SYSTEMIC LUPUS ERYTHEMATOSUS:
PATHOGENESIS, CLINICAL MANIFESTATIONS AND DIAGNOSIS

IN-DEPTH DISCUSSION II

Atherosclerosis in systemic lupus erythematosus

In 1974, Urowitz et al. [1] described the bimodal pattern of mortality in systemic lupus erythematosus (SLE) and found a second mortality peak in the long term outcome of SLE patients. Several epidemiological studies have analyzed this fact, suggesting the existence of an early and accelerated atherosclerosis in these patients. This condition has been recognized clinically with the diagnosis of coronary artery disease (CAD), namely myocardial infarction and angina, in young women with SLE, as well as cerebrovascular disease. In the largest series of SLE patients described since 1970, 6-20% of deaths were due to cardiovascular disease and 4-15% of deaths were due to cerebrovascular disease [2-4].

ETIOLOGICAL FACTORS OF ATHEROSCLEROSIS IN SLE

There is increasing evidence that traditional risk factors do not explain completely the atherosclerotic process in SLE, and recent studies have implicated new etiopathogenic factors.

Traditional risk factors for atherosclerosis

SLE patients have a high prevalence of “traditional” risk factors for atherosclerosis, related to clinical conditions and treatments received. Nephritis may be associated with hypertension, nephrotic syndrome may cause hyperlipidemia, and arthritis and fatigue may reduce a patient’s ability to exercise. These factors, along with smoking, obesity, diabetes mellitus and chronic renal failure may contribute to the increased prevalence of CAD in patients with SLE. In a 10-year prospective study of a cohort of 70 patients with lupus nephritis, the main causes of mortality were vascular complications (cardiovascular or cerebrovascular events) [5]. Additionally, the autopsy study of Bulkley and Roberts [6] showed that coronary atherosclerosis is a post-steroid era phenomenon. Petri et al. [7] have demonstrated that prednisone could indirectly accelerate atherosclerosis by increasing the levels of three traditional CAD risk factors, namely hypercholesterolemia, hypertension and obesity.

Steroid therapy is associated with increased total cholesterol, very low density lipoproteins cholesterol (VLDL-C) and low density lipoproteins cholesterol (LDL-C). Thus, corticosteroid treatment may accelerate atherosclerosis by worsening hypertension, hyperlipidemia, and diabetes mellitus, and by causing musculoskeletal morbidity that results in reduced physical activity.
Other risk factors implicated in cardiovascular events in SLE patients include older age at SLE diagnosis. In a recent study [8], the incidence of stroke and myocardial infarction in SLE was estimated after controlling for expected events based on known population based risk models. After adjustment for the classical risk factors, the risk for myocardial infarction and stroke was significantly increased, suggesting that the diagnosis of SLE or its treatment is the strongest known risk factor for cardiovascular disease in these patients.

**New risk factors for atherosclerosis**

Several studies have shown that lipid abnormalities occur in untreated SLE patients. This dyslipoproteinemia is characterized by elevated triglycerides and VLDL-C as well as reduced levels of high-density lipoprotein cholesterol (HDL-C) and apolipoprotein (Apo) A-1. Some authors have also found abnormalities in chylomicron (CM) clearance due to disturbances in their metabolism, characterized by decreased lipolysis and CM removal from the plasma. These facts, as well as the basal pattern of lipid abnormalities of the untreated disease, suggest that SLE disease process directly influences the metabolism of VLDL-cholesterol.

Elevation of serum homocysteine has recently been recognized as a risk factor for CAD in the general population. Some studies in SLE have found raised homocysteine levels and their association with an increased risk for arterial thrombotic events in SLE.

Currently, there is great interest in examining the role of inflammation in the pathogenesis of atherosclerosis. Several studies have reported that modest elevations in C-reactive protein or serum amyloid A seems to identify a subset of patients with a worse prognosis from CAD. In SLE, Manzi et al. [9] have recently reported an association between atherosclerosis and inflammatory markers, such as C-reactive protein and fibrinogen.

The pathogenesis of cardiovascular disease in SLE is likely multifactorial, involving an interaction between inflammation-induced and antiphospholipid antibody (aPL)-mediated vascular injury/thrombosis from the underlying disease as well as traditional risk factors. Many studies have shown the association of anticardiolipin antibodies (aCL) and the presence of CAD in SLE.

