Comparable effects of traditional cardiovascular risk factors on subclinical atherosclerosis in systemic lupus erythematosus and rheumatoid arthritis

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Abstract

Objective

Patients with rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE) have an increased premature prevalence of atherosclerosis. We aimed to determine whether there are differences in the prevalence of classic cardiovascular risk factors between SLE and RA. We also analysed the effect of traditional cardiovascular risk factors on the development of subclinical atherosclerosis in both conditions and if some disease-characteristic features are associated with these traditional cardiovascular risk factors.

Methods

This was a cross-sectional study encompassing 602 individuals, 276 SLE and 326 RA patients. Subclinical atherosclerosis (presence of carotid plaques and carotid intima-media thickness [cIMT]) was determined by carotid ultrasonography. A multivariable regression analysis was performed to evaluate whether classic cardiovascular-related risk factors differentially influence subclinical carotid atherosclerosis in SLE compared to RA patients.

Results

Age (interaction factor [if] p=0.000), hypertension (if p=0.034), and diabetes (if p=0.037) had a higher effect on cIMT in RA than in SLE subjects. However, these traditional cardiovascular factors did not yield different effects on the presence of carotid plaques in RA and SLE when the univariate interaction was analysed. In addition, no differences were found in the influence of hypertension, diabetes, dyslipidaemia or current smoking on cIMT or carotid plaque after adjusting for demographics, the presence of other traditional cardiovascular factors, and disease-related data. Moreover, the additive effect of several cardiovascular risk factors on the subclinical carotid atherosclerosis did not differ between the two diseases.

Conclusion

The influence of traditional cardiovascular risk factors on cIMT and carotid plaque is similar in RA and SLE.

Key words

rheumatoid arthritis, systemic lupus erythematosus, traditional cardiovascular risk factors, carotid plaque

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Received on August 9, 2019; accepted in revised form on October 7, 2019.

Funding: this work was supported by a grant to I.F-A. from the Spanish Ministry of Health, Subdirección General de Evaluación y Fomento de la Investigación, Plan Estatal de Investigación Científica y Técnica y de Innovación 2013-2016 and by Fondo Europeo de Desarrollo Regional - FEDER - (Fondo de Investigaciones Sanitarias, FIS PI14/00394, PI17/00083). Prof. González-Gay's research was supported by European Union FEDER funds and by the Fondo de Investigación Sanitaria (grants PI06/0024, PS09/00748, PI12/00060, PI15/00525 and PI18/00043) of the Instituto de Salud Carlos III (ISCIII, Health Ministry, Spain).
This work was also partially supported by RETICS Programs RD12/0009 (RIER), RD12/0009/0013 and RD16/0012 from the Instituto de Salud Carlos III (ISCIII, Health Ministry, Spain).

Competing interests: non declared.

Introduction

Rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) are conditions associated with increased mortality, largely as a consequence of cardiovascular disease (1). The higher rates of cardiovascular morbidity and mortality in patients with RA and SLE cannot entirely be explained by traditional risk factors, suggesting that the systemic inflammation that characterises these diseases may accelerate atherosclerosis (2). However, the role of traditional cardiovascular disease risk factors in inflammatory disorders related to cardiovascular disease remains unclear.

There is no unanimous consensus on the real impact of classic cardiovascular risk factors on cardiovascular disease in RA. With the exception of past cigarette smoking, one study suggested that these risk factors are not more prevalent in women with RA than in women without RA (3). However, differences in the prevalence of hypertension, diabetes, and dyslipidaemia were reported in studies that included both men and women (4). Other studies have also shown an increased prevalence of traditional risk factors in patients with RA, particularly in those with longstanding disease (5). In addition, there is some evidence of interactions between traditional cardiovascular risk factors and inflammation levels in RA. In a longitudinal study of 487 patients with RA, the predictors for rapid cIMT progression included both traditional cardiovascular risk factors and the baseline level of the erythrocyte sedimentation rate (ESR) (6). Moreover, a significant interaction between the number of cardiovascular risk factors and the ESR was reported.

Traditional risk factors for atherosclerosis seem to be prevalent among patients with SLE. Women from the Toronto Lupus Cohort had an increased prevalence of hypertension, diabetes, premature menopause, sedentary lifestyle, and at-risk body habitus than controls (7). Additionally, a high proportion of patients with SLE typically present metabolic syndrome (8).

The aim of the present study was to determine if there were differences in the prevalence of classic cardiovascular risk factors between SLE and RA. We also analysed the effects of traditional cardiovascular risk factors on the development of subclinical atherosclerosis in both conditions, and whether some disease-characteristic features are associated with these traditional cardiovascular risk factors.

