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# Accelerated atherosclerosis in patients with systemic lupus erythematosus: a review of the causes and possible prevention

## 系統性紅斑狼瘡患者中的加速動脈硬化症：成因及可能的預防方法之總覽

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 Systemic lupus erythematosus is an autoimmune disorder affecting multiple organ systems. Patients with systemic lupus erythematosus exhibit a bimodal pattern of mortality, with those who have had the disease for 5 to 10 years being at increased risk of cardiovascular disease, particularly myocardial infarction. Elevated levels of conventional cardiovascular risk factors promote vascular damage resulting in impairment of normal endothelial function. In addition, autoantibodies directed against oxidised lipoproteins, along with chronic secretion of inflammatory cytokines and suppression of fibrinolytic parameters, are thought to increase atherogenesis. Treatment with corticosteroids may also contribute to the accelerated atherosclerosis observed in these patients. This review discusses the accentuated relationship between conventional cardiovascular risk factors, systemic lupus erythematosus-induced inflammatory changes, and the early stages of atherogenesis and how careful monitoring of risk factors and use of appropriate therapies may reduce the progression of atheroma development in patients with systemic lupus erythematosus.

系統性紅斑狼瘡是一種影響多個器官系統的自體免疫疾病。系統性紅斑狼瘡患者的死亡率呈雙峰曲線，其中患病達5至10年的患者患心血管病，尤其是心肌梗塞的危險會增加。常規心血管危險因素程度的提高，增加了血管損傷的機會，使正常內皮功能遭破壞。此外，導引反氧化脂蛋白的自身抗體，連同發炎的細胞活素慢性分泌和溶解纖維蛋白參數的抑制，被認為會增加動脈粥樣化的形成。皮質類固醇治療也可能在這些患者中引發加速動脈硬化症。本文討論了常規心血管危險因素之間的重要關聯，系統性紅斑狼瘡引起的發炎的變化和動脈粥樣化形成的早期階段，以及如何仔細地監測危險因素和使用適當的治療來減少系統性紅斑狼瘡患者中動脈粥樣化的發展。

### Key words:

Arteriosclerosis;  
 Cardiovascular diseases;  
 Hong Kong;  
 Lupus erythematosus, systemic

### 關鍵詞：

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Systemic lupus erythematosus (SLE) is a systemic disease involving multiple organs that presents with a wide range of clinical manifestations and is characterised by autoantibody production.<sup>1</sup> The prevalence of this disorder has been reported to be four to five times higher in Hong Kong (260/100 000) than in Caucasian populations from the US (15-50/100 000) or UK (30/100 000).<sup>1</sup> Systemic lupus erythematosus primarily affects premenopausal (aged 16 to 55 years) females, who make up 90% of SLE cases.<sup>1</sup> It is uncommon in children and the elderly, but in these groups, one third of the patients are male. It has been thought that SLE carried a worse prognosis in Chinese patients,<sup>2</sup> but a recent study suggests that this is not the case.<sup>3</sup>

### Mortality and coronary artery disease

A bimodal mortality distribution in SLE patients was first reported in the late 1970s,<sup>4</sup> in a small 5-year prospective study of 81 patients, of whom 11 died.

The six early deaths resulted from active lupus nephritis or sepsis occurring in the first year of diagnosis. The five late deaths, which occurred after approximately 9 years, were attributed to myocardial infarction (MI). Other autopsy studies, however, reported that coronary artery disease (CAD) and MI only accounted for 4 to 5% of total deaths.<sup>5</sup> Studies of several large cohorts of US patients with SLE have reported the prevalence of CAD, presenting as angina pectoris, MI, or sudden death, as 8 to 15%.<sup>5-7</sup> Furthermore, traditional cardiovascular risk factors including diabetes, hypertension, and adverse lipid profiles [elevated total and low-density lipoprotein (LDL)-cholesterol and triglyceride levels] were also predictors of CAD in these studies, but corticosteroid therapy did not appear to increase risk.<sup>5-8</sup> The risk of hospitalisation resulting from acute MI and stroke in young female North American patients was approximately eight- and two-fold, respectively, that of age-matched controls, even after adjustment for multiple conventional CAD risk factors, suggesting that other factors associated with SLE may predispose to these events.<sup>9</sup> Improvements in patient management have reduced early deaths to one third the previous rate, particularly those from sepsis, but there have been concomitant increases in cardiovascular disease mortality rates.<sup>5</sup>

