CARDIOVASCULAR RISK PROFILE IN SYSTEMIC LUPUS ERYTHEMATOSUS AND RHEUMATOID ARTHRITIS: A COMPARATIVE STUDY OF FEMALE PATIENTS

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Abstract

Objective: Premature atherosclerosis is well-documented both in Systemic Lupus Erythematosus (SLE) and in Rheumatoid Arthritis (RA) patients, but cardiovascular (CV) risk is particularly high in lupus women. Although conventional CV risk factors do not fully explain the excessive risk in inflammatory diseases, they remain major contributors to atherosclerosis. The aim of the present study was to investigate whether CV risk factors are differentially associated with SLE and RA.

Methods: One hundred women with SLE, 98 with RA and 102 controls matched on age and without overt CV or renal disease were assessed for the presence of Framingham (hypertension, hypercholesterolemia, low HDL, diabetes, smoking) and other CV risks (atherogenic index of plasma (AIP), insulin resistance, obesity, central obesity, metabolic syndrome, uric acid, sedentarism, hypothyroidism and family history of premature CV disease).

Results: Modifiable CV risk factors are highly prevalent and occur more frequently in SLE and RA than in age-matched controls. Some differences in Framingham risk factors were found between SLE and RA, with hypertension being more common in young lupus women, hypercholesterolemia more frequent in RA and low HDL-C more frequent in SLE. However, the estimated 10-year Framingham CHD risk or the Reynolds Risk Score was comparable in both diseases. Although hypercholesterolemia was more frequent in RA, lupus women display a more atherogenic lipid profile, with significantly lower HDL-C levels (56.5±16 mg/dl versus 63.7±18; p=0.005), and more cases above the high risk cut-points for cholesterol/HDL-C (14% versus 4.1%; p=0.01) and for AIP (15% versus 6.1%; p=0.03). Also, uric acid levels are higher in SLE women (4.8±1.5 mg/dl) than in RA (4.1±1.1 mg/dl), p=0.001. On the other hand, insulin resistance is significantly higher in women with RA as compared with SLE (median HOMA-IR 3.5 [6.4]) versus 0.72 [2.5]; p<0.0001) and the difference remained significant after adjustment for BMI and corticosteroids.

Conclusions: Cardiovascular risk profile is distinct in SLE and RA women and the contribution of traditional CV risk factors to atherogenesis may be different in these two diseases. Prospective studies are necessary to understand how the control of modifiable risks can improve CV outcome in different inflammatory settings.

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Introduction

The importance of premature atherosclerosis in Systemic Lupus Erythematosus (SLE) and Rheumatoid Arthritis (RA) is well established in population and cohort-based studies. Atherosclerotic complications account for the majority of late deaths in SLE[1] and represent the primary cause of death in half of the RA patients[2,3]. The incidence rates of myocardial infarction (MI) and angina in premenopausal lupus women is 50 times higher than in matched controls[4] and among RA women the observed incidence of MI is also greater than expected[5]. Furthermore, studies dealing with subclinical atherosclerosis showed the magnitude of this problem to be superior in SLE and RA as compared to the general population[6,7].

However, some differences in CV risk appear to exist between the two diseases. While the reported risk of ischemic heart disease is 5-8 folds higher in SLE patients[8,9], this increased risk is only 2-3 folds higher in RA patients[10,11]. In both diseases the rela-

tive risk is more pronounced in youngest females[4,6,7].

Accelerated atherosclerosis in SLE and RA cannot be fully explained by traditional CV risk factors[8,11]. Nevertheless, conventional risk factors explain a substantial part of premature atherosclerosis[12,13] and, as many of them are modifiable, recommendations for their screening and control in inflammatory rheumatic disease have been developed[14,15].

The prevalence of hypertension, dyslipoproteinemia and sedentary lifestyle seems to be increased both in SLE and RA, though different studies provide a wide range of results [4,8,16,17,18]. However, there is limited information about the relative prevalence of CV risk factors in SLE and RA and to what extent this could account for the observed difference in CV events.

