Review

Increased risk of vascular events in systemic lupus erythematosus: is arterial stiffness a predictor of vascular risk?

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ABSTRACT

Patients with systemic lupus erythematosus (SLE) have an increased vascular morbidity and mortality. Several established vascular risk factors are more prevalent in this population but cannot fully explain the reported excess atherosclerotic burden. Emerging vascular risk factors may also contribute to the increased vascular risk in these patients although the evidence is limited and often conflicting. SLE-specific risk factors also play a role in the pathogenesis of atherosclerosis.

Given the multifactorial aetiology of vascular disease in SLE, an integrated index of risk could be useful in the management of these patients. Arterial stiffness possibly represents such an index and accumulating data suggest an increased prevalence of arterial stiffness in SLE. Many factors play a role in the loss of arterial elasticity in this population, including both emerging and established vascular risk factors. Arterial stiffness may emerge as a useful index for risk stratification in SLE and has the potential to guide therapeutic decisions in these patients.

Introduction

Systemic lupus erythematosus (SLE) is a non-organ-specific connective tissue disease that principally affects women and whose prevalence varies significantly between ethnic groups (1-3). SLE might affect any organ and was once associated with a high fatality rate (1). The introduction of disease-modifying agents for the treatment of lupus patients (*e.g.*, corticosteroids, antimalarial agents, methotrexate, azathioprine, cyclophosphamide, mycophenolate mophetil and biologic agents) (4) has substantially improved prognosis (1, 5-7). Nevertheless, life expectancy in patients with SLE is still reduced compared with the general population (6-8). During the first years after the diagnosis of SLE, infections and active disease are the commonest causes of death (5). Cardiovascular disease (CVD) becomes the prominent cause of death in later stages (5, 6). More recent studies suggested a blunting of this bimodal pattern (9). According to these studies, CVD was responsible for almost half of deaths and infections accounted for approximately one-third; these causes of death were evenly distributed throughout the course of SLE (9). In addition, no discernible peak of mortality was observed during the early years after SLE diagnosis (9).

SLE has increased vascular risk. SLE patients show an earlier onset and a greater prevalence of carotid atherosclerosis (10-14). Coronary artery calcification (CAC), another index of the atherosclerotic burden, also occurs earlier and is more frequent and extensive in SLE (15-17). Apart from subclinical atherosclerosis, SLE patients also have a greater risk of myocardial infarction (MI) and this difference is more pronounced in younger ages (18-20). Coronary heart disease (CHD) in SLE is mostly due to atherosclerosis; arteritis, thrombosis and vasospasm may also play a role (21). Other vascular events also occur more frequently in SLE patients; the risk of stroke is increased in this disease, particularly in younger patients (19). Mortality attributed to cerebrovascular disease is also higher in SLE (22). One fourth to one third of patients with SLE had abnormal ankle-brachial pressure index (ABPI), a marker of peripheral arterial disease (23, 24) as well as vascular morbidity and mortality (25). Patients with SLE might also develop abdominal aortic aneurysms (AAA) and at a younger age than the general population (26). Inflammatory (AAA) have also been reported in SLE (27). It should be noted that this

excessive risk is present in SLE even though most patients are young women and their vascular risk should be lower (28). It was suggested that SLE should be considered as a CHD equivalent (28).This review discusses the contribution of established and emerging vascular risk factors in the excessive atherosclerotic burden in SLE. We also briefly discuss the potential role of arterial stiffness in risk stratification in SLE. Risk factors for atherosclerosis also reduce arterial elasticity (29). Arterial stiffness in turn is an independent predictor of vascular morbidity and mortality in the general population (29). Measurement of arterial stiffness might also represent a useful tool in assessing vascular risk in SLE.

Established vascular risk factors in SLE

The majority of SLE patients are women and this should result in reduced vascular risk (1, 2, 30). However, the menopause appears to occur earlier in women with SLE (31). This might partly contribute to the earlier onset of CVD in these patients (31).

