Atherosclerotic Cardiovascular Disease in Systemic Lupus Erythematosus: the Beer Sheva Experience

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Abstract

Atherosclerotic disease is common in systemic lupus erythematosus and is the result of multiple pathogenic mechanisms that include traditional risk factors as well as SLE-related factors. Endothelial dysfunction and arterial stiffness contribute significantly to the atherogenic process. Dobutamine stress echocardiogram has not been shown to detect subclinical coronary artery disease; however, the high percentage of left ventricular outflow gradient requires further evaluation and follows-up studies.

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Accelerated atherosclerosis is a significant cause of morbidity and mortality in systemic lupus erythematosus. It is no longer a matter of dispute that SLE patients have an increased risk of developing atherosclerotic cardiovascular disease, particularly before the age of 50. The incidence of coronary heart disease in women with SLE aged 35–44 years has been estimated to be 50-fold greater than in the general population, and the cumulative prevalence of CAD in SLE patients was 8.9%. Early detection and management of atherosclerosis may reduce the morbidity and improve the survival of patients with SLE [1].

One of the primary objectives of the Soroka Medical Center Lupus Clinic is directed at unraveling the prevalence of atherosclerotic CVD in SLE as well as identifying possible pathogenic mechanisms and searching for early detection of clinical and subclinical CVD in patients with SLE.

Prevalence of atherosclerosis in SLE

We used ultrasonic biopsy to detect intimal and medial changes in the common carotid and common femoral arteries of patients with SLE and their matched controls. Ultrasonic biopsy is a non-invasive technique able to recognize early atherosclerotic changes in the blood vessel walls. The technique identifies alterations in the morphology of the posterior wall and atherosclerotic plaques and it has a high predictive value for development of symptomatic CVD [2].

Fifty-one consecutive SLE patients and their matched healthy contols were enrolled in the study [3]. The major outcome measures included the intima-media thickness of the posterior wall and the mean total ultrasonic biopsy score of the four vessels. This score ranges between 0 and 40, where a score of 0 indicates that all four vessels are normal and a score of 40 signifies symptomatic plaques in all vessels. We found that SLE patients have a high frequency of abnormal common carotid and common femoral arteries. This abnormality is manifested by early (pre-plaques) changes as well as by atherosclerotic plaques.

The intima-media thickness of the vessels of the cases and controls were not statistically different. However, the total ultrasonic biopsy score for patients with SLE was 1.8 times higher than that of the controls. Patients with SLE had significantly higher rates of atherosclerotic plaques with an odds ratio of 3.17; and 28% of the SLE patients had atherosclerotic plaque in at least one of the four vessels compared with only 10% in the control group. Similarly, 67% of the controls had normal scores in all vessels compared with only 37% of the SLE patients.

Univariate analysis identified that carotid and femoral atherosclerotic plaques were strongly associated with the age of patients, hypertension, CAD and stroke. Multivariate analysis revealed that atherosclerosis was significantly associated with age and marginally with hypertension.

Mechanisms of atherosclerosis in SLE

The etiology of the accelerated atherosclerosis in SLE in not known, but it has been linked to inflammation and endothelial dysfunction, a consequence of the inflammatory process [4].

Flow-mediated dilatation is a non-invasive method of measurement of endothelial dysfunction. It is based on the change in diameter of a conduit artery in response to increased flow, typically induced by a period of ischemia in the distal circulatory bed. FMD is depressed in subjects with atherosclerosis and cardiovascular risk factors [5]. We assessed endothelial dysfunction in patients with SLE and patients with essential hypertension and healthy controls using FMD [6]. Measurements of the brachial artery diameter were recorded: at rest; after FMD, defined as endothelium-dependent dilatation; and after the administration of 0.4 mg sublingual nitroglycerin spray, defined as endothelium-independent dilatation. The maximal percentage of increment in the diameter of the brachial artery was highest in the control group as compared to the SLE and essential hypertension patients. The percentage of change from baseline diameter was 13.5% (6.9)

SLE = systemic lupus erythematosus
CAD = coronary artery disease
CVD = cardiovascular disease

FMD = flow-mediated dilatation

in the SLE patients, 16.3% (6.9) in the essential hypertension group and 19.3% (8.3) in the control group ($P = 0.057$). The ratio between endothelial-independent dilation/endothelial-dependent dilatation was lowest in the control group versus patients with SLE and essential hypertension (1.1 ± 0.2 versus 1.6 ± 0.4 and 1.8 ± 0.7 respectively, $P < 0.001$).

In a subsequent study we performed digital arterial pulse wave analysis during deep breathing using the CardioMeter device (unpublished data). The device provides data regarding three physiologic indices: arterial stiffness, arterial flow, and heart rate variability [7]. The study included 40 women with SLE and 40 matched controls. For this test, the measures are a flow score and the augmentation index. The flow score was higher among SLE patients (4.38 ± 3) than in control patients (3.72 ± 2.5), though this comparison did not reach statistical significance ($P = 0.09$). The augmentation index was also higher among SLE patients (0.93 ± 0.2) compared with controls (0.91 ± 0.13) ($P = 0.08$). Correlation between the FMD testing and the CardioMeter testing was high. We are currently conducting further studies to determine the significance of the CardioMeter testing.

Screening for subclinical atherosclerotic disease

Chest pain or discomfort characteristic of angina is less common as a presenting symptom of ischemic heart disease in women compared with men. In addition, non-invasive stress testing for CAD in women demonstrates higher levels of test variability compared with men. Dobutamine stress echocardiogram has been validated particularly in the setting of intermediate pre-test probability for CAD, and it has the highest sensitivity and specificity for women [8].

We performed DSE in 30 consecutive SLE women without known CAD [9], 70% of whom had complained of chest discomfort or dyspnea prior to testing. All the DSE studies were negative for myocardial ischemia. Left ventricular function was normal in all patients. None of the patients had ventricular hypertrophy or obstructive cardiomyopathy. A left ventricular outflow gradient developed in 15 of 28 patients during the infusion of dobutamine. The mean gradient was 46.3 mmHg (range 16–109). This gradient resolved in all the patients during the recovery period following the study. This rate of LVOG is much higher than the 16% rate seen in non-SLE patients at our center and is more than double the reported rate in the general population. The data indicate that DSE is not a sensitive tool for detecting subclinical CAD before the development of critical stenosis. It has been suggested that the LVOG might be responsible in an unclear mechanism for the symptoms of chest pain and that treatment of this group of patients with beta-adrenergic blocking drugs completely alleviates these symptoms [10].

DSE = dobutamine stress echocardiogram
LVOG = left ventricular outflow gradient

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