We examined the presence of classic Framingham and other conventional CV risk factors in SLE and RA women of similar age and without overt cardiovascular disease or renal function impairment to specifically address whether major differences exist between these two chronic inflammatory diseases of different pathogenesis. The Framingham 10-year risk of major heart events was estimated and, given the inflammatory setting of the study population, Reynolds Risk Score was also calculated. In addition, we assessed the distribution of CV risk factors in a control group to distinguish which factors are overrepresented in SLE and RA.

Material and methods

Patients

Adult women, fulfilling the American College of Rheumatology criteria for SLE or RA and attending the rheumatology clinic at Hospital Garcia de Orta in Almada, Portugal, on a regular basis, were recruited between January and December 2009. The control group consisted of women without chronic inflammatory disorders (patients with tendinitis or with low back pain) attending the same clinic. Exclusion criteria were: pregnancy, breastfeeding, prevalent myocardial infarction, angina pectoris, coronary revascularization, ischemic stroke and impaired renal function. In order to guarantee representativeness of different age groups, participants were enrolled in a consecutive way and allocated according to age frequency to obtain a final

sample of 30% aged 18-39 years, 45% aged 40-59 years, and 25% aged ≥60 years. The study was approved by the local Ethics Committee and participants provided written informed consent.

Assessments

Participants underwent a structured interview, physical examination and laboratory evaluation. Age, ethnicity, menopausal status, number of years of education, smoking, physical activity, disease duration from the physician's diagnosis, current medication, co-morbidities and family history of CV events was assessed. Information on cumulative corticosteroid dose was obtained from review of patients' medical records. Current disease activity was evaluated using the SLE Disease Activity Index 2000 (SLEDAI2K)[19] and in RA patients 28 joints were examined for tenderness and swelling, and the disease activity score (DAS28) was calculated using erythrocyte sedimentation rate[20]. Damage was scored according to the Systemic Lupus International Collaborating Clinics/ACR Damage Index (SDI)[21] and RA functional status was evaluated using the Stanford Health Assessment Questionnaire Disability Index (HAQ)[22].

Standing height, weight, waist circumference and blood pressure were measured and body mass index (BMI) (Kg/m²) calculated. A fasting blood sample was obtained for measurement of plasma glucose, insulin, total cholesterol, high density lipoprotein (HDL-C), low density lipoprotein (LDL-C), triglycerides, uric acid and thyroid stimulating hormone (TSH). Insulin resistance was estimated by homeostasis model assessment (HOMA-IR) using the formula HOMA-IR= [fasting insulin (μU/ml) × fasting glucose (mmol/l)]/22.5. The ratio total cholesterol/HDL-C and the atherogenic index of plasma (AIP), defined as the logarithm of the ratio plasma triglycerides (mmol/l)/HDL (mmol/l)[23], were calculated. Cardiovascular risk factors were defined as follows: hypertension as a recorded blood pressure ≥140/90 mm/Hg or use of antihypertensive medication; dyslipidemia as a total cholesterol ≥200 mg/dl or LDL cholesterol ≥130 mg/dl or HDL cholesterol < 50 mg/dl or triglycerides ≥150 mg/dl or use of lipid-lowering agents; diabetes as a fasting glucose level ≥126 mg/dl, a self-reported physician diagnosis or pharmacologic treatment; insulin resistance was defined by an HOMA-IR in the top quartile of a non-diabetic population (>2.114)[24], impaired fasting glucose (≥110mg/dl) or diabetes; obesity was considered if

BMI ≥30 Kg/m2; central obesity if the waist circumference was above the IDF population recommended cut-points[25]; current smoker if the participant smoked ≥1 cigarettes per day during the last month; sedentary lifestyle if the amount of self-reported weekly exercise during the last 12 months was <3 times or <30 min per session; family history of premature CV events was defined as myocardial infarction or ischemic stroke occurred in a first-degree relative before the age of 55 years in males or before the age of 65 years in females. Metabolic syndrome was diagnosed according to the joint definition of the International Diabetes Federation, National Heart Lung and Blood Institute, American Heart Association, World Heart Federation, International Atherosclerosis Society and International Association for the Study of Obesity and using waist circumference ≥80 cm as the threshold for abdominal obesity[26].