Hypertension is more common in SLE (12, 14, 15, 31-34). Smoking was also more prevalent in SLE patients in some reports (15). High-density lipoprotein cholesterol (HDL-C) levels are lower in SLE (35-37). HDL also appears to have impaired ability to prevent oxidation of LDL in these patients (38). Triglyceride (TG) levels were also higher in patients with SLE (15, 17, 31, 35, 37, 39). Epidemiological studies suggested that TG might confer greater vascular risk in women than in men (40). Since the majority of patients with SLE are females, the increased TG levels might be particularly deleterious in this population (31). Nevertheless, more recent data questioned this gender-related difference in the TG-induced vascular risk (41). Total and low-density lipoprotein (LDL) cholesterol (LDL-C) levels appear to be lower in lupus patients in most studies (14, 17, 35) but a shift towards small dense LDL particles was reported in SLE (39). This LDL subfraction may increase vascular risk (42). Oxidized LDL levels were also higher in patients with SLE compared with controls and were associated with vascular disease (43-45). In apparently health men, oxidized LDL levels also predicted CHD events (46). The alterations in lipid profile in SLE appear to be related with disease activity (35, 47).

Type 2 diabetes mellitus (T2DM) was more common among patients with SLE (31, 48). Patients with SLE also had higher insulin levels and were more insulin resistant than healthy controls, despite a similar BMI in both groups (37, 48-50). The prevalence of the metabolic syndrome (MetS) also appears to be higher in patients with SLE, but this depended on the MetS definition used (51). Both insulin resistance and MetS increase the risk of vascular morbidity and mortality in the general population (52, 53). Patients with SLE had a greater waist-hip-ratio, suggesting an increase in visceral fat; this might partly explain the increased prevalence of insulin resistance, MetS and T2DM in SLE (31).

Physical inactivity represents an independent vascular risk factor (54, 55). Patients with SLE frequently lead a sedentary lifestyle, which was attributed to disease-related arthritis, depression and fatigue (31).

Despite the increased prevalence of vascular risk factors in SLE, they appear to be under-recognized and undertreated (56, 57).

Emerging vascular risk factors in SLE

The established vascular risk factors cannot fully explain the excess burden of subclinical atherosclerosis, vascular morbidity and mortality in SLE (10, 14, 15, 58, 59). After adjustment for risk factors included in the Framingham risk calculator, the relative risk for vascular morbidity and mortality among patients with SLE was still increased 7.9- to 17-fold (58). Other studies showed that, despite the presence of more excessive atherosclerosis in patients with SLE compared with controls, the 10-year vascular risk estimated by the Framingham risk equation was similar in both groups (17, 31). Thus, it appears that other risk factors, besides the established ones, could contribute to the excessive vascular risk of SLE patients. It was also proposed that disease-specific risk calculators should be developed for these patients if we want to reliably estimate their vascular risk (28). This might also be the case in other patient subgroups like those with chronic kidney disease (CKD) (60).

CKD is an independent vascular risk factor in patients with and without CHD (61-63). Renal involvement is a common manifestation of SLE that adversely affects prognosis (5, 31, 64, 65). On the other hand, a decrease in both creatinine levels and proteinuria with immunosuppressive treatment improved outcome (8, 66). The treatment of lupus nephritis has been reviewed elsewhere (67, 68). We previously showed that statins can improve renal function in CHD patients and this reduced vascular risk (62, 63). Whether this beneficial effect of statins also applies in lupus nephritis remains to be established.Elevated plasma homocysteine levels might increase the risk for CVD (69, 70) and lupus patients have higher circulating homocysteine levels (15, 17, 31, 43, 71). Moreover, homocysteine levels were an independent risk factor for CAC as well as arterial thrombosis, CHD and stroke in SLE (16, 64, 72-74).

Oxidative stress contributes to the atherosclerotic process (75). Patients with SLE showed increased levels of markers of oxidative stress in most studies (32, 39, 76-79). Oxidative stress results in elevated asymmetric methylarginine (ADMA) levels because it results in decreased ADMA catabolism (60). ADMA inhibits the synthesis of nitric oxide (NO) and was an independent risk factor for vascular morbidity and mortality in patients with kidney failure (80,81), CHD, PAD or T2DM (82-84). In SLE patients, ADMA levels correlate with disease activity and were associated with the presence of CAC and CVD (85,86).

Elevated lipoprotein (a) (Lp(a)) concentrations increase the risk of CAD and stroke (87, 88) and patients with SLE appear to have higher levels of Lp(a) (89). Lupus patients with established CVD had higher serum Lp(a) levels than those without CVD (73).

Paraoxonase-1 (PON-1) is an enzyme

located on HDL that prevents LDL oxidation (90). Low PON-1 activity might increase vascular risk (90) and was reported in SLE (36).

Increased plasma fibrinogen levels represent another independent vascular risk factor (91, 92) and were higher in SLE patients than in healthy individuals (93).