In addition, many patients with SLE are likely to have asymptomatic atheromatous vascular disease. In one study of 175 women (87% Caucasian; mean age, 44.9 years; standard deviation, 11.5 years), 40% had focal plaques identified in their carotid arteries by B-mode ultrasound,<sup>8</sup> which are often associated with atheroma in other vascular beds, especially the coronary arteries.<sup>10,11</sup> The high risk of CAD complications associated with SLE after adjustment for conventional risk factors has led to the suggestion that SLE itself is an independent cardiovascular risk factor.<sup>12</sup> Conventional and some novel risk factors for the development of atherosclerotic disease are listed in the Box. Epidemiological data thus highlight the high prevalence of both symptomatic and asymptomatic CAD in patients with SLE and the importance of conventional risk factors.

### Conventional risk factors in systemic lupus erythematosus

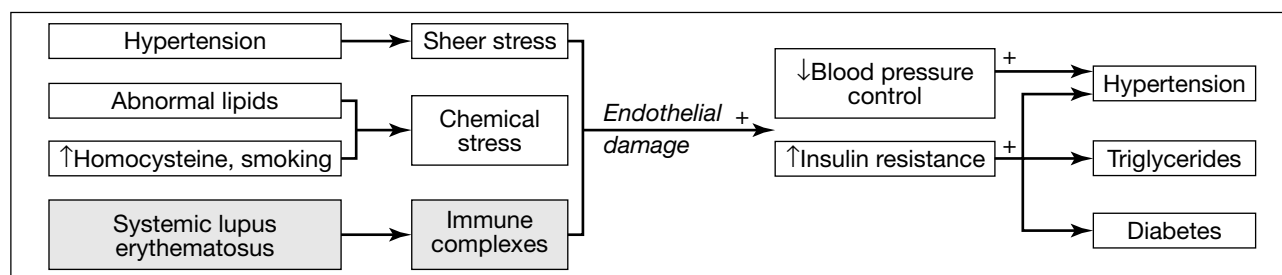
The healthy endothelium is involved in the maintenance of short-term blood pressure and flow homeostasis and

### Box. Risk factors for atherosclerosis in patients with systemic lupus erythematosus<sup>12,26,29,31</sup>

Non-modifiable risk factors
Ageing
Male sex
Genetic factors
Family history (shared genetic and environmental risk factors)
Modifiable risk factors
Diabetes mellitus
Hypertension
Dyslipidaemia (elevated low-density lipoprotein-cholesterol and triglycerides, low high-density lipoprotein-cholesterol)
Smoking
Obesity, particularly when centrally deposited
Insulin resistance
Fibrinogen
Lipoprotein(a)
Homocysteine
Cytokines (elevated plasminogen activator inhibitor, interleukins-1, 6, and 8, $\gamma$ -interferon, tumour necrosis factor- $\alpha$ , von Willebrand factor, and reduced tissue plasminogen-activator)
Low antioxidant levels (including reduced vitamins C, E, and $\beta$ -carotene)
Other risk factors (elevated thromboxane and thrombin and reduced prostacyclin)

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 prostacyclin (prostaglandin I<sub>2</sub> [PGI<sub>2</sub>]).<sup>13,14</sup> The enzymes associated with their production, NO synthase and phospholipase A<sub>2</sub>, can also be activated by increased intracellular Ca<sup>2+</sup> levels triggered by the coagulation cascade, in which NO and PGI<sub>2</sub> have an inhibitory role. The functioning endothelium also produces the vasoconstrictors thromboxane and endothelin-1, excessive levels of which may be associated with hypertension.<sup>15</sup>

