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Subclinical atherosclerosis in Systemic Lupus Erythematosus: Comparable risk with Diabetes Mellitus and Rheumatoid Arthritis☆

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ABSTRACT

Objective: Although a high risk of subclinical atherosclerosis has been reported in Systemic Lupus Erythematosus (SLE), it is not adequately compared with that observed in other rheumatic and non-rheumatic high-cardiovascular (CVD) risk diseases, such as Rheumatoid Arthritis (RA) and Diabetes Mellitus (DM). Our objective was to evaluate the relative risk (RR) of subclinical atherosclerosis in SLE, RA and DM patients compared to healthy controls, and examine potential associations with traditional and disease-related CVD risk factors in SLE.
Methods: We examined for atherosclerotic plaques 460 individuals (92% female) without CVD history, using carotid and femoral artery ultrasound: 115 SLE patients and matched 1:1 for age and gender RA, DM, and control subjects. Multivariate models were used to determine relative risk estimates for the number of atherosclerotic plaques in patient groups versus controls, and associations of plaques with traditional CVD and disease-related factors in SLE.
Results: A nearly two-fold higher number of atherosclerotic plaques in the carotid and femoral arteries was detected in each of SLE, RA and DM groups compared to controls, after adjusting for the effect of traditional CVD risk factors (RR = 1.80, 95% CI 1.05–3.08, p = 0.033, RR = 1.90 (1.11–3.26), p = 0.019, RR = 1.93 (1.14–3.28), p = 0.015, respectively). In SLE patients, the number of atherosclerotic plaques was associated with age (p < 0.001), smoking (p = 0.016), hypertension (p = 0.029), and cumulative corticosteroid dose (p = 0.007).
Conclusion: The relative risk of subclinical atherosclerosis in SLE was comparable to that found in RA and DM, indicating that SLE patients merit a similar diligence in CVD risk assessment and management measures.

1. Introduction

Atherosclerosis has a major impact on morbidity and mortality in systemic autoimmune diseases such as Rheumatoid Arthritis (RA) and Systemic Lupus Erythematosus (SLE) [1,2]. RA is associated with 1.5 to 2-fold increased risk of cardiovascular disease (CVD), which is attributed to traditional CVD risk factors and chronic inflammation [1]. An increased risk of CVD compared to the general population has also been reported in SLE [2,3], a systemic autoimmune disease mainly affecting young patients. Recent strategies in high CVD risk groups, including those in RA patients, are focused on identifying signs of atherosclerosis in the subclinical stage which can predict future CVD events, mostly by vascular ultrasound examination [4–6].

Although a high risk of subclinical atherosclerosis has been reported in SLE [7], it is not directly compared with that observed in other rheumatic and non-rheumatic conditions of high CVD risk, such as Rheumatoid Arthritis (RA) and Diabetes Mellitus (DM). There are only isolated studies comparing patients with SLE and those with RA with respect to subclinical atherosclerosis assessed by vascular ultrasound [8–10], and no studies comparing SLE with DM. Therefore, a question remains as to whether SLE should be considered as a CVD risk-equivalent condition to RA and DM requiring similar preventive and therapeutic measures [5,6].

Although there is increased prevalence of traditional CVD risk factors both in patients with SLE and RA, these factors fail to fully account for the increased CVD risk in these patients [2]. Current research has revealed a significant role of disease-related factors in the development and progression of atherosclerosis in SLE [2,11–13]. However, the

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interplay between traditional and disease-related atherogenic factors in SLE remains unclear.

Our aim was to evaluate the prevalence and extent of atherosclerotic plaques in the carotid and femoral arteries as identified by vascular ultrasound, among age- and gender-matched patients with SLE, RA and DM in comparison with healthy controls. In addition, we examined potential associations of subclinical atherosclerosis with traditional CVD and disease-related risk factors in patients with SLE.

2. Patients and methods

2.1. Study population

One hundred seventy one consecutive SLE patients who had regular follow-up in the outpatient Rheumatology Unit and fulfilled ≥4 ACR classification criteria for SLE [14] were recruited in 2012. Thirty four SLE patients were excluded: 24 due to prior history of CVD events (14 were SLE-related antiphospholipid syndrome with arterial events), 8 with DM, and 2 with malignancy. Twenty two eligible patients did not accept to participate in the study. The remaining 115 patients underwent a carotid and femoral ultrasound between 2012 and 2013 and matched on a 1:1 ratio for age and gender with healthy individuals (control group) and eligible RA and DM patients (either type I or type II) followed in the corresponding units of the First Department of Propaedeutic Internal Medicine. Since November 2009, any consenting patient with RA or DM without a history of CVD followed in the outpatient units was referred to the Cardiovascular Research Laboratory of the clinic for carotid and femoral ultrasound [15,16]. In the present study, candidate participants were all non-DM patients with RA and patients with DM, without a history of CVD, assessed between 2012 and 2013. A large number of healthy subjects were also recruited by the Cardiovascular Research Laboratory using community-based methods (flyers and brochures in the university and affiliated hospitals, outreach in local community centers).