Inflammation is involved in the pathogenesis of atherosclerosis (94). High-sensitivity C-reactive protein (hs-CRP) is a sensitive marker of inflammation and an independent vascular risk factor (95, 96). Paradoxically, hs-CRP levels do not correlate with lupus activity (97). Nevertheless, even lupus patients with low disease activity have higher hs-CRP levels compared with controls (12, 98). More importantly, CRP levels were independent predictors of increased carotid intima-media thickness (cIMT) (99) and vascular events in SLE (100). Serum levels of other markers of inflammation, including interleukin-6 (IL-6), tumour necrosis factor-α (TNF-α), monocyte chemoattractant protein-1 (MCP-1) and soluble CD40 ligand (sCD40L), are also independent risk factors for vascular morbidity and mortality in patients with and without CHD (101-105). Serum levels of IL-6, TNF-α, MCP-1 and sCD40L are increased in SLE (43, 48, 106, 107). IL-6 was independently associated with CAC in SLE patients (106).

Platelet-activating factor-acetylhydrolase (PAF-AH) is a phospholipase present mainly on LDL that appears to promote atherosclerosis (108). In the general population, PAF-AH levels independently increased risk for CHD events (108, 109). SLE patients with established CVD had higher PAF-AH levels than those without CVD (110). Transforming growth factor-β1 (TGF-β1) inhibits the proliferation and migration of vascular smooth muscle cells (VSMC) and might protect against atherosclerosis (111). In SLE, TGF-β1 activity was inversely associated with carotid atherosclerosis (112).

Adiponectin levels are reduced in insulin resistance (113) and are inversely related to the risk of vascular morbidity and mortality (114). Plasma adiponectin concentrations were inversely correlated with insulin resistance in SLE patients but were unexpectedly higher compared with controls (34). Leptin is an adipokine that plays a role in body weight regulation (115) and might also represent an independent risk factor for CHD (116). Plasma leptin levels were higher in SLE patients (34).

Matrix metalloproteinases (MMP) are a family of enzymes that degrade proteins of the extracellular matrix, such as collagen and elastin (117). They play a significant role in vascular remodelling, AAA development and expansion and plaque cap rupture (117, 118). Elevated MMP-3 and MMP-9 levels were independent risk factors for vascular morbidity and mortality in CHD patients (119) and in patients with carotid atherosclerosis, respectively (120). Both MMP-3 levels and MMP-9 activity are higher in patients with SLE in most studies (12, 121-123). Inflammation is an important stimulus for MMP production (118, 124). Therefore, the

