Endothelial function in systemic lupus erythematosus: relationship to disease activity, cardiovascular risk factors, corticosteroid therapy, and coronary calcification

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Objectives: Endothelial dysfunction is frequently present in patients with systemic lupus erythematosus and may increase their risk of premature coronary artery disease. In this pilot study we have characterized the relationship between endothelial function, measures of disease activity, and cardiovascular risk factors in patients with lupus.

Methods: Clinical characteristics and cardiovascular risk factors were evaluated in 20 patients with lupus. Flow-mediated dilation of the brachial artery was measured using high resolution ultrasound and the presence or absence of coronary calcification determined by electron-beam computed tomography. The relationship between these variables and flow-mediated dilation was determined using Spearman correlation coefficients (RHO) and Mann Whitney-Wilcoxon tests.

Results: Twenty patients (17 female) median age (interquartile range) 42.5 (32.0–47.5) years were studied. The median flow-mediated vasodilation was 3.6% (1.7%–7.7%). In patients with coronary calcification (n = 6), flow-mediated dilation was 2.1% (–0.42%–3.6%) compared with 4.0% (3.5%–8.3%) in those without (p = 0.12). There was no significant relationship between flow-mediated dilation and markers of disease activity, duration of disease, and cardiovascular risk factors. Lower flow-mediated dilation was associated with duration of corticosteroid therapy (RHO = –0.44, p = 0.05).

Conclusions: In these preliminary results, endothelial dysfunction is associated with long-term exposure to corticosteroids.

Keywords: flow-mediated dilation, endothelium, inflammation, atherosclerosis, systemic lupus erythematosus

Introduction

Systemic lupus erythematosus affects mainly young women, a group usually free of atherosclerosis. Epidemiological studies have shown a marked increase in the prevalence of myocardial infarction in patients with lupus (Manzi et al 1997). We (Asanuma et al 2003), and others (Roman et al 2003), have used noninvasive techniques to show that atherosclerosis is more frequent and occurs at a younger age in patients with lupus. However, in addition to these structural atherosclerotic changes, the effects of lupus on functional vascular responses are of interest since endothelial dysfunction may predispose to atherosclerosis, participate in its pathogenesis, and predict prognosis (Gonzalez and Selwyn 2003; Davignon and Ganz 2004). Therefore, strategies to identify the causes of endothelial dysfunction and to reverse it in

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populations with a high risk of coronary heart disease are of interest (Gonzalez and Selwyn 2003).

There is evidence that systemic lupus erythematosus is associated with endothelial dysfunction as determined by impaired flow-mediated dilation of the brachial artery (Lima et al 2002). This association has been reported to be independent of traditional cardiovascular risk factors, measures of disease activity, or drug therapy (El-Magadmi et al 2004; Johnson et al 2004). However, these studies either excluded patients with hypertension or hyperlipidemia, dichotomized corticosteroid exposure, or did not include novel cardiovascular risk factors such as homocysteine (Tam et al 2003), or lipoprotein (a) (Lp(a)). Both are suggested to play a role in the pathogenesis of vascular disease in patients with lupus.

We conducted a pilot investigation to study the relationship between endothelial function, measured as flow-mediated dilation of the brachial artery, and clinical characteristics, including novel cardiovascular risk factors, and cumulative exposure to corticosteroids in patients with lupus.

Methods

Twenty consecutive eligible patients older than 18 years of age were enrolled. They met the classification criteria for systemic lupus erythematosus; had duration of disease longer than one year; with no known cardiovascular disease; and were willing to undergo both electron beam computed tomography (EBCT) and measurement of flow-mediated dilation. These twenty patients were part of a larger cohort study to determine the prevalence of coronary calcification in lupus; details regarding their enrollment, clinical characteristics, the collection of clinical data and performance of laboratory tests, and EBCT have been published (Asanuma et al 2003). Post-ischemic flow-mediated dilation of the brachial artery, a noninvasive technique to measure endothelium-dependent, nitric oxide mediated responses in vivo (Corretti et al 2002) was performed and analyzed as we have described elsewhere (Dishy et al 2001). Flow-mediated dilation was expressed as the percent change in diameter of the brachial artery comparing resting and peak post-occlusion measurements. Nitroglycerin (0.4 mg sublingual) was administered to explore endothelium-independent dilation.

