Premature Atherosclerotic Cardiovascular Disease and Systemic Lupus Erythematosus
From Bedside to Bench

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Abstract
Cardiovascular morbidity and mortality in SLE is increased in patient with established disease, and SLE itself has been determined to be an independent risk factor for cardiovascular events. Autopsy studies have demonstrated that the coronary vessels of SLE patients have atherosclerotic plaque, and most cardiovascular events are not attributable to active vasculitis. It is believed that patients with inflammatory disease, including SLE, are more likely to have vulnerable plaque rupture, accounting for more frequent events. Elevated homocysteine levels have been associated with the presence and progression of atherosclerotic plaque. Enzyme polymorphisms involved in the folate-homocysteine pathway do not seem to contribute to differences in homocysteine concentration or atherosclerotic plaque. Recently, endothelial dysfunction has been identified as an early abnormality in ASCVD, and has been demonstrated in the vessels of SLE patients. Premature cardiovascular disease in SLE patients is likely attributable to the consequences of inflammation. There is preliminary evidence that type I interferons may be the initial stimulation of the cascade of atherosclerotic development, starting with endothelial damage, and abnormal vascular repair.

Cardiovascular disease remains the leading cause of death in females and, despite advances in prevention and therapy, deaths due to cardiovascular disease are increasing in American women. Females have higher mortality rates and are less likely to receive standard interventions after myocardial infarction than males.1,2 In systemic lupus erythematosus (SLE), it has been known for a long time that there is a bimodal mortality, with early mortality attributable to complications of glomerulonephritis, neuropsychiatric lupus, and infection, whereas late mortality is usually attributable to cardiac and cerebrovascular events.3 This cardiovascular mortality in SLE is significant, even after adjusting for traditional Framingham risk factors; SLE has been determined to be an independent risk factor for cardiovascular events. Unfortunately, to date, no risk factor or group of risk factors has been uniformly helpful in predicting which patients will have atherosclerotic cardiovascular events.4,5 A recent study suggested that a favorable risk profile in otherwise healthy young females confers a low risk of atherosclerotic cardiovascular disease (ASCVD) mortality, but that an accumulation of risk factors increases the mortality hazard ratio.6 These observations, in conjunction with the known prevalence of premature ASCVD in SLE patients, emphasize the double jeopardy for young females with SLE who are particularly vulnerable to under-diagnosis and inadequate treatment. Nonetheless, the development of novel laboratory biomarkers, the identification of genetic polymorphisms linked to cardiovascular risk factors, and new imaging techniques have all held the promise of a better prediction of SLE patients who are at an increased risk of cardiovascular events.

Vulnerable Plaque Rupture
Autopsy studies have demonstrated that the coronary vessels of SLE patients have the usual atherosclerotic plaque, and that most cardiovascular events are not attributable to active vasculitis.7,8 However, atherosclerotic plaque development is now better understood. Not all cardiovascular events are due to large obstructive plaques. Smaller plaques susceptible to plaque rupture can cause occlusive events. In general, acute coronary syndromes are caused by acute disruption of unstable atheroma. It is believed that patients...
with inflammatory disease, including SLE, are more likely to have vulnerable plaque rupture. These unstable atheromatous plaques have three histologic components: a large lipid core, many inflammatory cells, and a thin fibrous cap. It is postulated that systemic inflammation causes the fibrous cap to be thinned, with decreased smooth muscle synthesis and increased collagen breakdown. A recent autopsy study on patients with rheumatoid arthritis found that vulnerable plaques were more common in RA patients than in controls. In addition, inflammation was observed more frequently in the media of the left circumflex and the adventitia of the left anterior descending artery in patients with rheumatoid arthritis, compared to controls. It is postulated that the same process of a vulnerable plaque rupture occurs in patients with SLE. As well, it is postulated that the process of plaque destabilization begins with endothelial activation. Endothelial activation occurs more commonly in SLE patients due to upregulation of inflammatory cytokines, as discussed further below.

**Homocysteine: A Marker of ASCVD in SLE**

One noninvasive way of measuring ASCVD and plaque burden is to image calcification within the coronary vessel. Coronary artery calcification (CAC) is present in atherosclerotic plaque and is usually the tip of the atherosclerotic iceberg. It is an active process, which can occur early in coronary atherosclerotic plaque development. It is regulated in a fashion similar to bone mineralization, and it is very specific for the presence of atherosclerotic plaque. One way to measure CAC is to use electron beam computed tomography (EBCT). In this method, tomographic scanning of epicardial coronary arteries is performed in rapid thin slice (1.5 to 3 mm) segments, and calcium deposits are detected in the walls of coronary arteries. The scans are triggered by EKG (electrocardiogram) during late diastole, with a breath hold. The procedure takes about 15 minutes and requires no IV contrast. Deposits as small as 2 mm can be seen. The specificity of the technique is near 100%; the sensitivity is 95% for angiographic lesions with more than 50% stenosis and 50% for lesions with 20% stenosis. EBCT has been utilized in longitudinal studies, where the degree of CAC was shown to correlate with future ASCVD events in asymptomatic subjects. The limitations to EBCT include obesity and breast attenuation.

