Systemic lupus erythematosus (SLE) is a chronic inflammatory disease of unknown cause that can affect any organ, and is characterized by a wide range of autoantibodies. Several studies of large cohorts of SLE patients have reported an increased prevalence of symptomatic subclinical cardiovascular disease (CVD). It is currently believed that accelerated atherosclerosis in SLE results from a combination of numerous risk factors. In addition to a high prevalence of traditional risk factors, inflammatory processes in SLE are considered to be important in atherogenesis. Chronic activation or damage to the endothelium in SLE may trigger the inflammatory cascade and thereby promote atherogenesis. Several forms of endothelial insult are being recognized in SLE, including hypercholesterolemia, hyperhomocysteinemia, mechanical stress from hypertension, increased oxidative stress and immunologic injury as a result of immune complex deposition. This review updates the modifiable risk factors in SLE. The main focus is on the potential utility of these risk factors. The putative mechanisms of accentuated risk as a result of underlying inflammation, and evidence for association with premature atherosclerosis are discussed. Strategies that may be useful in preventing the progression of atheroma in this population include close monitoring and aggressive treatment of the traditional risk factors as in patients with high risk of CVD. The role of antioxidants and immunomodulators are also explored.

Key words: atherosclerosis, homocysteine, hyperlipidemia, oxidative stress, risk factors, systemic lupus erythematosus
Premature atherosclerosis in SLE

WHY ARE SLE PATIENTS AT INCREASED RISK OF PREMATURE ATHEROSCLEROSIS?

It is currently believed that atherosclerosis in the general population results from a combination of numerous risk factors. In addition to traditional risk factors, inflammatory processes are now considered to be important in atherogenesis [13]. The healthy endothelium is involved in the maintenance of short-term blood pressure and flow homeostasis and prevention of unwarranted clotting. The endothelium responds to increased blood flow or pressure, activating protein kinase B, which stimulates the production of the vasodilators nitric oxide (NO) and prostaglandin I, [14,15]. The enzymes associated with their production, NO synthase and phospholipase A2, can also be activated by increased intracellular calcium levels triggered by the coagulation cascade, in which NO and prostaglandin I, have an inhibitory role. The functioning endothelium also produces the vasoconstrictors thromboxane and endothelin-1, excessive levels of which may be associated with hypertension [16]. Loss of the functional integrity of the endothelial cell lining following injury triggers a cascade involving the coagulation, kinin, complement, and fibrinolytic systems, which normally leads to repair of the injured site with restoration of normal function.

Inflammatory processes probably contribute to athrogenesis in SLE, a disease characterized by chronic inflammation. Chronic activation or damage to the endothelium may lead to imbalance in these interacting systems and thereby promote athrogenesis. Several forms of endothelial insult are recognized: chemical stress such as from smoking, hypercholesterolemia or hyperhomocysteinemia; mechanical stress from hypertension; and immunologic injury (Figure 1). Many of these factors have been reported to be present in patients with SLE [3,17,18]. In essence, it is believed that the interaction between traditional risk factors, inflammation-induced and antibody-mediated vascular injury or thrombosis, and immune dysregulation from the underlying disease, all play important roles in endothelial dysfunction that accelerate the atherosclerotic process in SLE, as depicted in Figure 2.

THERAPEUTIC OPPORTUNITIES

It is important that physicians caring for SLE patients are aware of the risk of CVD complications associated with this disorder since atheromatous disease is otherwise unusual in premenopausal women, except for diabetics. Modifiable risk factors should be monitored routinely if possible (Table). Once identified, the risk factors should be treated aggressively by...
Table. Potential treatment for the modifiable risk factors for premature atherosclerosis in systemic lupus erythematosus

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>Insulin or oral hypoglycemic agents</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Antihypertensives</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>Statins, antimalarial agents</td>
</tr>
<tr>
<td>Smoking</td>
<td>Smoking cessation</td>
</tr>
<tr>
<td>Obesity</td>
<td>Diet and exercise</td>
</tr>
<tr>
<td>Prothrombotic state</td>
<td>Antimalarial agents</td>
</tr>
<tr>
<td>Insulin resistance</td>
<td>Antimalarial agents</td>
</tr>
<tr>
<td>Low antioxidant levels</td>
<td>Antioxidant supplements</td>
</tr>
<tr>
<td>Hyperhomocysteinemia</td>
<td>Folic acid supplement</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>Smoking cessation, exercise, alcohol intake, estrogen, fibrates(?)</td>
</tr>
<tr>
<td>Lipoprotein(a)</td>
<td>Apheresis, estrogens, niacin, gemfibrozil, o3-fatty acids</td>
</tr>
<tr>
<td>Cytokines and inflammatory markers</td>
<td>Immunomodulating agents(?)</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>Angiotensin-converting enzyme inhibitor</td>
</tr>
</tbody>
</table>

Figure 1. Mechanisms and consequences of endothelial damage in patients with systemic lupus erythematosus (SLE).