Spearman correlation coefficients were used to evaluate the association between flow-mediated dilation and the continuous variables. Mann Whitney-Wilcoxon tests were used to compare the distribution of flow-mediated dilation scores between different levels of categorical variables. No corrections for multiple comparisons were performed because we are presenting nonsignificant as well as significant results (Senn 1997) in a setting where the goal of data exploration was to generate hypotheses. All analyses used a two-sided significance level of 5% and were performed with the use of SAS software, version 8.02 (SAS institute, Cary, NC, USA).

Results

The demographic characteristics and cardiovascular risk factors for the twenty patients and their relationship to flow-mediated dilation are shown in Tables 1 and 2. A longer duration of corticosteroid use was associated with reduced flow-mediated dilation (Spearman correlation coefficient [RHO] = –0.44, p = 0.05). Although statistically non-significant, directionally similar findings were found for current

Table 1 Characteristics of patients with systemic lupus erythematosus

Categorical variables	Number	
Female sex	17	(85%)
White race	16	(80%)
Current smokers	6	(30%)
Hypertension	11	(55%)
Current use of hydroxychloroquine	12	(60%)
Current use of corticosteroids	16	(80%)
Current use of antihypertensives	11	(55%)
Current use of statins	3	(15%)
Postmenopausal status	5	(29%)
Presence of coronary calcium	6	(30%)
Age (years)	42.5	(32.0–47.5)
Body mass index (kg/m^2)	29.9	(26.8–33.1)
Systolic blood pressure (mm/Hg)	122.5	(114.0–141.0)
Diastolic blood pressure (mm/Hg)	80.5	(74.0–87.0)
Disease duration (years)	5.5	(4.0–11.0)
Pack years smoking	0	(0–14)
Framingham risk score	5	(1–9)
SLE disease activity index (SLEDAI)	3	(0–6)
SLE disease damage index (SLICC)	1	(0–1)
Total hemolytic complement	199.5	(175.0–288)
Erythrocyte sedimentation rate (mm/h)	25	(10–51)
C-Reactive protein (mg/dL)	0.4	(0.4–1.0)
High-density lipoprotein cholesterol (mg/dL)	42.5	(33.0–56.0)
Low-density lipoprotein cholesterol (mg/dL)	102.0	(77.0–136.0)
Triglycerides (mg/dL)	133.5	(73.5–156.5)
Lipoprotein(a) (mg/dL)	30.0	(15.5–58.5)
Homocysteine (μmol/L)	9.2	(7.7–11.5)
Coronary calcium (Agatston units)	0	(0–17.6)
Corticosteroid duration (years)	5	(4–9.5)
Corticosteroid cumulative dose (g)	33.2	(8.9–74.8)

Values are median (interquartile range) or number (%).
Abbreviations: SLE, systemic lupus erythematosis.

Table 2 Relationship of patients' characteristics and flow-mediated dilation (FMD)

Categorical variables	FMD (%) Median (IQR) Present	Absent	p-values
Female sex	3.9 (1.8–8.3)	3.3 (–0.4–3.5)	0.15
White race	3.9 (1.3–8.8)	3.6 (3.5–3.9)	0.89
Current smokers	2.6 (1.0–3.7)	4.0 (3.3–8.3)	0.32
Hypertension	3.5 (1.8–4.5)	4.2 (1.0–9.4)	0.55
Current use of hydroxychloroquine	3.6 (1.7–8.8)	3.7 (1.4–4.3)	0.57
Current use of corticosteroids	3.5 (1.7–4.3)	10.9 (5.4–11.1)	0.11
Current use of antihypertensives	3.6 (2.6–5.5)	3.9 (0.5–10.1)	0.91
Current use of statins	1.8 (–2.8–3.5)	3.9 (3.3–8.3)	0.13
Postmenopausal status	1.8 (1.0–3.7)	4.3 (3.5–8.8)	0.24
Coronary calcium	2.1 (–0.4–3.6)	4.0 (3.5–8.3)	0.12