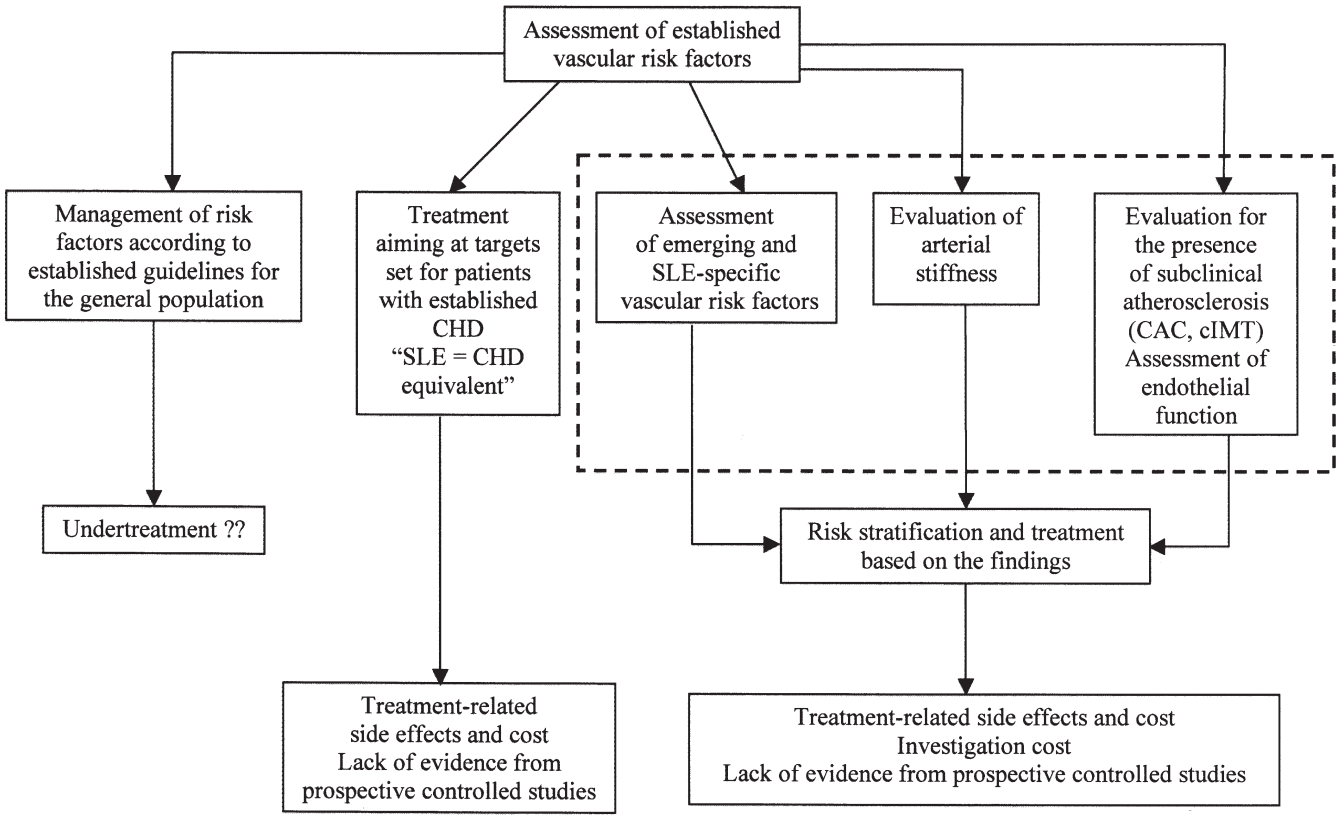

Fig. 1. Potential strategies for the management of vascular risk in patients with systemic lupus erythematosus (SLE). The investigations in the dotted frame can be combined to further improve risk stratification. (CHD: coronary heart disease; CAC: coronary artery calcification; cIMT: carotid intima-media thickness).

increased inflammation in SLE might account for the increased MMP-3 and MMP-9 levels in this disease (121). Indeed, MMP-3 correlated with erythrocyte sedimentation rate and CRP levels in SLE patients (121).

Tissue inhibitors of metalloproteinases (TIMP) are enzymes that bind and inactivate MMP (118, 124). In patients with suspected CHD, higher TIMP-1 levels increased the risk of vascular mortality (125). In some but not all studies, TIMP-1 levels were higher in SLE patients (12, 122).

Disease-related vascular risk factors in SLE

Disease duration and activity were independent risk factors for carotid atherosclerosis in SLE in some but not all studies (10, 14, 33, 126). Disease duration also increased the risk of vascular events (100) and disease activity was a strong predictor of mortality (127).Antiphospholipid antibodies are frequently present in SLE and increase the risk of venous and arterial thrombosis (1). In cross-sectional studies, these autoantibodies were also independently associated with carotid atherosclerosis, CAC and CVD in SLE patients even though others did not confirm this relationship (10, 14, 73, 128, 129). In prospective studies, the presence of antiphospholipid antibodies increased the risk of vascular events and death in SLE (64, 65, 100, 128). In the general population, the relationship between antiphospholipid antibodies and MI or stroke is questionable (130-134). These antibodies cross-react with antibodies against oxidized LDL (135, 136) and might enhance its uptake by macrophages (137). This uptake represents an initial step of atherosclerotic plaque formation (94). Antiphospholipid antibodies might also cross-react with HDL-C and apolipoprotein A-I (Apo A-I), a major constituent of the HDL complex, possibly reducing the antiatherogenic effects of HDL (138).

SLE patients also have higher levels of antibodies against oxidized LDL (44). These antibodies were associated with vascular disease in some but not all studies in SLE patients (44, 139). They were also an independent risk factor for progression of carotid atherosclerosis (140) and MI (131, 141) in the general population.

Antibodies against lipoprotein lipase are also frequently detected in patients with SLE and positively correlate with serum TG levels (142). Therefore, these antibodies might contribute to the increased vascular risk in SLE by influencing TG levels (142).

Anti-endothelial cell antibodies are also present in SLE and correlate with disease activity (143). *In vitro* studies showed that these autoantibodies induce endothelial activation and may thus contribute to atherogenesis (144).