Methods

Study participants

This was a cross-sectional study that included 602 individuals, 276 patients with SLE and 326 with RA. All were 18 years old or older and were included in the study if they fulfilled ≥4 American College of Rheumatology (ACR)-1997 classification criteria for SLE (9) and the 2010 ACR/EULAR diagnostic criteria for RA (10). Patients had been diagnosed by rheumatologists and were periodically followed-up at rheumatology outpatient clinics. For the purpose of inclusion in the present study, SLE and RA disease duration needed to be ≥1 year. SLE and RA patients undergoing biologic therapy were not excluded. Likewise, since glucocorticoids are often used in the management of SLE and RA, patients taking prednisone were not excluded. In the present study the use of any lipid-lowering agent, not only statins, was allowed. None of the patients had established cardiovascular disease. However, patients were excluded if they had a history of cancer or any other chronic disease, evidence of active infection or a glomerular filtration rate <60 ml/min/1.73m^2. The study protocol was approved by the Institutional Review Committee at Hospital Universitario de Canarias, Hospital Doctor Negrín, and Hospital Marqués de Valdecilla, all in Spain, and all subjects provided informed written consent (approval no. 2015/84).

Assessments and data collection

Patients were assessed for cardiovascular risk factors and medication. They completed a questionnaire and underwent a physical examination to determine anthropometric measurements and blood pressure. Medical records were reviewed to ascertain specific diagnoses and medications. Hypertension was defined as a systolic or a diastolic blood pressure higher than 140

and 90 mmHg, respectively. Dyslipidaemia was considered ongoing if one of the following factors was present: total cholesterol >200 mg/dl, triglyceride >150 mg/dl, HDL cholesterol <40 in men or <50 mg/dl in women, or LDL cholesterol >130 mg/dl. An atherogenic index was calculated using the total cholesterol/HDL cholesterol ratio. SLE disease activity and damage were assessed using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI-2K) (11) and the SLICC/ACR Damage Index (SDI) (12), respectively. For the purposes of the present study, the SLEDAI index was split into none (0), mild (1–5), moderate (6–10), high, and very high activity (>10). Disease severity was measured as well, using the Katz Index (13). In patients with RA, disease activity was measured using the Disease Activity Score in 28 joints (DAS28) (14), while disease disability was determined using the Health Assessment Questionnaire (HAQ) (15). Clinical Disease Activity Index (CDAI) (16) and Simple Disease Activity Index (SDAI) (17) scores for RA disease activity were calculated as previously described. Moreover, standard techniques were used to measure plasma glucose, C-reactive protein, and serum lipids.

Carotid ultrasound assessment

Carotid ultrasounds were performed as previously reported (18, 19) to assess carotid intima-media wall thickness (cIMT) in the common carotid artery and to detect focal plaques in the extracranial carotid tree in patients with SLE and RA. A commercially available scanner, Mylab 70, Esaote (Genoa, Italy) equipped with a 7–12 MHz linear transducer and an automated software-guided radiofrequency technique – Quality Intima Media Thickness in real-time (QIMT, Esaote, Maastricht, Holland) – was used for this purpose. Based on the Mannheim consensus, plaque criteria in the accessible extracranial carotid tree (common carotid artery, bulb and internal carotid artery) were defined as follows: a focal protrusion in the lumen measuring at least cIMT >1.5 mm; a protrusion at least 50 % greater than the surrounding cIMT; or an arterial lumen encroaching >0.5 mm (19).

Table I. Demographic data of the 326 rheumatoid arthritis and 276 systemic lupus erythematosus patients.