Figure 2. Summary of the interaction between different risk factors leading to endothelial damage in systemic lupus erythematosus (SLE). Risk factors that can cause direct endothelial damage are shaded. APLS = antiphospholipid syndrome; HT = hypertension; LDL = low-density lipoprotein; oxLDL = oxidized low-density lipoprotein; β2GP1 = β2 glycoprotein 1; EDNO = endothelial derived nitric oxide.
means of patient education and lifestyle modification in terms of diet, exercise, smoking cessation and weight reduction. Other potential treatments for the modifiable risk factors are discussed in the following paragraphs.

**Antimalarial agents**

Hydroxychloroquine is the most commonly prescribed antimalarial medication for lupus and is useful in the management of mucocutaneous manifestations, arthritis and mild constitutional symptoms [19]. Hydroxychloroquine has many additional benefits in lupus patients. It has been reported to lower total and low-density lipoprotein (LDL)-cholesterol and triglyceride (TG) levels in patients with rheumatoid arthritis or SLE [20]. A cholesterol-lowering effect was also identified in a longitudinal cohort study of 264 SLE patients, with a mean follow-up time of 3 years: a dose of prednisone 10 mg was associated with an increase in serum cholesterol levels of 75 mg/L, which was offset by the use of hydroxychloroquine [21]. Use of hydroxychloroquine has also been shown to be associated with lower pulse wave velocity in premenopausal women, suggesting a potential protective effect against future development of major vascular disease [22].

The effects of antimalarials on fasting lipid profiles in SLE are scanty. We did a study on the relative effect of antimalarial agents on fasting lipid fractions in patients with active SLE [23]. A total of 123 patients were studied; 73.2% were taking prednisone (mean dose of 10.9 ± 9.2 mg/day), 48.0% were taking antimalarial agents and 30.8% were taking both. Total cholesterol, very-low-density lipoprotein (VLDL)-cholesterol, and LDL-cholesterol levels were significantly lower in patients taking antimalarial agents, particularly in those patients taking concomitant prednisone.

The lipid-lowering effect of antimalarial agents in lupus patients who are not on prednisone, and the effects on other lipoproteins, e.g. lipoprotein(a) levels, remain controversial [20,21,24,25]. Therefore, in another study, we investigated the effects of hydroxychloroquine in 65 SLE patients who were either on a low dose of prednisone or not on prednisone, and demonstrated that hydroxychloroquine had no significant effect on the serum lipid profile of these lupus patients with mild or inactive disease [26].

Hydroxychloroquine, a platelet inhibitor, has also been reported to reduce thromboembolic events in patients with SLE and antiphospholipid syndrome [27–29]. Antimalarials have been reported to significantly improve insulin resistance and glycemic control in SLE patients, with and without type 2 diabetes, which should also contribute to a reduction in cardiovascular risk [30].

**Statins**

As elevated cholesterol levels are a strong risk factor for future renovascular, cerebrovascular and cardiovascular events, lipid-lowering therapy is important. In addition to antimalarials, the 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, or statins, are not only useful in treating elevated cholesterol levels, but have also been shown to reduce cardiovascular events and total mortality in high-risk groups [31]. The statins may also be particularly useful for treating patients with SLE, as they appear to have additional antithrombotic and anti-inflammatory effects [32,33].

Atorvastatin significantly reduced arterial stiffness in patients with rheumatoid arthritis. The greatest improvements were seen in patients with more active disease, suggesting that, in addition to the beneficial effects of cholesterol reduction, immune modulation may contribute to the cardioprotective effect of statins [34]. However, lupus-like syndrome or severe acute hepatitis have been documented after taking statins [35–38]. An ongoing multicenter, randomized, controlled trial, Atherosclerosis Prevention in Pediatric Lupus Erythematosus (APPLE), testing the efficacy of statins in preventing premature atherosclerosis in children and adolescents with SLE will guide future therapeutic intervention [39].