Antibodies to lipoproteins are consistently found in SLE, including antibodies to β-2-glycoprotein I -which is an HDL associated protein that have prognostic significance for the inflammatory process in SLE, as well as antibodies to other HDL-associated proteins such as apoA-1 and apoA-2.

Vaarala et al [10] described in 1993 the existence of a cross-reaction of antibodies to oxidized LDL as a possible mechanism involved in the development of accelerated atherosclerosis in SLE. It is conceivable that antibodies to oxidized LDL may enhance the accumulation of oxidized LDL in the endothelial cell walls.
DIAGNOSIS OF SUBCLINICAL CARDIOVASCULAR DISEASE IN SLE

The diagnosis of the asymptomatic atherosclerotic disease in SLE may lead to an early and effective treatment of atherosclerosis with a preventive effect over their clinical complications.

B-mode carotid ultrasound

The carotid arteries are easily accessible to noninvasive studies using ultrasound techniques. This technique provides no risk or discomfort to the patient and, in trained hands, it can provide accurate and reliable measurements of atherosclerosis in its subclinical stages. B-mode ultrasound allows detection and measurement of the intima-media wall thickness (IMT) and the degree of plaques in the carotid arteries. IMT may be the most sensitive marker for the earliest stages of atherosclerosis and is considered to be a marker of generalized atherosclerosis.

Recent studies have analyzed and measured the IMT and identified the existence of atherosclerotic plaques in patients with SLE. Manzi et al. [9] have also studied the prevalence of carotid atherosclerosis and associated risk factors in 175 women with SLE, measuring the carotid plaque and the IMT by B-mode ultrasound. In addition, traditional cardiovascular risk factors were determined at the time of the ultrasound scan. The independent variables related to plaque development were older age, higher systolic blood pressure, higher levels of LDL cholesterol, prolonged treatment with prednisone and a previous coronary event.

Older age, a previous coronary event and elevated systolic blood pressure were also associated with an increased severity of the plaque. However, the risk factors related to increased IMT were older age, elevated pulse pressure and higher Systemic Lupus International Collaborating Clinics (SLICC) disease damage score.

Electron beam computed tomography

Currently, new technology provides a noninvasive way to evaluate directly the coronary arteries. Coronary artery scanning by electron beam computed tomography (EBCT) has been shown to detect noninvasively and accurately calcified atherosclerotic plaque by both intravascular ultrasound and histologic criteria.

Myocardial perfusion studies

Some studies have analyzed ischemia in SLE using coronary perfusion studies, such as thallium perfusion scan or dual-isotope myocardial perfusion imaging (DIMPI). These perfusion techniques rely on perfusion abnormalities, which could lead to a gross underestimation of the atherosclerotic burden and risk for future myocardial infarction.

PREVENTION AND TREATMENT

A well-optimized control of SLE should include management of hypertension and dyslipemia, minimizing steroid dose and controlling other factors such as obesity or smoking. In addition, clinicians should routinely evaluate these patients for atherosclerotic risk factors and aggressively treat any that are present.

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Some authors suggest a more aggressive management of the lipid abnormalities in patients with SLE. Hallegua and Wallace [11] recommended that SLE patients should be started on lipid lowering agents earlier and the doses of these medications could be increased to maximal doses in order to keep the LDL levels at the recommended level of \( \leq 130 \text{mg/mL} \) if patients do not have any symptoms of CAD. If CAD is present, then LDL levels should be reduced to \( \leq 100 \text{mg/ml} \), or to a level as low as possible.

There is a growing body of evidence that antimalarial agents may have beneficial effects on lipid profiles in SLE. Several studies have correlated the use of antimalarials with a reduction in cholesterol or triglyceride levels.

**FINAL REMARKS**

The marked increased morbidity and mortality in SLE from accelerated atherosclerosis requires a higher state of vigilance in our SLE patients, and they must be monitored closely for symptoms and signs of CAD. Primary prevention of CAD is of paramount importance by checking and treating hyperlipidemia, hyperglycemia and hypertension, counseling patients to stop smoking, exercise and help them lose weight. We should use the lowest dose of corticosteroids, adding other drugs, such as antimalarials or immunosuppressive agents. Finally, clinicians should be proactive in the use of non-invasive techniques in the screening for CAD.
REFERENCES