	RA=326	SLE=276	
Female, n (%)	233 (71)	263 (95)	**0.000**
Age, years	62 ± 13	51 ± 12	**0.000**
BMI, mg/cm^2	28.5 ± 5.1	27.5 ± 5.7	**0.031**
Waist circumference, cm	98 ± 13	92 ± 13	**0.000**
Hip circumference, cm	106 ± 11	104 ± 11	**0.032**
Waist to hip circumference ratio	0.92 ± 0.08	0.89 ± 0.07	**0.000**
Comorbidity			
Hypertension, n (%)	166 (51)	110 (40)	**0.007**
Dyslipidaemia, n (%)	235 (72)	139 (50)	0.80
Current smoking, n (%)	29 (9)	68 (25)	**0.033**
Diabetes, n (%)	61 (19)	14 (5)	**0.000**
Number of cardiovascular risk factors	1.24 ± 1.00	1.09 ± 0.93	0.054
Analytical data			
CRP, mg/l	3.50 (1.60-6.85)	1.90 (0.90-4.90)	0.085
Cholesterol, mg/dl	202 ± 37	200 ± 38	0.63
Triglycerides, mg/dl	134 ± 82	128 ± 80	0.44
LDL, mg/dl	118 ± 32	111 ± 29	**0.020**
HDL, mg/dl	57 ± 16	63 ± 21	**0.000**
Apolipoprotein A, mg/dl	170 ± 28	180 ± 37	**0.006**
Apolipoprotein B1, mg/dl	109 ± 59	96 ± 24	**0.004**
Apo B/Apo A index	0.65 ± 0.29	0.55 ± 0.17	**0.000**
Atherogenic index	3.80 ± 1.32	3.40 ± 1.08	**0.000**
Disease-related data			
Disease duration, years	9.3 ± 8.8	17.6 ± 9.8	**0.000**
Rheumatoid factor, n (%)	188 (58)	34 (12)	**0.000**
ACPA, n (%)	161 (49)	–	–
Anti-hypertension treatment, n (%)	167 (51)	104 (38)	**0.001**
Statins, n (%)	126 (39)	75 (27)	**0.003**
Current prednisone, n (%)	156 (48)	131 (47)	0.97
Prednisone, mg/day	5 (3-6)	5 (5-7.5)	0.087
DMARDs, n (%)	284 (87)	211 (76)	**0.001**
Number of DMARDs	1.2 ± 0.8	0.9 ± 0.6	**0.000**
Hydroxychloroquine, n (%)	66 (20)	190 (69)	**0.000**
Methotrexate, n (%)	243 (75)	32 (12)	**0.000**
Leflunomide, n (%)	44 (13)	0 (0)	**0.000**
Salazoypyrin, n (%)	14 (4)	0 (0)	**0.000**
Mycophenolate mofetil, n (%)	–	23 (8)	–
Azathioprine, n (%)	–	32 (12)	–
Anti TNF-alpha therapy, n (%)	53 (16)	–	–
Tocilizumab, n (%)	18 (6)	–	–
Rituximab, n (%)	10 (3)	8 (3)	0.90
Belimumab, n (%)	–	4 (1)	–
Cyclophosphamide, n (%)	–	1 (0)	–
Carotid intima media assessment			
Carotid plaque, n (%)	170 (52)	99 (36)	**0.000**
bilateral, n (%)	112 (34)	53 (54)	**0.000**
cIMT, mm	0.734 ± 0.172	0.631 ± 0.108	**0.000**

Data represent mean ± SD or median (IQR) when data were not normally distributed.
BMI: body mass index; C3 C4: complement; CRP: C reactive protein; LDL: low-density lipoprotein DMARD: disease-modifying anti-rheumatic drug; ACA: anticardiolipin; HDL: high-density lipoprotein; ANA: antinuclear antibodies; ENA: extractible nuclear antibodies; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; SLEDAI categories were defined as: 0, no activity; 1-5 mild; 6-10 moderate; >10 activity; SLICC: Systemic Lupus International Collaborating Clinics/American Colleague of Rheumatology Damage Index; cIMT: carotid intima media thickness; ACPA: anti-citrullinated protein antibodies.

Statistical analysis

Demographic and clinical characteristics were described in patients with SLE and RA as mean ± standard deviation or percentages for categorical variables. For non-normally distributed continuous variables, data were expressed as a median and interquartile

Table II. Univariate RA and SLE related data relation with traditional cardiovascular risk factors.