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. Imbalance in these interacting systems, however, may promote atherogenesis. Several forms of endothelial insult are recognised: chemical stress such as smoking, hypercholesterolaemia or hyperhomocysteinaemia, mechanical stress from hypertension, and immunological injury (Fig 1). Many of these factors have been reported to be present in patients with SLE.<sup>16,17</sup>



**Fig 1. Mechanisms and consequences of endothelial damage in patients with systemic lupus erythematosus**

Development of systemic lupus erythematosus-induced immune complexes reduces endothelial function, promoting the development of complications associated with atherogenesis

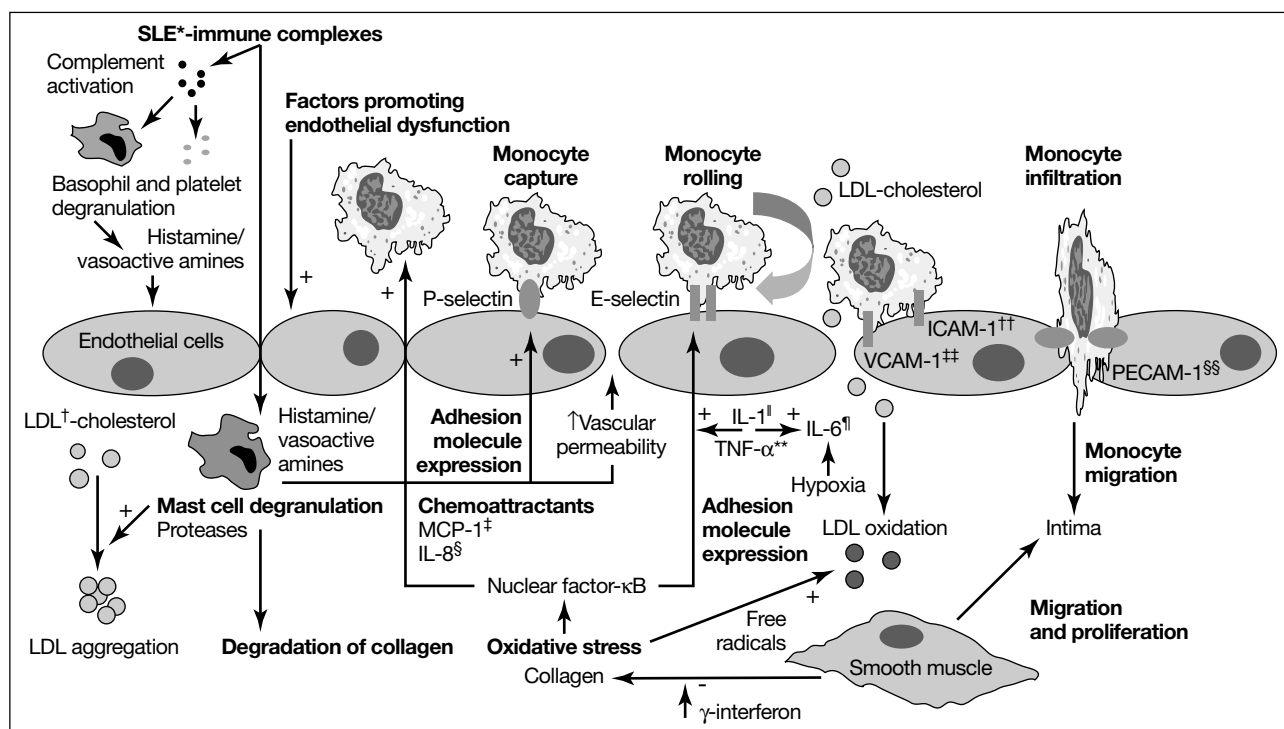
Both adult and paediatric SLE patients with untreated active disease present with an atherogenic lipid profile, with elevated triglycerides and very-low-density lipoprotein (VLDL)-cholesterol and reduced high-density lipoprotein (HDL)-cholesterol<sup>1</sup>—a profile similar to that of patients with diabetes. Elevated levels of interleukin-1 and  $\gamma$ -interferon have been reported to suppress lipoprotein lipase (LPL) activity.<sup>18,19</sup> Low LPL activity reduces the catabolism of triglyceride-rich VLDL and subsequent formation of LDL. Steroid therapy further elevates triglyceride levels, possibly through a similar effect on LPL activity,<sup>20,21</sup> or by promoting insulin resistance<sup>22</sup>—another risk factor for cardiovascular disease—which stimulates hepatic VLDL production.<sup>23</sup> In an inception cohort of 134 Caucasian SLE patients recruited from 1974 to 1987, 75.4% had raised total cholesterol levels ( $\geq 5.2$  mmol/L) within 3 years of diagnosis, sustained throughout the study in 40.3% of cases.<sup>24</sup> Coronary artery disease-related events occurred in 3.0% with normal cholesterol levels, 6.4% of the group with fluctuating levels of cholesterol, and 27.8% of those with sustained elevations of cholesterol. Furthermore, 79% of all CAD events occurred in the latter group.<sup>24</sup>