**Antihypertensives**

Aggressive treatment of hypertension is important in reducing vascular events, particularly in patients with renal complications. In patients with high-risk renal disease, angiotensin-converting enzyme inhibitors (ACEIs), calcium channel blockers and β-blockers are all beneficial [40]. ACEIs may have benefits in addition to their blood pressure-lowering efficacy in the treatment of diabetic renal disease [41]. Reducing the level of microalbuminuria in diabetics is renoprotective and cardiovasculo-protective [42]. However, direct comparisons between ACEIs and other antihypertensives are not available in patients with SLE, and the merits of reducing the level of microalbuminuria in non-diabetic patients are uncertain.

**Folate supplementation**

A recent meta-analysis reported that in prospective studies, the increase in the risk of cardiovascular events due to elevated homocysteine levels is modest [43]. After adjustment for conventional cardiovascular risk factors, a 25% lower homocysteine level was associated with an 11% lower CVD risk and a 19% lower stroke risk. Folate supplementation to reduce homocysteine levels may be considered [44], but homocysteine levels are not routinely monitored. Folic acid may have beneficial effects independent of lowering
homocysteine levels [45,46], including antioxidant properties and upregulation of endothelial NO synthase [45]. Unfortunately, two recent randomized trials on folate supplementation did not show any beneficial effect on secondary prevention of CVD despite the lowering of homocysteine levels [47,48]. Therefore, the use of folate supplements cannot be recommended at this moment.

**Antioxidant supplementation**
The majority of the large-scale prospective studies on antioxidant vitamins, including vitamins C and E or a combination, failed to demonstrate any benefit in preventing CVD events [49], probably because the target populations already had established atherosclerotic disease. Since oxidative stress is involved in the early atherogenic process, antioxidant vitamins may be useful in preventing progression. Data suggest that supplementation with vitamins C or E alone can improve endothelial dysfunction in some conditions associated with increased oxidative stress [50–52], but not in other conditions [53–56]. We evaluated the effects of long-term antioxidant vitamins on markers of oxidative stress and antioxidant defence and endothelial function in 39 SLE patients [57]. Patients were randomized to receive either placebo or vitamins (500 mg vitamin C and 800 IU vitamin E daily) for 12 weeks. After treatment, plasma ascorbic acid and α-tocopherol concentrations were significantly increased only in the vitamin-treated group, associated with a significant decrease in plasma malondialdehyde level. Other oxidative stress markers and antioxidant levels remained unchanged in both groups. Flow-mediated dilatation, von Willebrand factor and plasminogen activator inhibitor-1 levels remained unchanged in both groups. The results showed that antioxidant supplementation only had a modest effect on lipid peroxidation, but did not affect other oxidative stress markers or endothelial function in patients with SLE, probably because the underlying inflammatory process was not suppressed.

**Anti-inflammatory agents**
As atherosclerosis is an inflammatory disease, corticosteroids could be expected to have an antiatherogenic effect, a possibility supported by one experimental study using an animal model [58]. In contrast, corticosteroids have well-known metabolic effects that could, in theory, be proatherogenic [21], and advanced atherosclerosis has been described in patients treated with steroids [59]. It should be noted that treatment is implemented due to higher inflammatory reactivity and a history of steroid treatment could simply reflect a higher inflammatory activity, which, per se, could be an important risk factor [60,61]. Relatively little is known about the role of other treatments in SLE in relation to CVD. One study did not find any association between other medications commonly used in SLE and CVD [60]. However, Roman et al [62] described a negative association between immunosuppression and atherosclerosis.

**Other potential agents**
The lack of standardized assays has limited the use of conditional risk factors such as fibrinogen and lipoprotein(a). A drug that specifically lowers fibrinogen levels is not yet available. Nevertheless, smoking cessation, exercise and reduced alcohol intake can lower fibrinogen levels [63]. Estrogen and fibrate lower both fibrinogen and lipoprotein(a) levels [64–67]. Niacin and ω3-fatty acids have been reported to lower lipoprotein(a) levels [68,69]. No outcome studies are available to show that lowering of these risk factors leads to a reduction in vascular events.

**Conclusion**
The importance of conventional risk factors in increasing the burden of atherosclerosis in the lupus population is well documented. Efforts need to be intensified to aggressively treat these and other modifiable risk factors or to prevent their onset as summarized in the Table. Well-conducted clinical trials are now needed to advance beyond these initial recommendations.

**REFERENCES**