	OR (95% CI), *p*-value							
	RA				SLE			
	Diabetes	Hypertension	Smoking	Dyslipidaemia	Diabetes	Hypertension	Smoking	Dyslipidaemia
RA- and SLE-related data								
CRP, mg/l	1.01 (0.99-1.02)	1.02 (0.99-1.04), 0.062	0.99 (0.93-1.04)	**0.99 (0.97-1.00), 0.012**	0.97 (0.84-1.10)	1.02 (0.99-1.05)	1.00 (0.98-1.03)	1.01 (0.98-1.04)
Disease duration, years	0.99 (0.97-1.03)	1.02 (0.99-1.05)	**0.89 (0.81-0.96), 0.004**	0.99 (0.97-1.02)	1.05 (0.99-1.10), 0.096	1.02 (0.99-1.04)	**0.96 (0.94-0.99), 0.017**	**1.04 (1-00-1.08), 0.031**
Rheumatoid factor	**0.37 (0.21-0.67), 0.001**	0.73 (0.46-1.14)	2.13 (0.76-5.98)	0.91 (0.56-1.51)	–	–	–	–
ACPA	**0.45 (0.25-0.81), 0.008**	**0.63 (0.40-0.99), 0.045**	**2.96 (1.13-7.76), 0.028**	0.84 (0.51-1.37)	–	–	–	
Current prednisone	0.76 (0.43-1.33)	1.42 (0.92-2.20)	**2.33 (1.04-5.21), 0.040**	1.27 (0.78-2.08)	1.07 (0.34-3.15)	**1.98 (1.21-3.24), 0.007**	0.70 (0.40-1.23)	1.23 (0.66-2.28)
DMARDs	1.15 (0.48-2.72)	1.25 (0.65-2.41)	1.58 (0.44-5.66)	0.95 (0.46-1.99)	1.07 (0.29-3.97)	0.68 (0.38-1.20)	1.49 (0.74-2.99)	0.95 (0.45-2.02)
Hydroxicloroquine	**1.91 (1.01-3.59), 0.046**	**2.57 (1.44-4.59), 0.001**	-	0.65 (0.36-1.15)	0.76 (0.25-2.33)	0.71 (0.42-1.20)	1.21 (0.66-2.25)	0.72 (0.35-1.45)
Methotrexate	0.69 (0.37-1.26)	0.98 (0.59-1.61)	2.22 (0.73-6.77)	0.88 (0.50-1.56)	2.18 (0.58-8.28)	1.18 (0.56-2.49)	1.22 (0.54-2.78)	0.73 (0.29-1.82)
Mycophenolate mofetil	-	-	-	-	**2.51 (1.05-6.03), 0.039**	1.37 (0.54-3.49)	**0.24 (0.08-0.70), 0.009**	
Anti-TNF-alpha therapy	0.88 (0.40-1.92)	1.49 (0.81-2.72)	1.52 (0.51-4.47)	0.94 (0.49-1.81)	–	–	–	
SLE-related data								
SLICC					5.09 (0.65-39.60)	**2.02 (1.13-3.60), 0.018**	**0.52 (0.29-0.94), 0.030**	0.83 (0.39-1.76)
SLICC ≥ 1					**1.37 (1.13-1.65), 0.001**	**1.29 (1.13-1.48), 0.000**	0.87 (0.74-1.02), 0.086	**1.42 (1.22-1.64), 0.000**
Katz Index					1.17 (0.93-1.48)	**1.35 (0.18-1.55), 0.000**	0.89 (0.76-1.03)	1.22 (0.91-1.65)
Katz Index ≥ 3					1.63 (0.55-4.79)	**2.69 (1.62-4.47), 0.000**	0.74 (0.41-1.32)	**2.5 (1.42-3.89), 0.001**
SLEDAI					0.95 (0.83-1.09)	**1.05 (1.01-1.10), 0.031**	1.02 (0.99-1.06)	0.99 (0.86-1.14)
SLEDAI activity categories								
No activity					ref.	ref.	ref.	ref.
Mild					0.52 (0.13-2.09)	1.09 (0.60-1.96)	1.53 (0.76-3.07)	0.91 (0.44-1.89)
Moderate					0.96 (0.24-3.90)	1.12 (0.56-2.26)	1.24 (0.53-2.92)	0.96 (0.38-2.41)
High or Very High					–	**2.68 (1.02-7.03), 0.045**	**3.43 (1.27-9.30), 0.015**	1.31 (0.33-5.21)
ANA profile								
Anti DNA positive					0.67 (0.16-2.78)	1.57 (0.83-2.98)	1.29 (0.64-2.62)	0.93 (0.41-2.11)
ENA positive					0.25 (0.06-1.11), 0.069	1.13 (0.47-2.70)	0.39 (0.14-1.10), 0.075	0.42 (0.16-1.12), 0.082
Antiphospholid autoantibodies								
Lupus anticoagulant					3.20 (0.94-10.88), 0.062	0.99 (0.55-1.78)	0.97 (0.50-1.88)	1.22 (0.69-2.19)
ACA IgM					1.38 (0.28-6.67)	0.71 (0.33-1.55)	1.70 (0.75-3.84)	**0.24 (0.09-0.64), 0.005**
ACA IgG					0.70 (0.15-3.32)	0.84 (0.40-1.78)	0.84 (0.40-1.78)	1.02 (0.55-1.89)
Anti beta2 glicoprotein IgM					1.68 (0.34-8.22)	1.08 (0.48-2.45)	0.77 (0.28-2.16)	0.63 (0.27-1.52)
Anti beta2 glicoprotein IgG					0.46 (0.06-3.71)	0.84 (0.41-1.72)	0.46 (0.17-1.24)	0.75 (0.36-1.55)
C3, mg/dl					1.01 (0.99-1.03)	1.01 (0.99-1.02), 0.10	1.00 (0.99-1.01)	**1.02 (1.01-1.03), 0.000**
C4, mg/dl					1.02 (0.95-1.09)	0.99 (0.96-1.03)	1.01 (0.97-1.05)	1.03 (0.99-1.07), 0.065
RA-related data								
DAS28	1.09 (0.87-1.36)	0.91 (0.76-1.08)	1.19 (0.86-1.66)	1.21 (0.99-1.48), 0.062				
DAS28-CRP	**1.28 (1.01-1.64), 0.046**	**1.38 (1.12-1.69), 0.002**	1.18 (0.79-1.75)	1.02 (0.82-1.27)				
SDAI	0.99 (0.98-1.02)	1.00 (0.99-1.01)	0.99 (0.97-1.02)	1.01 (0.99-1.04)				
CDAI	1.00 (0.99-1.01)	**0.99 (0.99-0.99), 0.000**	1.01 (0.99-1.01)	**1.01 (1.00-1.01), 0.024**				