For estimation of absolute 10-year risk for major coronary heart disease (CHD) events we utilized the predictive model based on the Framingham risk score algorithm developed by Wilson *et al*[27]. This algorithm assesses the probability of having a MI or cardiac death during the next 10 years on the basis of the risk factor profiles and was developed for people 30 to 74 years old. The model includes gender, age, diabetes, smoking status, blood pressure, total cholesterol and HDL cholesterol as risk predictors. The Reynolds Risk Score predicts global cardiovascular risk (MI, coronary revascularization, ischemic stroke and cardiovascular mortality) and incorporates C-reactive protein levels (CRP) and family history of premature CV disease[28]. The 10-year risks were categorized into low (predicted risk <10%), intermediate (predicted risk 10-20%) and high (predicted risk >20%)[29].

Statistical analysis
Calculations were performed using SPSS 17.0 software for Windows and a 2-tailed p value <0.05 was selected as significant. Continuous variables are presented as means ± standard deviations or medians and inter-quartile ranges depending on whether the data were normally distributed or not. Categorical variables are reported as proportions. Comparisons between SLE and RA groups were made using chi-square or Fisher's exact test and Student t-tests for independent samples. The Mann Whitney U tests were used to compare variables that were highly skewed. Intergroup differences in CV risk factors were also calculated

between each age stratum: 18-39 years, 40-59 years and ≥ 60 years. We also compared the disease group (SLE plus RA) with the control group using the same tests.

To evaluate the independence of the association between the diagnosis and CV risk factors we used binary logistic regression analysis. HOMA-IR, AIP and cholesterol/HDL-C ratio were dichotomized below and above high risk cutoffs. Multiple linear regression analysis was used to assess the independent relationship between diagnosis and lipid levels.

Results

Demographic and disease characteristics
We studied 300 women, 100 with SLE, 98 with RA and 102 controls, with a similar mean age, but a higher proportion of non-Caucasians among patients (14% of SLE and 11.2% of RA versus 2.9% of controls). The educational level and the proportion of postmenopausal women were comparable in the three groups (Table I). The median duration since SLE diagnosis was 6.6 (range 0.5 - 34) years. Arthritis had occurred in 78%, renal disease in 28%, serositis in 26%, hemolytic anemia in 15% and lupus psychosis in 5% of SLE cases. All SLE patients were ANA positive, 80% were anti-dsDNA positive and 37% tested positive either for anti-cardiolipin, lupus anticoagulant or both. At the time of the evaluation 83% had low disease activity (SLEDAI2K <6) and 42% presented some irreversible damage (SDI≥1). Sixty patients were taking steroids in a median daily dose of 7.5 mg (range 1.25 to 60 mg) of prednisolone equivalent. The majority (73%) was currently on antimalarials and 24% on immunossupressants.

The median duration of RA was 7.6 (range 0.5 to 30) years, 59.2% had erosive disease and 88.8% tested positive either for rheumatoid factor (RF), anti-CCP antibodies or both. The mean disease activity score (DAS28) was 4.24 and the mean HAQ 1.15. Fifty two (53.1%) patients were taking corticosteroids in a median dose of 5 mg/day (range 2.5 to 15 mg), 89 (91%) were currently receiving synthetic DMARDs, the most commonly used was methotrexate in 81 cases, and 39 (40%) were on biologics.

