AR) es una enfermedad inflamatoria crónica, con destrucción progresiva de las articulaciones, que lleva a la discapacidad. En la mitad de los pacientes, la mortalidad se asocia con eventos coronarios, causados por factores de riesgo (FR) clásicos y/o el proceso inflamatorio.* ***Objetivo:*** *Explorar la relevancia del medio inflamatorio sistémico en la AR sin la carga de FR tradicionales.* ***Métodos:*** *Las mujeres con AR, sin los FR tradicionales (n = 30) fueron comparados contra mujeres sanas (n = 31). El índice de masa corporal, presión arterial, glucemia, creatinina sérica, colesterol total (CT), lipoproteínas de alta densidad (HDL-c), colesterol de lipoproteínas de baja densidad (LDL-c), triglicéridos (TG) y LDL oxidada (LDLox), velocidad de sedimentación de los eritrocitos, proteína C reactiva de alta sensibilidad (PCR-us), cocientes de lípidos para la evaluación de riesgos (TC/HDLc, LDLc/HDLc, colesterol LDLox/noHDL, TG/HDLc), y el espesor ultrasonográfico de la capa íntima-media carotídea (IMT), fueron estimados o medidos.* ***Resultados:*** *hsCRP y LDLox fueron significativamente mayores en los pacientes con AR. Los valores de IMT estaban dentro de la normalidad, pero el espesor se incrementó ligeramente en la carótida izquierda, lo que sugiere cambios ateroscleróticos tempranos. En los pacientes con AR la inflamación está asociada con una mayor concentración de oxLDL. No se comprobó aterosclerosis pero un espesor ligeramente mayor en la carótida izquierda, los hace propensos a desarrollar la enfermedad.* ***Conclusiones:*** *En los pacientes con AR sin FR vascular, un seguimiento especial debe ser implementado para frenar el desarrollo de la aterosclerosis.*

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, autoimmune and inflammatory joint disease, affecting about 1% of the world population, mainly women.[1] Recently, RA was found in 1.6% of individuals in a vast sample assembled in a cross-sectional, community-based study performed in 5 geographic regions of Mexico. Although the prevalence of AR is not overwhelming in Mexico, it is a common cause of rheumatologic consult in the national health system, as well as a source of catastrophic events, like cardiac and cerebrovascular diseases, thus a cause of onerous expenses, mainly out-of-the pocket.[2,3]

While the exact pathophysiologic etiology of the disease has not been completely elucidated, a recent genome-wide association meta-analysis revealed 101 risk loci and 98 biological candidate genes.[4] Yet another proposed risk factor for RA is obesity, a clearly inflammatory disease, which has been associated with an almost 4-fold increase in the risk for developing RA, mainly in women.[5]

The inflammatory processes of RA, as the roles of the major histocompatibility complex class II antigens, CD4+ T cells, and the cascade of cellular and soluble inflammatory mediators and cytokines have been characterized.[6] Thus, the overall clinical relevance of the disease resides in its marked capacity to disable, including its association to complications leading to shortening of life span and decrease in quality of life.[7]

In this regard, it has been found that the majority of deaths in RA are related to cardiovascular diseases (CD), mainly ischemic heart disease.[8-10] The true link (i.e., subjacent molecular pathways) between RA and CD remains controversial,[11] but several pathogenic conditions, as traditional coronary risk factors, systemic inflammation and the collateral effects of steroids and other disease-modifying therapies,[12] have been suggested as main contributors, even in early RA. Heretofore it has not been established the true weigh of inflammation in the genesis of the atherosclerotic complications of RA. Therefore, the aim of the present study was to determine, with a practical preventive scope, the importance of the inflammatory systemic milieu in RA in patients without the burden of traditional vascular risk factors (dyslipidemia, hypertension, smoking or diabetes).