Only *p*-values inferior to 0.10 are shown; those significant are depicted in bold.

RA: rheumatoid arthritis; SLE: systemic lupus erythematosous; C3 C4: complement; CRP: C reactive protein; ACPA: anti-citrullinated protein antibodies; ANA: antinuclear antibodies; ENA: extractible nuclear antibodies; DMARD: disease-modifying anti-rheumatic drug; ACA: anti-cardiolipin; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index. SLEDAI categories were defined as: 0, no activity; 1-5 mild; 6-10 moderate; >10 activity; SLICC: Systemic Lupus International Collaborating Clinics/American Colleague of Rheumatology Damage Index; DAS28: Disease Activation Score using 28 joints; CDAI: Clinical Disease Activity Index; SDAI: Simple Disease Activity Index.

range (IQR). Demographic and clinical characteristics between patients with RA and SLE were compared using chi-square tests for categorical variables or Student *t*-tests for continuous variables (data expressed as the mean ± standard deviation). For non-normally distributed continuous variables, either a Mann-Whitney U-test was performed or a logarithmic transformation was made and data were expressed as a median (interquartile range). Multivariable logistic and linear regressions were performed to assess the relation of traditional cardiovascular risk factors with carotid subclinical atherosclerosis. Interaction factors were added to the regression models when we were interested in the comparison of the effect (beta coefficients) between RA and SLE patients. All of the analyses used a 5% two-sided significance level and were performed using SPSS software, v. 24 (IBM, Chicago, IL, USA); and STATA software, v. 15/SE (Stata Corp., College Station, TX, USA). A *p*-value <0.05 was considered statistically significant.

Results

Demographic, analytical and disease-related data

A total of 276 SLE patients with a mean ± SD age of 51±12 years, and 326 RA patients 62±13 years were included in the present study. Demographic and disease-related characteristics of the participants are shown in Table I. Body mass index (27.5±5.7 *vs*. 28.5±5.1kg/m^2, p=0.031) and the average waist circumference (92±13 *vs*. 98±13 cm, p<0.001) were higher in RA patients. Traditional cardiovascular risk factors were common in both diseases. Whereas hypertension, dyslipidaemia and diabetes were more prevalent in patients with RA, current smoking was found to be more frequent in those with SLE. The total number of cardiovascular risk factors was higher in RA patients although statistical significance was not reached (1.24±1.00 *vs*. 1.09±0.93, p=0.054). Regarding carotid ultrasound assessment, 36% of the SLE patients and 52% of the RA patients had carotid plaques (p<0.001). The average cIMT was 0.631±0.108 and 0.734±0.172 mm for respectively SLE and RA patients (p<0.001). Further data including disease duration, disease-related scores, prednisone use, biologic therapy and use of statins are shown in Table I and Supplementary Table S1.

Univariate RA- and SLE-related data associations with traditional cardiovascular risk factors

The analysis of RA- and SLE-related data revealed some significant relations with traditional cardiovascular risk factors (Table II). Disease duration was associated with current smoking in both RA and SLE patients, but it was only related with dyslipidaemia in the latter. C-reactive protein (CRP) was positively associated with dyslipidaemia in RA, but was not linked to classic cardiovascular risk factors in SLE. Prednisone use was associated with smoking in RA and with hypertension in SLE patients. Concerning the use of DMARDs in both diseases, only hydroxychloroquine showed a positive relation with diabetes and hypertension in RA patients. No relation with DMARDS was found in SLE, with the exception of mycophenolate mofetil, which was positive and negatively associated with hypertension and dyslipidaemia, respectively.

In RA, the presence of both rheumatoid factor and ACPA was negatively associated with diabetes. ACPA status, but not rheumatoid factor, was positive and negatively associated with smoking and hypertension, respectively. Regarding disease activity scores, DAS28-CRP was positively associated with the occurrence of diabetes and hypertension, whereas CDAI showed a positive relation with dyslipidaemia and a negative relation with hypertension.