### Immunological mechanisms in systemic lupus erythematosus that contribute to atherosclerosis

The formation of immune complexes in patients with SLE is strongly associated with acceleration of atherogenesis.<sup>16,17</sup>

The presence of autoantibodies to  $\beta_2$ -glycoprotein-1 (also called cardiolipin or apolipoprotein H), an HDL-associated protein and major antigen for anticardiolipin antibodies, is strongly associated with inflammation in patients with SLE,<sup>16</sup> as are autoantibodies to components of oxidised LDL.<sup>17</sup> In patients with SLE, immune complexes activate complement, which in turn acts on mast cells and basophils to release vasoactive amines. These amines, which include histamine and 5-hydroxytryptamine, promote endothelial cell retraction and increased vascular permeability, induce the expression of endothelial adhesion molecules, and attract polymorphs that subsequently infiltrate the area of damage.<sup>25</sup> Thrombin and inflammatory cytokines such as interleukin-1, interleukin-6, and tumour necrosis factor- $\alpha$  are also involved in this process.

Following the trigger of adhesion molecule expression, preformed P-selectin is rapidly but transiently translocated to the endothelial surface, and within hours E-selectin is also expressed (Fig 2). Subsequently, integrin molecules on the leukocytes bind to immunoglobulin superfamily receptors. For example,  $\beta_2$ -integrins bind to intercellular adhesion molecule-1, and monocyte  $\alpha_4\beta_1$  integrin binds to vascular cell adhesion molecule-1 (VCAM-1).<sup>26</sup> These molecules promote the capture and rolling of the leukocytes.<sup>25</sup> Pro-oxidant molecules stimulate endothelial nuclear factor  $\kappa$ B (NF- $\kappa$ B), thereby promoting expression of



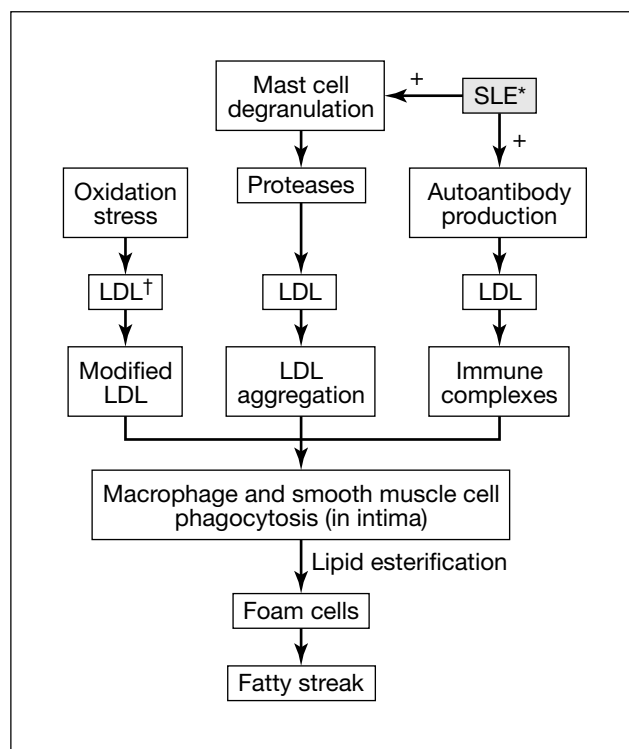
- \* SLE systemic lupus erythematosus
- † LDL low-density lipoprotein
- ‡ MCP-1 monocyte-chemotactic protein-1
- § IL-8 interleukin-8
- || IL-1 interleukin-1
- ¶ IL-6 interleukin-6
- \*\* TNF- $\alpha$  tumour necrosis factor- $\alpha$
- †† ICAM-1 intercellular adhesion molecule-1
- ‡‡ VCAM-1 vascular cell adhesion molecule-1
- §§ PECAM-1 platelet-endothelial cell adhesion molecule-1