PATIENTS AND METHODS

A convenience sample of 30 patients with rheumatoid arthritis (RA) and 31 individuals serving as matching controls were recruited, all of them women, aged 25-50 years, from the outpatient clinic of Hospital 1o de Octubre, Mexico. RA was diagnosed with the criteria of the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR).[13] Patients were excluded if they had three or more ATP III traits of the metabolic syndrome, diabetes mellitus, hypertension, smoking or alcohol drinking habits (or other drug addictions), clinically evident ischemic heart disease, antecedent of stroke or peripheral artery disease, obesity (body mass index ≥ 30), rheumatoid cachexia, pregnancy, any acute inflammatory ailment or chronic serious disease, and were under therapeutic regimes with statins, fibrates, ACE inhibitors or AT1 angiotensin receptor antagonists, or antioxidants. Control individuals were non-rheumatic healthy women, of the same age group, without any of the abovementioned exclusion criteria. Protocol was approved by both Ethics and Research Institutional Committees and the survey was conducted according with the Declaration of Helsinki, Good Clinical Practices and Mexican Federal Regulations. In all patients the body mass index (BMI) was calculated dividing the weight by the squared height (kg/m2). Blood pressure was measured with a mercurial sphygmomanometer, under the standardized technique. A blood sample was obtained by venous puncture and fasting serum glucose, creatinine, total cholesterol (TC); high-density lipoprotein (HDL-c) and triglycerides (TG), were determined by means of colorimetric assay kits, according with the manufacturer's instructions. Low-density lipoprotein cholesterol (LDL-c) was calculated using the Friedewald equation. Non-HDL-c was estimated subtracting HDL-c to TC. It is known that non HDL-c represents all cholesterol fractions with apo B100 thus, signaling the atherogenic mass of total cholesterol. The

oxidized fraction of LDL was assessed through a commercial ELISA kit, following manufacturer's instructions. Inflammatory markers were also obtained: high-sensitivity C reactive protein (hsCRP) and erythrocyte sedimentation rate (ESR).

To assess cardiovascular risk in this group of young and middle-aged women without tobacco consumption, we used several indexes derived from the lipid profile: the two classical coronary quotients CT/HDL-c and LDL-c/HDL-c, expressing the relation between the atherogenic and protective cholesterol fractions.[14] Moreover, we used the index TG/HDL-c,[15] which reflects both, the inverse relation between triglycerides and «good» cholesterol and two of the lipid triad's components, exhibiting also an acceptable correlation with insulin resistance.[16] This index has been used as a predictor of ischemic heart disease, general mortality, and diabetes in women, and young people pertaining to different ethnic groups, including Mexican population.[17-19] Finally, we used a ratio between LDLox/non-HDL-c in order to assess the relation between the oxidized fraction of LDL-c and the gross mass of atherogenic cholesterol. In all patients and healthy subjects, ultrasonographic images (Siemens® Acuson CV70 Ultrasound System together with an L10-5 vascular transducer) of right and left carotid arteries were obtained, with patients laying in dorsal decubitus with their necks in slight overextension rotated to the opposite side of the exam. Four selected points (i.e., superior and inferior for both right and left carotid sections) were measured, in the near and far carotid walls, one cm below of the bifurcation and in the bifurcation itself. Intima media thickness (IMT) was measured with the electronic caliper of the sonograph machine in real time.[20]

Statistical analysis

Quantitative variables are presented as mean ± standard deviation. Independent t-tests were performed in order to assess intergroup differences, considering a statistically significant result when $p < 0.05$. Furthermore, we conducted Pearson's correlation analyses between the statistically significant variables from the t-tests (as the independent variable) and the rest; again, $p < 0.05$ was considered as statistically significant.

RESULTS

Table I gathers the blood pressure and metabolic data obtained in both RA and control groups. The two groups were very similar and in them, BMI, glycaemia, serum creatinine, blood pressure, classical lipid variables, and the derived indexes were among the limits of normality. Nevertheless, oxLDL was 36% higher in the RA women than in controls, and also, oxLDL/Non HDL cholesterol was 42% higher in RA patients. Otherwise, it was not surprising that inflammation markers hsCRP and ESR were elevated in RA patients, typically inflammated individuals, in comparison with normal controls and naturally, rheumatoid factor, one RA diagnostic marker was 13 times higher in RA patients.

Table II shows the IMT values in the 4 specified sites in both carotid arteries. Although all values were among the normal range (0.5-1.2 mm), notwithstanding, IMT in the inferior point in left carotid was thicker, slightly but statistically significant, in RA patients than in healthy women. In consequence, the combined IMT in the left artery was greater in RA patients. When the comparison is made with all the considered points, the differences between both groups disappear.

In the RA group, statistically significant correlations were found between rheumatoid factor and oxLDL/Non-HDL-c ($r = 0.37$, $p = 0.04$), left carotid inferior IMT and diastolic pressure ($r = 0.49$), and combined left carotid IMT and age ($r = -0.37$, $p = 0.04$).

Finally, *table III* shows the type of anti-RA drugs used in the patients of this series.

DISCUSSION

The main findings of this work were: increased oxLDL values, high oxLDL/NonHDLc ratios, and left carotid IMT among the RA patients as compared with control group.