The calcification score is reported as a raw score and also may be reported as an age and gender-adjusted score relative to that of historical age and sex-matched controls as a percentile category. The adjusted scores are important in evaluating patients who are nontraditional cardiovascular risk patients. These patients may have low calcification scores; nevertheless, they may have a calcification score that is much higher than an age- and sex-matched controls. In our study, we looked at female SLE patients between the ages of 25 and 65 who met the American College of Rheumatology (ACR) criteria for the diagnosis of SLE and compared them to a control population that was age, race, and gender matched. We found that more SLE patients than controls had CAC (p = 0.009) and their scores were significantly higher (87.9 vs. 9.6, p = 0.002) than controls. For both groups, those with CAC were approximately 10 years older than those without. In addition to age, a significant determinant of positive CAC status in both groups was the number of cardiovascular risk factors. In patients with SLE, CAC was associated with a higher homocysteine concentration, a lower glomerular filtration rate (GFR), and longer disease duration. In contrast, in controls, total cholesterol and BMI (body mass index) correlated positively with CAC. When multivariate logistic regression method was applied to candidate explanatory variables, homocysteine concentration, age, and disease duration contributed significantly to CAC status. Other groups have also shown that subclinical atherosclerosis, measured either by CAC or carotid duplex ultrasound, is more common in SLE patients than age matched controls, and the prevalence is about one-third of the cohorts studied.
Folate-Homocysteine Pathway

Since homocysteine appeared important in the presence and progression of ASCVD, we looked at whether enzyme polymorphisms involved in the folate-homocysteine pathway could be contributing to the differences in homocysteine concentration in SLE patients. Seven functional polymorphisms and six genes in the folate homocysteine pathway were considered: 5,10-methylenetetrahydrofolate reductase (MTHFR) 677C > T, MTHFR 1298A > C, cystathionine β synthase (CBS) 844ins68, methionine synthase (MTR) 2756A > G, methionine synthase reductase (MTRR) 66A > G, thymidylate synthase (TYMS) 1494del6, and dihydrofolate reductase (DHFR) c.86 + 60_78 in 163 SLE patients and 160 controls. We found that homocysteine levels were higher in African-American than in Caucasian SLE patients and African-American controls. Genotype distributions were significantly different in African-American and Caucasian controls for six of the seven polymorphisms. However, genotype distributions for each polymorphism did not differ significantly between SLE patients and controls, even after stratification by race. GFR was negatively correlated to homocysteine levels and, therefore, was adjusted as a covariate in the models of the effects of the polymorphisms on homocysteine levels. In SLE patients, none of the seven polymorphisms were associated with homocysteine concentrations. There were no genotypic associations with median CAC scores in either SLE patients or controls, with and without stratification by race. Our conclusion, therefore, was that polymorphisms and folate homocysteine metabolizing enzymes did not predict higher homocysteine levels or CAC scores in SLE patients.

In a recent publication, higher C3 correlated with plaque progression, although this group did not report on homocysteine in their SLE cohort. Therefore, the search for novel biomarkers or genetic polymorphisms that may predict or more closely correlate with ASCVD in SLE patients is still under investigation. Insulin resistance has been linked to ASCVD in SLE patients; however, the literature is mixed and remains controversial.

Endothelial Dysfunction in SLE

More recently, endothelial dysfunction has been identified as an early abnormality in ASCVD. It is felt that the initial factor in atheroma formation is endothelial cell injury. Vascular damage repair is mediated by bone marrow-derived endothelial progenitor cells (EPCs) and myelomonocytic-circulating angiogenic cells (MCACs). In patients with ASCVD, abnormal vascular repair and a decreased number and abnormal function of EPCs and MCACs have been identified. More recently, Denny and coworkers (Kaplan’s group) have identified that EPCs are decreased in SLE patients, and the decreased EPC numbers correlate with disease activity indices in SLE. In vitro studies identified that these EPCs and MCACs in SLE patients are abnormal in the capacity to become mature endothelial cells with proangiogenic stimulation. Additionally, her group found that interferon alpha induces EPC and MCAC apoptosis.

In light of the cumulative data that lupus patients have an interferon signature that correlates with disease activity and severity, it may be that interferon alpha is the primary cytokine mediator of accelerated atherosclerosis in SLE patients.

In summary, premature ASCVD in SLE patients is likely attributable to the consequences of inflammation. Upregulation of interferon alpha may be the initial stimulation of the cascade of atherosclerotic development, starting with endothelial damage, and abnormal vascular repair. Homocysteine has been determined to be a marker for the presence and the progression of ASCVD. It may be a useful initial first test in the evaluation of SLE patients to determine subclinical atherosclerotic disease. To date, it appears that genes involved in homocysteine metabolism do not contribute to hyperhomocysteinemia or atherosclerosis in SLE patients. Future studies may identify candidate genes that increase the risk of ASCVD in SLE patients.

Disclosure Statement

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References