Framingham CHD risk factors and predicted 10-year risk
The presence of Framingham CHD risk factors, i.e. hypertension, hypercholesterolemia, low-HDL,

Table I. Demographic and clinical characteristics of study subjects

Characteristic	SLE (n = 100)	RA (n = 98)	Controls (n = 102)
Age, years	46.6 ± 13.4	49.2 ± 13.7	47.7±13.4
Caucasian, (%)	86 (86)	87 (88.8)	99 (97.1)
Education, years	8.5 [8]	9 [8]	9 [8]
Postmenopausal, (%)	50 (50)	54 (55.7)	55 (53.9)
Disease duration, years	6.6 [6.8]	7.6 [9.1]	–
SLEDAI2K	2 [4]	–	–
DAS 28	4.24 ± 1.28	–	–
SDI	0 [1]	–	–
HAQ	1.15 ± 0.7	–	–
NSAIDs, (%)	28 (28)	62 (63.3)	23 (22.5)
Steroids, (%)	60 (60)	52 (53.1)	–
Current steroid dose, mg	7.5 [12]	5 [0]	–
Cumulative steroid dose, g	7.7 [18]	6.4 [15]	–
Methotrexate therapy, (%)	9 (9)	81 (82.7)	–
Antimalarial therapy, (%)	73 (73)	19 (19.4)	–
TNF blocker therapy, (%)	–	39 (40)	–
Immunosuppressive therapy, (%)	24 (24)	–	–

Continuous variables are presented as means ± SD or median [IQR] according to the distribution and categorical variables as absolute values and proportions (%)

diabetes and smoking, occurred very often in the studied population: 83% of SLE, 79.6% of RA and 81% of control women presented at least on risk factor. The mean number of Framingham CHD risk factors was similar in SLE, RA and controls (1.56±0.9; 1.57±0.9 and 1.51±1.1, respectively). Patients were significantly more likely to have hypertension (OR=1.97, 95%CI 1.19-3.24, p=0.008); otherwise the distribution of CHD risk factors was similar in the 3 groups. The mean Framingham 10-year risk of major CHD events was 4.4% for SLE, 4.9% for RA and 4.5% for controls. Similarly, Reynolds Risk Score did not show significant differences among the groups: SLE 2.5%; RA 2.8%; controls 2.2%.

Hypertension was significantly more prevalent in SLE women aged 18-39 years (34.3%) than in RA women within the same age range (11%; p=0.04). The mean values of systolic and diastolic blood pressure in SLE and RA were 128±21/76±11 mmHg and 127±21/75±12 mmHg, respectively, but more women in the SLE group received anti-hypertensive treatment (45% vs 32.6%; p=0.05). Differences between SLE and RA groups could be detected in the prevalence of hypercholesterolemia and low-HDL, but again lupus patients were found to receive lipid-lowering treatment more frequently than RA (39% vs 20.4%; p=0.004).

Lipid levels and atherogenic index of plasma

Fasting lipid levels were measured in all participants and mean values are shown in Table III. To determine the independent association of SLE and RA diagnosis with lipid levels we used multiple regression analysis adjusted for the identified potential confounders (lipid lowering therapy and current corticosteroid dose). SLE diagnosis was significantly associated with lower levels of total cholesterol as well as HDL-C and LDL-C. However, when we calculated the balance between risk and protective lipid fractions, lupus women were more likely to have cholesterol/HDL ratio (OR=3.92, 95%CI 1.24 to 12.48, p=0.02) and AIP values (OR=2.77, 95%CI 1.03-7.49, p=0.04) above the high risk cut-points.

Distribution of other CV risk factors

Several CV risk factors have been described beyond the classic Framingham ones. We evaluated the presence of insulin resistance, obesity, abdominal obesity, metabolic syndrome, hypothyroidism, uric acid levels and family history of premature CV disease. Table IV shows the presence of these risk factors in SLE, RA and control women.