Although ischemic heart disease is nowadays the second leading cause of general mortality in Mexico,[21] national data about the

occurrence of this disease in RA patients are lacking. Contrary to the generalized idea that the relative importance of atherosclerotic risk factors is the same in all groups of human beings pertaining to different geographic regions, Mexico has a population with peculiar characteristics. As example, dysmetabolic obesity and overweight, hypertension, type 2 diabetes mellitus, and hypertriglyceridemia and hypoalphalipoproteinemia (lipid disorders with no strict correlation with overweight and obesity), are the main vascular risk factors in our country.[22,23] Results reported here show that in these RA patients without the cluster of traditional vascu-

Table I. Anthropometric, metabolic, blood pressure and inflammatory data of women with rheumatoid arthritis and controls.

Variable	RA	Control	p value
Age (years)	40 ± 1.4	37.9 ± 1.2	n.s.
Weight (kg)	54 ± 5.6	57.5 ± 5.8	n.s.
Height (m)	1.56 ± 0.06	1.58 ± 0.04	n.s.
BMI (kg/m2)	23.2 ± 0.3	22.4 ± 0.3	n.s.
Glycaemia (mg/dL)	89.8 ± 1.8	86.5 ± 1-5	n.s.
TC (mg/dL)	169.5 ± 4.5	175.4 ± 4.6	n.s.
TG (mg/dL)	128.6 ± 8.6	109.5 ± 7.3	n.s.
HDL-c (mg/dL)	53.7 ± 2.5	52.5 ± 2.3	n.s.
LDL-c (mg/dL)	90 ± 22.9	100 ± 24	n.s.
oxLDL (mg/dL)	19.08 ± 2.54	12.08 ± 1.46	0.01
TC/HDL	3.34 ± 0.92	3.46 ± 0.76	n.s.
LDL/HDL	1.8 ± 0.73	2.02 ± 0.64	n.s.
TG/HDL	2.65 ± 0.27	2.24 ± 0.21	n.s.
oxLDL/Non-HDLc	0.177 ± 0.026	0.101 ± 0.028	0.01
Creatinine (mg/dL)	0.68 ± 0.03	0.71 ± 0.02	n.s.
Rheumatoid factor (U/mL)	155.6 ± 30.9	11.8 ± 0.6	< 0.0001
hsCRP (mg/dL)	0.52 ± 0.14	0.18 ± 0.03	0.02
ESR, mm/hour	29.7 ± 2.5	20.2 ± 1.7	0.001
Leukocytes, cells per mcL x 10^{-2}	7.03 ± 0.36	6.35 ± 0.33	n.s.
Hemoglobin (g/L)	13.5 ± 0.2	20.7 ± 0.9	n.s.
Systolic blood pressure, mmHg	111.3 ± 1.7	113.7 ± 1.1	n.s.
Diastolic blood pressure, mmHg	71.8 ± 1.3	73.3 ± 1.1	n.s.

Table II. Intima media thickness in both carotid arteries.

Variable	RA	Control	p value
Right carotid superior IMT (mm)	0.54 ± 0.02	0.50 ± 0.02	n.s.
Right carotid inferior IMT (mm)	0.52 ± 0.02	0.50 ± 0.01	n.s.
Left carotid superior IMT (mm)	0.52 ± 0.02	0.48 ± 0.01	n.s.
Left carotid inferior IMT (mm)	0.56 ± 0.02	0.49 ± 0.02	0.03
Combined right carotid IMT (mm)	0.52 ± 0.02	0.50 ± 0.01	n.s.
Combined left carotid IMT (mm)	0.54 ± 0.01	0.48 ± 0.01	0.04
Combined 4 carotid sites IMT (mm)	0.53 ± 0.01	0.49 ± 0.01	n.s.

Table III. Type of DMARD and other anti-RA medications.

Drug (s)	Number of patients	Known CV effect
Methotrexate	23	Reduction of CV risk
Leflunomide	16	Hypertension in a small proportion. In general, no added major CV risk
Infliximab	4	Higher mortality in advanced heart failure
Etanercetp	4	Reduction in CV risk markers
Hydroxycloroquine	2	Retinotoxicity; cardiac toxicity, very rare
Other	3	-
Monotherapy	8	
Combination of 2 drugs	18	
Combination of 3 or more	4	

lar risk factors, the IMT, precise index of early, subclinical atherosclerosis, is not abnormal.[24] However, thickness in the left carotid inferior prespecified point of measurement of IMT was slightly greater than in the right artery. This fact is not surprising, because several studies have shown that there is a time-related difference in the natural appearance of atherosclerosis in left carotid artery.[25] Cross-sectional intima-media in the left-sided segments of the carotid artery correlates better with coronary angiography.[26] Furthermore, in necropsy studies, Solber and Eggen[27] found that the intimal area affected by raised atherosclerotic plaques was wider in the left carotid artery. Appear as though that the flow pattern is different in both carotid arteries, and although is not completely supported by evidence, vascular shear rate seems to be lower in the left carotid, phenomenon that can bring out the development of atherosclerosis.