All SLICC, Katz and SLEDAI indexes yielded a positive association with hypertension in SLE patients. Some correlations with these indices were also found with diabetes, hypertension and smoking, both in a continuous and dichotomous fashion. The presence of ANA, anti-DNA, and ENA were not linked to any cardiovascular risk factor (anti-Ro, anti-La, anti-RNP, and anti-Sm specificities assessed individually did not yield any associations - data not shown). Except for anticardiolipin IgM antibody, which showed a negative relation with dyslipidaemia, antiphospholipid antibodies were not associated with traditional cardiovascular factors. Finally, C3 serum levels were positively associated with the presence of dyslipidaemia (Table II).

Differences in the effects of traditional cardiovascular risk factors on carotid subclinical atherosclerosis in RA versus SLE patients

Gender, age, body mass index (BMI), waist circumference, and systolic pressure were strongly associated with cIMT or with the presence of carotid plaque in both RA and SLE patients. Similarly, with the exception of smoking, traditional cardiovascular factors were associated with subclinical atherosclerosis in both diseases (Table III). Age (interaction factor -if- p=0.000), hypertension (if p=0.034), and diabetes (if p=0.037) were found to have greater effects on cIMT in RA patients compared to SLE subjects in the univariate analysis. However, no differences in the effects of traditional cardiovascular factors on the presence of carotid plaque were found when univariate interaction was assessed. In RA patients, diabetes maintained a greater effect on cIMT when the analysis was adjusted for sex, age, BMI and waist circumference. However, this relation was lost when the adjustment was performed using other traditional cardiovascular risk factors or disease-related data like CRP serum levels, disease duration, and current prednisone use. In addition, no differences were found in the influence of hypertension, diabetes, dyslipidaemia or current smoking on cIMT or the presence of carotid plaque after adjusting for demographics, the presence of other traditional cardiovascular factors, and disease-related data.

Differences between RA and SLE patients in the effect of none, one or multiple cardiovascular risk factors on carotid atherosclerosis

The effect of the addition of several cardiovascular risk factors on the presence of carotid plaque and cIMT in RA and SLE patients was highly significant in both diseases (Table IV). This effect was stronger in the association with carotid plaque when compared to

Table III. Differences of the effect of demographics and traditional cardiovascular risk factors on carotid subclinical atherosclerosis.

	Beta coef. comparison between RA and SLE patients															
	RA patients (n=326)				**SLE patients (n=276)**				Unadjusted		Model 1		Model 2		Model 3	
	cIMT		Carotid plaque		cIMT		Carotid plaque		cIMT	Plaque	cIMT	Plaque	cIMT	Plaque	cIMT	Plaque
	beta coef. (95%CI)	*p*	OR (95%CI)	*p*	beta coef. (95%CI)	*p*	OR (95%CI)	*p*								
Male	125.54 (83.57-167.50)	**0.000**	2.45 (1.41-4.25)	**0.001**	53.28 (-7.03-113.59)	0.083	2.13 (0.70-6.53)	0.19	0.14	0.83						
Age, years	8.34 (7.13-9.55)	**0.000**	1.16 (1.12-1.20)	**0.000**	4.86 (3.87-5.85)	**0.000**	1.11 (1.08-1.15)	**0.000**	**0.000**	0.10						
BMI, mg/cm^2	1.96 (-1.93-5.85)	0.32	1.00 (0.96-1.05)	0.863	3.82 (1.43-6.21)	**0.002**	1.03 (0.99-1.08)	0.14	0.23	0.41						
Waist circumf., cm	2.26 (0.60-3.92)	**0.008**	1.02 (1.00-1.04)	0.10	2.22 (1.25-3.20)	**0.000**	1.02 (1.00-1.04)	**0.034**	0.77	0.85						
Hip circumf, cm	-0.16 (-2.21-1.90)	0.88	0.98 (-0.95-1.01)	0.13	2.63 (1.24-4.01)	**0.001**	0.74 (0.98-1.03)	0.74	**0.022**	0.16						
Systolic press., mmHg	2.97 (2.00-3.94)	**0.000**	1.03 (1.02-1.05)	**0.000**	1.83 (1.19-2.47)	**0.000**	1.02 (10.1-1.04)	**0.001**	0.054	0.38						
Diastolic press., mmHg	0.22 (-1.54-1.99)	0.80	1.00 (0.98-1.02)	0.762	0.07 (-0.21-0.37)	0.59	1.00 (0.99-1.01)	0.69	0.87	0.87						
Comorbidity																
Hypertension	100.73 (62.59-138.87)	**0.000**	4.40 (2.69-7.22)	**0.000**	49.56 (22.79-76.32)	**0.000**	3.03 (1.82-5.04)	**0.000**	**0.034**	0.30	0.64	0.36	0.53	0.24	0.42	0.20
Dyslipidaemia	9.81 (-35.67-55.29)	0.67	2.75 (1.70-4.47)	**0.000**	18.28 (-19.95-56.51)	0.34	3.70 (2.21-6.21)	**0.000**	0.79	0.55	0.33	0.74	0.31	0.74	0.38	0.65
Diabetes	**105.77 (53.43-158.11)**	**0.000**	3.12 (1.57-6.23)	**0.001**	-5.62 (82.80-71.56)	0.88	4.75 (1.45-15.57)	**0.010**	**0.037**	0.55	**0.004**	0.47	0.27	0.73	0.31	0.69
Current smoking	-14.40 (-72.67-43.86)	0.62	1.04 (0.46-2.37)	0.92	16.70 (-14.21-47.63)	0.28	1.31 (0.75-2.30)	0.30	0.25	0.65	0.19	0.45	0.12	0.40	0.085	0.51