**Fig 2. Immunological mechanisms of endothelial damage in patients with systemic lupus erythematosus**  
 Systemic lupus erythematosus-induced immune complexes activate complement and cause mast cell degranulation; this triggers the immune cascade that promotes polymorph binding and infiltration into the vascular intima, following endothelial damage-induced increases in vascular permeability

VCAM-1 and monocyte chemoattractant protein-1 (MCP-1),<sup>26</sup> and subsequently monocyte infiltration, by interaction with platelet-endothelial cell adhesion molecule.<sup>27</sup> In diabetic patients, advanced glycosylation endproducts also mediate prolonged expression of NF- $\kappa$ B, and may be a mechanism for the similar increased risk of cardiovascular complications.<sup>28</sup> Nitric oxide induces the endogenous inhibitor of NF- $\kappa$ B, I $\kappa$ B $\alpha$ , which reduces expression of both VCAM-1 and MCP-1.<sup>29</sup>

Infiltration of monocytes into the intima is usually followed by macrophage colony-stimulating factor-mediated differentiation into tissue macrophages, which express scavenger receptors (Fig 2).<sup>17,30</sup> Native LDL is not taken up by the macrophages to a great extent, but LDL that is acetylated or oxidised is rapidly taken up via the scavenger receptors.<sup>17,30</sup> In patients with SLE, autoantibodies targeted predominantly against LDL, as well as damaging the endothelium, form immune complexes that are also actively taken up by macrophage scavenger receptors.<sup>16,17,31</sup>

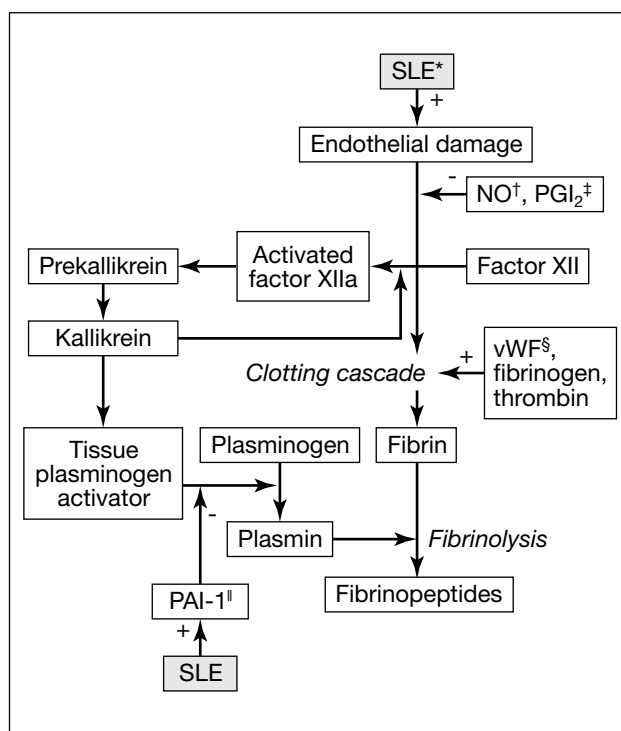
Cholesterol from the phagocytosed LDL particles becomes esterified, with the formation of foam cells. Smooth muscle cells also take up modified LDL and form similar foam cells, which contribute to the formation of fatty streaks that are the earliest gross pathological abnormalities observed during atherogenesis (Fig 3).



