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High prevalence of subclinical cardiovascular abnormalities in patients with systemic lupus erythematosus in spite of a very low clinical damage index

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Abstract *Background and aim:* To evaluate the prevalence of subclinical cardiovascular (CV) abnormalities in systemic lupus erythematosus (SLE) stratified according to SLE-related organ damage using the Systemic Lupus International Collaborating Clinics (SLICC) damage index.
Methods and results: We selected SLE patients without clinically overt CV events ($n = 45$, 56% with SLICC = 0, 44% with SLICC = 1–4). CV evaluation was performed using cardiac and vascular echo-Doppler techniques. Post-ischemic flow-mediated dilation (FMD) over nitroglycerine-mediated dilation (NMD) of the brachial artery <0.70 defined endothelial dysfunction.

The prevalence of preclinical CV abnormalities (CVAbn, including at least one of the following—carotid atherosclerosis, left ventricular (LV) hypertrophy, low arterial compliance, LV wall motion abnormalities, aortic regurgitation, FMD/NMD < 0.70)—was 64% (16/25) in patients with SLICC = 0 and 80% (16/20) in those with SLICC > 0 (p = not significant (NS)). In particular, the prevalence of carotid atherosclerosis (28% vs. 16%), of LV hypertrophy (12% vs. 6%) and of LV wall motion abnormalities (15% vs. 12%), of low global arterial compliance (18% vs. 10%), prevalence of aortic regurgitation (30% vs. 18%) and/or aortic valve fibrosclerosis (10% vs. 8%), FMD < 10% (14 ± 5% vs. 14% ± 6) and prevalence of FMD/NMD < 0.70 (53% vs. 52%) were comparable in SLE patients with SLICC > 0 and in those with SLICC = 0 (all p = NS).

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Of the SLE patients without carotid atherosclerosis, LV hypertrophy, low arterial compliance, LV wall motion abnormalities and aortic regurgitation ($n = 17$), endothelial dysfunction was detected in 50% of those with SLICC = 0 (6/12) and in 40% of those with SLICC > 0 (2/5, p = NS).
Conclusions: SLE patients with SLICC = 0 often have an elevated CV risk profile due to subclinical manifestations of CV disease detectable by cardiac and vascular echo-Doppler evaluations.

Introduction

Current guidelines for clinical management of systemic lupus erythematosus (SLE) suggest early identification and treatment of cardiovascular (CV) risk factors [1] to reduce the CV disease (CVD) burden on those patients [2]. However, guidelines do not recommend a specific strategy for early identification of high-risk patients. The Systemic Lupus Collaborating Clinics/American College of Rheumatology Damage Index (SLICC) is a validated prognostically relevant clinical tool for standardized assessment of SLE-related organ damage [3–5]. Thus, SLICC may be thought of as a reasonable tool for risk stratification of SLE patients.

Solid experience in asymptomatic subjects with traditional CV risk factors demonstrates that CV abnormalities (CVAbn) predict CV events independently [6,7]. Cardiovascular target organ damage may be a preclinical manifestation of CVD [7]. Systemic lupus erythematosus is associated with elevated CV risk above and beyond traditional CV risk factors [8–10]. Recent studies [11–13] proposed the use of ultrasound imaging for CVD screening in SLE patients. Thus, early identification of CVAbn may significantly improve identification of CV risk in patients with SLE. However, the extent to which preclinical manifestations of CVAbn disease are present in SLE patients without clinically relevant SLE-related organ damage (i.e. SLICC = 0) is unclear. Accordingly, our aim was to evaluate the prevalence of CVabn in SLE patients with SLICC = 0 compared to those with overt SLE-related organ damage (SLICC > 0).

Methods

Study population

Between March 2004 and July 2005, 48 consecutive patients with SLE were clinically evaluated using standardized methodology [14]. All subjects gave written informed consent to participate in the study according to the Declaration of Helsinki, and the study was approved by an independent local Ethics Committee. Patients with a history of myocardial infarction, stroke or transient cerebral ischemic attack were excluded a priori (3 patients) and for the current analyses, the study sample comprised of 45 SLE patients subdivided according to a SLICC = 0 ($n = 25$) or a SLICC > 0 ($n = 20$), of whom there were 45% with SLICC = 1, 35% with SLICC = 2, 15% with SLICC = 3 and 5% with SLICC = 4). All patients underwent extensive non-invasive CV evaluation using standard methodology [15–17].

Assessment of traditional CV risk factors comprised of a family history of CVD (myocardial infarction or stroke in a first degree relative before the age of 50 in men and before age of 60 in women), smoking habits, essential arterial hypertension (systolic blood pressure (SBP) > 140 or diastolic BP (DBP) > 90 mmHg or the use of anti-hypertensive drugs), cholesterol levels and a history of hypercholesterolemia (total cholesterol level higher than 200 mg/dL or the use of statins). The presence of diabetes was defined according to the American Diabetes Association criteria [18]. Renal insufficiency was defined as age- and gender-specific estimated creatinine clearance rates <90 ml/min/1.73 m^2. In the study sample, 31% had arterial hypertension, of whom 45% were on angiotensin I converting enzyme inhibitors, 64% were on calcium channel blockers, 9% on selective beta-1 blockers and 27% on diuretics. In those patients medication withdrawal for 3–4 weeks was considered unethical. The proportion of patients in each medication class did not differ between those with SLICC = 0 and those with SLICC > 0 (all $p > 0.1$). Disease related damage and activity of disease were defined by the SLICC and the European Consensus Lupus Activity Measure (ECLAM), respectively. Renal (defined as the presence, at any time, of lupus nephritis, nephrotic syndrome or renal insufficiency due to lupus nephritis) and central nervous system involvement (psychosis, seizures, organ brain syndrome) was assessed. Data on SLE-specific therapies were also collected. A preliminary study demonstrated that enrolled SLE patients were affected by a higher CVAbn burden compared to control subjects of comparable mean age, gender distribution and prevalence of major traditional CV risk factors [19]. Thus, the study sample was considered representative of the more general population of SLE patients, and the findings of this preliminary study indirectly validated our methodology.

Carotid artery ultrasonography

The presence of carotid plaques was evaluated by ultrasonography [20]. Briefly, both right and left common, internal and external carotid arteries were examined at multiple views to evaluate the presence of plaque defined as a focal protrusion of more than 50% of the surrounding intima-media thickness (IMT). IMT was measured at end-diastole by an electronic calliper at the level of the far wall of the common carotid arteries approximately 1 cm below the carotid bulb without including eventual plaques in the measurement; 3–5 measurements were obtained and averaged. Within-subjects test–re-test reproducibility of the method for measurements of IMT in nine randomly selected subjects was elevated (intraclass correlation