Model 1: adjusted for sex, age, BMI and waist circumference. Model 2: model 1 + each cardiovascular risk factor is adjusted for the others. Model 3: model 1 + 2 + CRP serum levels, disease duration, and current prednisone.
BMI: body mass index; OR: odds ratio; cIMT, carotid intima media thickness.
Beta coef. are expressed in microns (waist/hip circumference as mm).

Table IV. Differences between RA and SLE patients in the effect of none, one or multiple cardiovascular risk factors on carotid atherosclerosis.

	No risk factors (n=98)			1 CV risk factor (n=240)			2 CV risk factor (n=207)			3 or 4 CV risk factor (n=55)		
	Carotid plaque (odds ratio 95% CI, p)											
		p	*p**		*p*	*p**		*p*	*p**		*p*	*p**
RA	**0.27 (0.13- -0.56), 0.000**	0.57	0.31	**2.51 (1.16-5.45), 0.020**	0.78	0.33	**4.49 (2-06-9.78), 0.000**	0.55	0.37	**6.07 (2.24-16.40), 0.000**	0.77	0.78
SLE	**0.37 (0.18- -0.75), 0.006**			**2.15 (1.01-4.57), 0.048**			**3.18 (1.44-7.05), 0.004**			**9.00 (2.33-34.73), 0.001**		
	microns CIMT (beta coef. 95% CI, p)											
		p	*p**		*p*	*p**		*p*	*p**		*p*	*p**
RA	**-85 (-142- -28), 0.004**	0.57	0.26	50 (-9-108), 0.094	0.78	0.65	**109 (48-170), 0.001**	0.55	0.12	**121 (43-200), 0.003**	0.77	0.64
SLE	-30 (-67-8), 0.12			18 (-19-55), 0.34			35 (-1-78), 0.12			**79 (11-146), 0.023**		

p and *p** represent the *p*-value for the unadjusted and adjusted interaction models (comparison between RA and SLE patients).
*p** adjusted for age, sex, BMI and waist circumference.
Beta coefficients were calculated assuming 'no risk factors' as the reference category.
Traditional cardiovascular risk factors are diabetes, hypertension, smoking and dyslipidaemia.

cIMT. However, when beta coefficients were compared between both diseases, neither non-adjusted nor adjusted analyses disclosed significant differences, showing, therefore, that the effect of the addition of several cardiovascular risk factors over the subclinical carotid atherosclerosis did not differ between both diseases.

Discussion

Traditional risk factors for cardiovascular disease in the general population include hypertension, cigarette smoking, diabetes, older age, and dyslipidaemia. These five classic risk factors are estimated to be responsible for more than half of cardiovascular mortalities (20). Most individuals who experience coronary heart disease events have at least one of these risk factors. There is also an increased risk when multiple risk factors are present (21). Similar to what was extensively reported in the general population, these traditional risk factors are likely to explain some of the increased cardiovascular risk observed in RA and SLE patients, or other autoimmune diseases like Sjögren's syndrome (23) . However, it is possible that the disease itself or its interaction with genetic and traditional cardiovascular risk factors, combined with a chronic pro-inflammatory state, may constitute the key elements leading to accelerated atherosclerosis in both conditions.

In our study we found a high prevalence of traditional cardiovascular risk factors in patients with RA and SLE. Hypertension and dyslipidaemia reached a frequency of 50%, while current smoking in SLE and diabetes in RA were found in 20% of patients. These findings are in keeping with previous reports (4, 6, 7, 22, 23).