Exclusion criteria were clinical atherosclerotic CVD or active malignancy for all subjects, rheumatic disease for patients with DM and controls, and DM for subjects with SLE, RA and controls. Clinical atherosclerotic CVD was defined as a history of myocardial infarction, stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, and peripheral arterial disease of atherosclerotic origin. We used the 2010 ACR/European League Against Rheumatism (EULAR) classification criteria for RA [17], and the 2010 American Diabetes Association criteria for the diagnosis of DM [18]. The study was approved by the hospital's local Institutional Review Board and informed consent was obtained from all the participants according to the declaration of Helsinki.

2.2. Recorded parameters

The following parameters were recorded at the time of examination: (a) Demographic data: age, gender, ethnicity; (b) Laboratory data: complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein, glucose, serum creatinine, lipid profile, hemoglobin A1c, and immunological tests (antinuclear and anti-DNA antibodies, C3 and C4 levels, and antiphospholipid antibodies, namely anti-cardiolipin antibodies, anti-β2GPI antibodies and lupus anticoagulant); (c) traditional CVD risk factors: hypertension (use of antihypertensive drugs and/or office blood pressure measurement higher than 139/89 as average of 3 sequential readings with 1 min interval in the supine position after at least 10 min of rest (Microlife WatchBP Office, Microlife AG, Widnau, Switzerland)), dyslipidemia (use of lipid-lowering treatment or LDL > 160 mg/dl [19]), smoking history (current smoker, pack years of smoking), physical activity level (measured in minutes of exercise per week), family history of CVD, Body Mass Index (BMI) calculated as weight/(height^2) (kg/m^2), and, (d) disease-related factors: disease duration (time from disease diagnosis), history of renal, cardiac, pulmonary and central nervous system involvement, Safety of Estrogens in Lupus Erythematosus National Assessment–SLE Disease Activity Index (SELENA-SLEDAI) [20], Systemic Lupus International Collaborating Clinics (SLICC)/ACR damage index score [21], 28-joints disease activity-ESR (DAS28-ESR) score [22], and current medication use. Medications for SLE and RA patients included corticosteroids, hydroxycloroquine, immunosuppressives (cyclophosphamide, azathioprine, mycophenolate mofetil, methotrexate, leflunomide, and cyclosporine), and biologic agents (belimumab, rituximab, adalimumab, infliximab, etanercept, abatacept, golimumab, certolizumab, and anakinra). In patients with SLE, the cumulative corticosteroid dose until the time of examination was also recorded.

2.3. Vascular ultrasound

All participants underwent the same vascular ultrasound examination (GK) as previously described [15,16]. A single blinded experienced operator performed all assessments using a high-resolution B-mode ultrasound device (Vivid 7 Pro, GE Healthcare®) with a 14-MHz multi-frequency linear transducer. Participants were examined while lying supine in a dimly lit, quiet room. Participants were asked to avoid vasoactive medications, caffeine and cigarette smoking, and requested to fast for at least 3 h prior to the examination. Atherosclerotic plaque presence was detected in the far walls of 8 arterial sites (left and right common carotid arteries, carotid bulbs and internal carotid arteries, and left and right common femoral arteries). Plaques were defined as focal areas in the near and far walls of the above-mentioned arteries where intima-media thickness (IMT) was ≥1.5 mm, or showed increase of either 0.5 mm or 50% compared to the IMT of the adjacent vascular wall.

2.4. Statistical analysis

For the evaluation of the extent of subclinical atherosclerosis, we used the total number of atherosclerotic plaques detected in any of the 8 arterial sites examined as the outcome variable. Because the outcome followed a Poisson distribution with overdispersion, we applied negative binomial regression models to investigate the effect of traditional and disease-related risk factors on the number of atherosclerotic plaques.

The following traditional CVD risk factors were included a priori into all models: age, arterial hypertension, dyslipidemia, cigarette smoking, family history of CVD, BMI and physical activity level. Disease and control groups were entered in the models as a categorical variable with four levels (0 = healthy controls, 1 = SLE, 2 = RA, 3 = DM). We derived relative risk (RR) estimates for the change in the number of atherosclerotic plaques in each disease group compared to controls, after adjustment for known potential confounding risk factors.

The identification of factors associated with subclinical atherosclerosis in SLE was assessed through multivariate negative binomial regression. Traditional CVD risk factors were included in the model along with SLE-related factors associated with atherosclerosis according to the literature, such as disease duration, disease activity and damage as measured by SELENA-SLEDAI and SLICC/ACR damage index scores respectively, lupus nephritis, antiphospholipid antibodies, and medications [7,12]. Statistical analysis was performed using version 12.0 of STATA software (College Station™, Texas, USA).

3. Results

3.1. Study population

We examined by vascular ultrasound 115 SLE patients (female 92%, mean age: 44.4 ± 12.2) matched 1:1 for age and sex with DM, RA and control groups. All 460 participants were Caucasian and their characteristics at the time of vascular ultrasound examination are shown in