\* SLE systemic lupus erythematosus  
† LDL low-density lipoprotein

**Fig 3. Formation of foam cells in systemic lupus erythematosus**

Mast cell degranulation and autoantibodies triggered by systemic lupus erythematosus result in modification of low-density lipoprotein, which is taken up by macrophages and smooth muscle cells, leading to the formation of fatty streaks



\* SLE systemic lupus erythematosus  
† NO nitric oxide  
‡ PGI<sub>2</sub> prostaglandin (prostaglandin I<sub>2</sub>)  
§ vWF von Willebrand factor  
¶ PAI-1 plasminogen activator inhibitor-1

**Fig 4. Effects of systemic lupus erythematosus on the coagulation cascade**

Systemic lupus erythematosus-induced endothelial damage triggers the coagulation cascade and inhibits fibrinolysis

### Coagulation abnormalities in systemic lupus erythematosus

Systemic lupus erythematosus is likewise a procoagulant state (Fig 4),<sup>1</sup> possibly resulting from the associated endothelial damage. Tissue injury triggers the activation of the coagulation cascade, releasing factor XII to form factor XIIa, which reciprocally activates kallikrein that in turn degrades bradykininogen to bradykinin, further promoting vascular permeability and vasodilation (Figs 2 and 4). Von Willebrand factor (vWF), which is the carrier for coagulation factor VIII and the cofactor for platelet and collagen binding, is released constitutively.<sup>32,33</sup> Following endothelial damage, however, levels of vWF, which is released concomitantly with P-selectin, rise two- to three-fold.<sup>32</sup> When deposited on the exposed extracellular matrix, vWF triggers platelet aggregation, which is amplified by platelet degranulation and activation of platelet glycoprotein IIb/IIIa receptors.<sup>25</sup> Following platelet adhesion to the damaged area, the clot is stabilised with fibrin strands, formed by the thrombin-mediated cleavage of fibrinogen.<sup>25</sup> High levels of fibrinogen, an acute phase protein, represent a known risk factor for atherosclerosis,<sup>33,34</sup> and fibrinogen levels are elevated in SLE.<sup>8</sup> Plasminogen activator inhibitor-1 (PAI-1), which suppresses fibrinolysis, is also elevated in patients with SLE.<sup>35</sup> High levels of PAI-1 have been associated with increased risk of subsequent MI.<sup>36</sup>

The prevalence of any thrombotic event in a cohort of SLE patients recruited from Baltimore, US was reported to be two per 100 patients per year.<sup>37</sup> Independent predictors of thrombosis included markers of immune-complex-mediated injury, homocysteine, antiphospholipid antibodies, and other conventional risk factors for atherosclerosis.<sup>6,8,9,38-40</sup> The procoagulant state is particularly evident in antiphospholipid antibody syndrome (APS). The 'lupus anticoagulant' consists of immunoglobulin G and immunoglobulin M antibodies that react with the phospholipid portion of the prothrombin-thrombin activator complex, thereby inhibiting it. Paradoxically, it has a hypercoagulable effect, even in patients without SLE, causing arterial and venous thrombosis, thrombocytopenia, and recurrent abortion.<sup>1</sup>

Lipoprotein(a) [Lp(a)] is a form of LDL-cholesterol that contains apolipoprotein a, a protein that resembles plasminogen and may interfere with fibrinolysis. When levels of Lp(a) exceed 0.78 mmol/L, the risk of cardiovascular and cerebrovascular disease is reported to be increased,<sup>41-43</sup> although this was only noted when LDL-cholesterol levels were also elevated.<sup>44</sup> In 68 patients with APS, either primary or secondary to SLE, plasma levels of Lp(a) were elevated relative to 22 healthy control subjects.<sup>45</sup> Moreover, APS patients with maximal elevation of Lp(a) showed lower fibrinolytic activity, with lower D-dimer and higher PAI-1 levels, than patients with Lp(a) in the normal range.<sup>45</sup>