In the classical «cholesterol hypothesis»[28] atherosclerosis begins when LDL particles are transported from serum to the subendothelial space through several pathways and become trapped in the proteoglycan network. Once seized there, the particles can be attacked by reactive oxygen species (ROS), which are continuously formed during cell metabolism.[29] Both, the minimal modified oxidized LDL (mmLDL), or the advanced oxidized form (oxLDL) are powerful inducers of inflammation.[30] The particle itself or some of its oxidation products like lysophosphatidylcholine, activate endothelial cells, which produce different immobilizing, chemotactic, and colonizer molecules that recruit monocytes, immobilize them in the subendothelium and help to transform these white cells in resident macrophages that, through scavenger receptors, take-up oxidized cholesterol and fatten up to convert themselves in foam cells, fundamental phenomenon of early atherosclerosis. More recently, it has been evident that oxLDL exists not only in the subendothelial space, but also in blood stream in apparent contradiction with the classical paradigm.[31] It is known that oxLDL is recognized by an endothelial receptor (the lectin-like oxidized low-density lipoprotein receptor-1, LOX-1), that permits the uptake of the serum oxidized lipoprotein by endothelial cells, which subsequently extrude the lipid to the subendothelial region.[32] Furthermore, the coupling of oxLDL to its receptor activates the multitranscriptional nuclear factor-kappa B that increases the production of ROS, as well as adhesion and prothrombotic molecules, and activates histolytic enzymes, inflammatory reactions, and apoptotic mechanisms.[33] How oxLDL exists in the plasma of normal persons or increases in subjects with carbohydrate intolerance or in those with acute coronary syndromes is not completely understood. There are two possible explanations that not exclude each other: in one hand, oxidation of the lipoprotein could be secondary to the effect of soluble oxidant enzymes or metal-catalyzed reactions. The other possibility is that the oxidized LDL made up in the subendothelial space can reach the circulation in a normal exchange or through the atheroma

breach caused by plaque fracture or fissure.[34] As there is a proportional relationship between the seriousness of atherosclerotic lesions and the severity of the coronary syndromes in one side, and the serum concentration of oxLDL in the other, it is possible that the elevation of the oxidized lipoprotein corresponds to the leak of the lipid through the fractured plaque.[35] Such phenomenon would explain the worsening of atherosclerosis after a plaque rupture and the bursting of an acute coronary syndrome.[36] The increase in plasma oxLDL (irrespective of its origin) possibly can accelerate or complicate atherosclerosis, even when levels of LDL are in the range of normality. In fact, our results shown that elevated oxLDL was the only vascular risk factor of these RA patients. No true thickening of the carotid intima-media was disclosed, only a value significantly greater (but still in the range of normality) in a segment of the left carotid artery prone to develop atherosclerosis.

With respect to the anti-rheumatic medication, the drugs mostly used, methotrexate and leflunomide, had favorable effects on lipid profile and cardiovascular risk. In fact, the use of TNF-α inhibitors and DMARDs in RA reduce the incidence of cardiovascular events, at least in patients newly diagnosed.[37,38]

The oxLDL fraction initiates immune responses that induce the production of antibodies anti-oxLDL, whose relation with atherosclerosis is not completely established. The real clinical importance of oxLDL has not been fully established, in both the coronary risk and its influence on the immune and inflammatory status of RA. In one hand, LDL mildly oxidized has been found in synovial fluid of the affected joints.[39] In animal models, LOX-1 and oxLDL have been found in arthritic joints mediating both inflammation and cartilage destruction.[40] So, at least, from the rheumatologic point of view, the increased concentration of oxLDL foretells a greater joint affectation and severity of the disease. Although we could not find manifest carotid atherosclerosis in these patients, the increased oxLDL in them foresees vascular damage later on, as inflammation is a recognized factor for the initiation, the progression and complication of the atherosclerosis plaques. From the practical point of view, in patients without blown-up LDL hypercholesterolemia and other classical coronary risk factors, the better way of reducing the oxLDL plasma concentration is the specific treatment of the arthritis with the usual DMARDs. As oxLDL increases with higher concentrations of LDL-c, powerful statins could provide an additional benefit, preventing both, rheumatic and vascular damages. Moreover, the pleiotropic effects of statins could also bring supplementary cardiovascular protection in these high-risk patients.

The main limitations of this work are: the small number of patients included, the non-probabilistic approach. Nevertheless, our results suggest a correlation between atherosclerotic plaque development and RA particularly related to the increased risk provided by oxLDL levels, however, more work with a higher sample is necessary in order to verify this results.

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