HOMA index and uric acid levels are significantly higher in patients than in controls, as well as the proportion of insulin resistance, central obesity,

Table II. Distribution of traditional Framingham CHD risk factors in women with SLE, RA and non-inflammatory controls

	SLE (n =100)	RA (n = 98)	p-value	Controls (n=102)
Hypertension, (%)	53 (53)	43 (43.9)	ns	33 (32.4)*
18-39y	12 (34.3)	3 (11.1)	0.04	2 (6.5)†
40-59y	25 (58.1)	16 (36.4)	ns	16 (33.3)
≥60y	16 (72.7)	24 (88.9)	ns	15 (65.2)
Hypercholesterolemia, (%)	37 (37)	53 (54)	0.01	57 (55.9)
18-39y	12 (34.3)	9 (33.3)	ns	13 (41.9)
40-59y	11 (25.6)	26 (60.5)	0.001	27 (56.3)
≥60y	7 (37.2)	18 (66.7)	ns	17 (73.9)
Low HDL-C, (%)	39 (39)	20 (20.4)	0.005	24 (23.8)
18-39y	15 (45.5)	5 (18.5)	0.02	7 (22.3)
40-59y	15 (37.5)	9 (20.9)	ns	11 (23.4)
≥60y	9 (37.4)	6 (22.2)	ns	6 (26.1)
Diabetes, (%)	8 (8)	7 (7.1)	ns	7 (6.9)
Current smoker, (%)	15 (15)	17 (17.3)	ns	19 (18.6)
18-39y	7 (20)	6 (22)	ns	9 (29)
40-59y	8 (18.6)	11 (25)	ns	10 (20.8)
≥60y	0	0	ns	0
Framingham CHD risk ≥ 10%, (%)	11/88 (12.5)	16/91(17.6)	ns	15/91 (16.5)

*significant difference between patients and controls p=0.008; †p=0.04

Table III. Lipid levels and atherogenic index of plasma

	SLE (n=100)	RA (n=98)	Adjusted p*	Controls (n=102)
Total cholesterol, mg/dl	191.6 ± 43.5	203.3 ± 33.8	0.001	206.9 ± 33.8
LDL-C, mg/dl	114.7 ± 37	122.8 ± 28	0.01	127.9 ± 29
HDL-C, mg/dl	56.5 ± 16	63.7 ± 18	0.006	62.2 ± 15
Triglycerides, mg/dl	125.3 ± 78	103.9 ± 44	ns	98 ± 41
Cholesterol/HDL-C >5, (%)	14 (14)	4 (4.1)	0.01	9 (8.8)
AIP >0.21, (%)	15 (15)	6 (6.1)	0.03	6 (5.9)

The proportion of patients receiving lipid lowering medication was: SLE-39%; RA-20.4%; controls- 24.5% (p=0.009)
AIP– atherogenic index of plasma
*adjusted for use of lipid lowering therapies, and current corticosteroid dose

metabolic syndrome and hypothyroidism. More RA than SLE women are insulin resistant (OR=3.33, 95%CI 1.75-6.36, p=<0.0001) and the association between insulin resistance and RA diagnosis remained significant after adjustment for BMI and current corticosteroid dose (p=0.02).

We found uric acid concentration to be higher in lupus women, even in the absence of renal impairment or history of gout. The relationship between uric acid and SLE diagnosis remained sig-

nificant irrespective of the use of anti-hypertensive medication (p=0.004). Additionally, more RA patients had a positive family history of premature cardiovascular events.

Discussion

In the present study we found CV risk factors to be very common in SLE and RA women and that some