### Renal complications in patients with systemic lupus erythematosus and cardiovascular disease

Renal manifestations of SLE are highly variable in their clinical presentation, ranging from mild proteinuria to rapidly progressive glomerulonephritis.<sup>1,46</sup> One study has suggested that SLE patients with nephrotic syndrome and end-stage renal disease are more likely to develop atherosclerosis.<sup>47</sup> Furthermore, patients with renal disease, whether with or without SLE, have a high burden of cardiovascular disease, with approximately 50% of patients who start renal replacement therapy already having ischaemic heart disease or cardiac failure.<sup>48</sup> In patients starting dialysis, 80% were reported to have left ventricular hypertrophy.<sup>48</sup> Renal impairment is a strong predictor of future cerebrovascular and cardiovascular events.<sup>48-51</sup> The risk factors described that promote atherogenesis also contribute to deteriorating renal function, producing a vicious cycle of renal failure and vascular events.

### Prevention of coronary artery disease in lupus patients

It is important that physicians caring for SLE patients be aware of the risk of CAD complications associated with this disorder; atheromatous disease is otherwise unusual in premenopausal females, except for diabetics. Modifiable risk factors should be identified and treated aggressively

(Box). These include patient education, and lifestyle modification in terms of diet, exercise, and weight reduction. New Asian guidelines regarding obesity, introduced in 2000, highlight the onset of metabolic disorders that promote cardiovascular disease at lower levels of obesity than previously recognised.<sup>52,53</sup> Steroid therapy should be used judiciously, and lipid- and blood pressure-lowering therapies used aggressively as in diabetic patients. Folate supplementation to reduce homocysteine levels may be considered,<sup>54</sup> but homocysteine levels are not routinely monitored.

The antimalarial agents, besides being efficacious for treating skin and joint disease in SLE, may have additional benefits.<sup>1</sup> Hydroxychloroquine was reported to lower total and LDL-cholesterol and triglyceride levels in patients with rheumatoid arthritis or SLE,<sup>12,55</sup> but this was not found in Hong Kong Chinese patients, in whom cholesterol levels were generally lower than those seen in the studies with Caucasian patients.<sup>56</sup> A cholesterol-lowering effect was also identified in a longitudinal cohort study of 264 SLE patients, with a mean follow-up time of 3.0 years<sup>57</sup>: 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.<sup>57</sup> Hydroxychloroquine has also been reported to reduce thromboembolic events in patients with SLE and APS.<sup>37,58</sup> The antimalarials have been reported to significantly improve insulin resistance and glycaemic control in SLE patients, with and without type 2 diabetes, which should also contribute to a reduction in cardiovascular risk.<sup>59</sup>

As elevated cholesterol levels are a strong risk factor for future renovascular, cerebrovascular, and cardiovascular events,<sup>24</sup> lipid-lowering therapy is important. In addition to the antimalarials, which may help to prevent increases in cholesterol levels associated with steroid therapy,<sup>12,55,57</sup> 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.<sup>60</sup> The statins may also be particularly useful for treating patients with SLE, as they appear to have additional antithrombotic and anti-inflammatory effects.<sup>61,62</sup>

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 (ACE) inhibitors, calcium channel blockers, and  $\beta$ -blockers are all beneficial.<sup>63</sup> Angiotensin-converting enzyme inhibitors may have benefits in addition to their blood pressure-lowering efficacy in treatment of diabetic renal disease<sup>64</sup>; however, direct comparisons between ACE inhibitors and other antihypertensives are not available in patients with SLE.

### Conclusion

The inflammatory process and production of immune complexes associated with SLE, interacting with increased

levels of conventional risk factors, promote the initiation and progression of atherogenesis. Lifestyle modification and aggressive use of medications, to modify cardiovascular risk factors while maintaining effective control of the inflammatory process, are likely to reduce the morbidity and mortality associated with atheromatous vascular disease in SLE patients, and should be encouraged in patients with chronic disease.

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