Continuous variables	Spearman correlation coefficient	p-values
Age (years)	–0.08	0.74
Body mass index (kg/m^2)	0.00	0.98
Systolic blood pressure (mm/Hg)	–0.20	0.41
Diastolic blood pressure (mm/Hg)	–0.34	0.14
Disease duration (years)	–0.26	0.26
Pack years smoking	–0.09	0.71
Framingham risk score	–0.27	0.25
SLE disease activity index (SLEDAI)	–0.05	0.85
SLE disease damage index (SLICC)	–0.26	0.27
Total hemolytic complement (units)	0.11	0.65
Erythrocyte sedimentation rate (mm/h)	–0.19	0.42
C-Reactive protein (mg/dL)	0.02	0.94
High-density lipoprotein cholesterol (mg/dL)	–0.15	0.54
Low-density lipoprotein cholesterol (mg/dL)	–0.14	0.55
Triglycerides (mg/dL)	–0.20	0.41
Lipoprotein(a) (mg/dL)	0.04	0.86
Homocysteine (μmol/L)	–0.27	0.26
Coronary calcium (Agatston units)	–0.37	0.11
Corticosteroid duration (years)	–0.44	0.05
Corticosteroid cumulative dose (g)	–0.39	0.09
Corticosteroid maximum dose (g)	–0.43	0.06

Abbreviations: IQR, interquartile range; SLE, systemic lupus erythematosis.

corticosteroid use ($p = 0.11$), cumulative corticosteroid dose ($p = 0.09$), and maximum oral corticosteroid dose ($p = 0.06$).

Duration of corticosteroid use (RHO = –0.08, $p = 0.73$), cumulative dose of corticosteroid (RHO = 0.12, $p = 0.62$), current corticosteroid use ($p = 0.33$) and presence of coronary-artery calcification ($p = 0.25$) were not significantly associated with endothelium-independent, nitroglycerin induced vasodilation.

Discussion

Our findings suggest that in this population of patients with systemic lupus erythematosus with no known cardiovascular disease, duration of corticosteroid therapy was significantly associated with decreased flow-mediated dilation and that cumulative and current corticosteroid use trended in the same direction. In contrast, Lima et al (2002) found no association between flow-mediated dilation and corticosteroid use. A possible reason for this difference is that Lima et al (2002) excluded patients with cardiovascular risk factors such as smoking, hypertension, and hypertriglyceridemia. It is possible that the adverse effects of corticosteroids on endothelial function may be more marked in patients with cardiovascular risk factors. Given the result of Spearman correlation coefficient analysis, 20% of the variation in flow-mediated dilation is explained by corticosteroid duration.

Age, disease duration, disease activity, and acute phase reactants were not significantly associated with flow-mediated dilation. There was no significant association between flow-mediated dilation and any traditional or novel cardiovascular risk factors, such as homocysteine and Lp(a). However, these negative findings should be interpreted with caution because they may be the result of lack of power to detect significant associations due to the small number of patients ($n = 20$). Thus, larger studies are required to confirm our findings.

Glucocorticoids have been postulated as potential risk factors for atherosclerosis in patients with lupus for several years. (Urowitz and Gladman 1980) However, associations between corticosteroids and osteoporotic fractures, cataracts and coronary artery disease in these patients were more apparent when cumulative prednisone was evaluated, suggesting that time of exposure is an important determinant of damage associated with corticosteroid use. (Zonana-Nacach et al 2000). Previous studies of endothelial dysfunction in lupus have either included exposure of glucocorticoids as a dichotomous variable or have excluded individuals with hypertension and hyperlipidemia (Lima et al 2002; El-Magadmi et al 2004). This approach could have biased the results, and made it more difficult to show an association between glucocorticoids and endothelial dysfunction.

In addition, there was a trend for patients with coronary-artery atherosclerosis to have impaired flow-mediated dilation, but the number of patients with calcification was small and further studies to explore the relationship between structural measure of vascular damage and endothelial function will be of interest. The fact that none of the variables associated with decreased flow-mediated dilation were associated with decreased responses to nitroglycerin

suggests that the effects of corticosteroids may be on the endothelium itself, rather than nonspecific structural effects.

This preliminary study has several limitations. First, the power to estimate other significant associations is limited. Second, longer glucocorticoid use could be a marker of more severe disease over time. Third, the cross-sectional design may not be sufficient to assess the contribution of variables involving time such as disease activity over time. Fourth, as a pilot study, the association between time of exposure to corticosteroids and endothelial dysfunction is hypothesis-generating rather than definitive. Further studies are required to evaluate the role of disease severity and to evaluate the association between cumulative corticosteroid exposure and endothelial dysfunction that we have observed.

Acknowledgments

This work was supported by grants HL04012, HL65082, and GM 5MO1-RR00095 from the National Institutes of Health, USA, and a grant from the Lupus Foundation of America, Nashville Chapter, USA. Dr Asanuma was supported by Merck Sharp and Dohme Foundation International Fellowship in Clinical Pharmacology and by the Japan Research Foundation for Clinical Pharmacology.

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