Table IV. Distribution of other conventional cardiovascular risk factors

	SLE (n =100)	RA (n = 98)	p-value	Controls (n=102)
HOMA-IR	0.72 [2.5]	3.5 [6.4]	0.0001	0.46 [0.9]*
Insulin resistant, n (%)	35 (35)	61 (62.2)	0.0001	20 (19.6)*
Obesity, n (%)	28 (28)	31 (32)	ns	28 (27.5)
18-39y	8 (22.9)	5 (19.2)	ns	3 (9.3)
40-59y	15 (27.3)	12 (34.9)	ns	14 (29.2)
≥ ≥60y	5 (22.7)	14 (51.4)	ns	11 (47.8)
Central obesity, n (%)	72 (72)	78 (79.6)	ns	64 (62.3)**
18-39y	20 (57.1)	20 (66.3)	ns	11 (35.5)**
40-59y	35 (81.4)	33 (75.6)	ns	34 (70.8)
≥60y	17 (77.3)	25 (95.8)	ns	19 (82.6)
Sedentary lifestyle, n (%)	84 (84)	87 (88.7)	ns	83 (82.2)
18-39y	28 (80)	20 (74.1)	ns	24 (80)
40-59y	35 (81.4)	42 (95.5)	ns	42 (87.5)
≥60y	21 (95.5)	25 (92.6)	ns	17 (73.9)
Metabolic Syndrome	27 (27)	25 (25.5)	ns	16 (15.7)†
18-39y	5 (14.3)	2 (7.7)	ns	0 (0)†
40-59y	12 (27.9)	12 (27.3)	ns	7 (14.6)
≥60y	10 (45.5)	10 (37)	ns	9 (39.1)
Hypothyroidism (%)	7 (7)	11 (11.2)	ns	3 (2.9)†
Uric acid, mg/dl	4.8 ± 1.5	4.1 ± 1.1	0.001	3.8 ± 1.0*
Family history of premature CV disease, n (%)	2 (2)	14 (14.3)	0.002	14 (13.7)

*significant difference between patients and controls p=0.0001; ** p=0.02; †p=0.04

differences could be detected between these two inflammatory diseases and the control population. Metabolic syndrome, as well as some features of this syndrome, such as hypertension, insulin resistance, and central obesity, are overrepresented among SLE and RA patients. Decreased thyroid function was also found more frequently in both patient groups.

We could also depict differences in the prevalence of CV risk factors between SLE and RA women. With regard to Framingham risk factors, hypertension is more common in young lupus women and the alterations in lipid profile are distinct in SLE and RA patients. Despite lower total cholesterol, lupus women present a more atherogenic lipid profile characterized by lower HDL-C and a more harmful balance between risk and protective lipid fractions. Furthermore, the association of atherogenic lipid profile with SLE diagnosis persists, irrespective of the use of lipid-lowering agents or corticosteroids. Indeed, systemic inflammation may induce alterations in lipoprotein profile and

in SLE patients it was shown that both disease activity and medication (corticosteroids and lipid-lowering agents) contribute to the changes in lipids that occur over time[30]. Active RA is also associated with a more atherogenic lipid profile and these changes have been documented even years before RA was diagnosed[31]. Furthermore, not only the levels of atheroprotective lipids are decreased, but also their function may be impaired in inflammatory rheumatic diseases[32]. Thus, identification of a more atherogenic lipid profile in lupus women, despite low disease activity and greater use of lipid-lowering agents is of interest because this suggests that the mechanisms underlying dyslipoproteinemia may differ in different inflammatory conditions.

In the general population, increased uric acid levels are an independent marker of cardiovascular disease[33] and arterial stiffness may represent the link between hyperuricemia and atherosclerosis[34]. We found higher uric acid levels in lupus women, despite normal creatinine levels and the absence

of gout. This increase was independent of the use of anti-hypertensive medication. We cannot rule out a subclinical renal impairment underlying the increased uric acid. Nevertheless, elevated uric acid may represent an additional risk for CV disease in lupus patients.

Insulin resistance, which is fundamental to the metabolic syndrome, was associated with symptomatic cardiovascular disease in the general population[35]. We found HOMA-IR to be significantly increased in RA as compared with SLE and this increase to be independent of BMI or corticosteroids. A previous study also demonstrated higher HOMA index in RA than in SLE and the association of insulin resistance with inflammation and coronary atherosclerosis[36]. This may be an important target to reduce CV risk in this patient population.

Hypothyroidism is associated with a wide range of metabolic changes, including increased BMI and adverse lipoprotein profile. There is also a relationship between hypothyroidism, vascular dysfunction and accelerated atherosclerosis[37]. Although hypothyroidism was more frequent in patients than in controls, its prevalence was similar in SLE and RA women.

A comprehensive identification of cardiovascular risk profile of SLE and RA is an opportunity to improve health management of these patients. As most of the identified risk factors are susceptible of intervention and modification, future research is crucial in order to establish to what extent the control of modifiable risk factors can improve cardiovascular outcome of these patients.

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