Although the pathogenesis of RA and SLE are different, in our study we observed that the impact of traditional cardiovascular risk factors on subclinical atherosclerosis in both conditions was similar. We also found that some disease-related factors in both conditions were univariately associated with the classic traditional cardiovascular factors. Our results confirmed previously reported findings that ACPA positivity is more common in smokers than in non-smokers with RA (24). Smoking has also been associated with more severe clinical presentations manifested as increased disability and radiographic damage in RA (25). We also observed a relationship of disease activity, damage and severity score with hypertension in our patients with SLE. This was expected, as nephritis and renal impairment are common complications in SLE. In addition, the SLE score includes items related to hypertension and renal function. In our study we aimed to determine whether there were differences in the association of traditional cardiovascular risk factors with subclinical carotid atherosclerosis in SLE versus RA. However, we did not observe any differences in the influence of the classic cardiovascular risk factors on the presence of carotid plaque in the univariate analysis. Although the effect of hypertension and diabetes on cIMT was higher in RA in the univariate analysis, it was lost in the multivariable analysis. Thus, it is possible that the traditional cardiovascular risk factors can have an additive effect rather than a combined effect with disease-related factors in terms of their atherogenic effects in RA and SLE.

To the best of our knowledge, there are no studies comparing the effects of the traditional cardiovascular risk factors on subclinical atherosclerosis in SLE and RA. A recent report showed that atherosclerotic plaque progression is accelerated in SLE compared to RA and healthy controls after adjusting for traditional risk factors, and regardless of disease activity status (26). Similarly, the relative risk of subclinical atherosclerosis in SLE was found to be comparable to that observed in RA and diabetes mellitus, indicating that SLE patients merit similar diligence in their cardiovascular risk assessments and management measures (27). This is supported by the fact that in a recent report that aim to determine practices regarding CV risk assessment in SLE amongst rheumatologists, CV risk assessment and preventative measures were inconsistent when rheumatologists monitored SLE patients, indicating a care gap (30).

Previous reports highlighted the potential impact of traditional cardiovascular risk factors on cardiovascular disease in RA and SLE. With regard to myocardial infarction and cardiovascular morbidity, a recent meta-analysis (28) provided evidence that hypertension, type 2 diabetes, smoking, hypercholesterolaemia and obesity all have significant impacts on RA, with the magnitude of effects being similar to that for the general population. Baseline factors associated with rapid progression of atherosclerosis in patients with RA included the number of cardiovascular risk factors (OR 1.27 per risk factor, 95% CI 1.01 to 1.61) and the ESR (OR 1.12 per 10 mm/h, 95% CI 1.02 to 1.23). The ESR×cardiovascular risk factor and ESR×medication product terms were significant, suggesting that these variables modify the association between the ESR and cIMT progression (6). Smoking and hypertension, followed by total cholesterol, had the highest attributable risk in a collaborative study that encompassed 6,000 patients with RA who had a mean follow-up of 5.8 years. The attributable risk for DAS28 and seropositivity were comparable in magnitude to that for lipids. Seventy percent of cardiovascular events were attributable to all cardiovascular risk factors and RA characteristics combined (separately, 49% cardiovascular risk factors and 30% RA characteristics) (29). These data suggest that traditional risk factors play an important role and may explain a portion of the increased risk of cardiovascular morbidity and mortality observed in RA patients. On the other hand, the association between RA and SLE and cardiovascular risk factors has been linked to the presence of a pro-inflammatory state. However, this does not seem to be the only mechanism involved in the increased cardiovascular risk observed in such patients. In this regard, a recent genome-wide association study involving 2,989 RA patients, which encompassed 6,308,944 polymorphisms across the whole genome, supported the contention that a genetic component influences the risk of cardiovascular disease in RA. Indeed, it strongly suggested that genetic variations contribute to the development of subclinical atherosclerosis in patients with RA (33).

In our study, although statins were employed more frequently in RA, athero-

genic index and LDL cholesterol serum levels were significantly higher in RA in comparison to SLE patients. We do not have an exact explanation for this finding. This could be related to a higher awareness of use of statins in RA or maybe the use of statins was the consequence of this higher dyslipidaemia in these patients. Nevertheless, the suboptimal and inaccurate use of lipid-lowering drugs is a phenomenon frequently observed in both RA and SLE (30).

In conclusion, in our study we have found that SLE patients have a high prevalence of traditional cardiovascular factors similar to that described in RA. The effect of these classic cardiovascular risk factors in SLE is also similar to that observed in RA. No interaction between traditional cardiovascular risk factors and disease-related data on the development of subclinical atherosclerosis was found. Treatment and prevention of classic cardiovascular risk factors deserves special attention in SLE and RA patients due to their attributable role in the development of subclinical atherosclerotic disease.

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