Autoantibodies might be present many years before the diagnosis of SLE and this might contribute to the early onset of atherosclerosis in these patients (145).

Some of the therapeutic agents used in SLE might contribute to the excess vascular risk in this disease. Azathioprine use was independently associated with carotid atherosclerosis in SLE (14) and was more common in SLE patients with established CVD than in those without (110). In prospective studies, treatment with azathioprine was an independent risk factor for vascular events (100). Besides azathioprine, prolonged treatment with corticosteroids or a cumulative intake >30 g was also associated with CAC, carotid atherosclerosis and CVD (73, 110, 146, 147). Corticosteroids might also increase the risk for AAA (26, 148). The relationship between azathioprine or corticosteroid use and increased atherosclerosis might reflect more severe disease (14). This might be the case particularly with azathioprine, which has rather few vascular side effects (149). In contrast, corticosteroids promote the development of obesity and hypertension and impair glucose metabolism (149, 150). They also reduce HDL-C and increase total cholesterol and TG levels (149). Corticosteroids might also attenuate the lipid lowering effects of statins (151). Interestingly, some studies reported that patients with carotid atherosclerosis were less likely to have received steroid therapy than patients without atherosclerosis (10). This was attributed to the anti-inflammatory effects of steroids (150). The adverse vascular effects of steroids are also dose-dependent and might not be apparent at lower doses (1).

Non-steroidal anti-inflammatory drugs (NSAIDs) are frequently administered to SLE patients for pain relief (1). The cyclooxygenase-2 selective NSAIDs might increase vascular risk and they should probably be avoided in SLE (1). Conventional NSAIDs might also have prothrombotic actions and could also further compromise renal function (1).Not all therapeutic agents used in SLE have atherogenic effects. No previous use of cyclophosphamide was associated with increased carotid atherosclerosis (10). Treatment with antimalarial drugs might increase HDL-C and decrease LDL-C levels and can also attenuate corticosteroid-induced dyslipidaemia (152-154). Antimalarial drugs might also possess antithrombotic and anti-inflammatory properties and could improve glucose metabolism (97, 150). Their use reduced the risk for arterial and venous thrombosis and prolonged survival in SLE (155).

In some studies, lupus-specific risk factors had a higher predictive value for the presence of carotid atherosclerosis than conventional risk factors (14). In contrast, others reported that these lupus-related risk factors could not predict the development of atherosclerosis (15).

Arterial stiffness and vascular disease

It appears that both established and emerging vascular risk factors contribute to the increased prevalence of atherosclerosis in SLE. However, their predictive value might not be optimal when assessed separately. An index of vascular risk that integrates all these risk factors could be particularly useful in SLE patients. Arterial stiffness is such an index.

A variety of markers of arterial elasticity have been proposed and the most commonly used are pulse wave velocity (PWV) and augmentation index (AIx) (29). PWV is the velocity of arterial pulse wave transmission between 2 arteries (more frequently the carotid and femoral) (29). AIx represents the augmentation of central pulse pressure during late systole by the earlier return of

wave reflection due to arterial stiffening (29). Both PWV and AIx are measured by applanation tonometry, where the pressure within a manometer flattened against an artery equates to the pressure within the artery (29). Measurement of both PWV and AIx is simple, rapid, non-invasive and reproducible (29). Other methods of evaluating arterial elasticity are also in use, such as the analysis of the diastolic portion of the pulse wave, which provides both large artery elasticity (C_1) and small artery elasticity (C2) (29). Peterson's elastic modulus is an index of regional arterial stiffness and Young's modulus is Peterson's elastic modulus adjusted for arterial wall thickening (11, 156-157). Stiffness index β assesses the elastic properties of arteries independently of the effects of distending pressure (11, 156-158).

Most established vascular risk factors are also implicated in the development of arterial stiffness. Several studies showed that age (159-162), hypertension (160,163), smoking (164-166), elevated LDL-C levels (165), increased TG and low HDL-C levels are risk factors for arterial stiffness (159, 160, 163, 167). T2DM also reduces arterial elasticity (160, 167). Even in non-diabetic individuals, increasing glucose levels and serum insulin levels are risk factors for arterial stiffness (168, 169). Central adiposity is also related to the loss of arterial elasticity (169-171). Inactive subjects had reduced arterial elasticity compared with active individuals (172) whereas physical activity attenuated the age-related increase in arterial stiffness (161, 162).

Emerging risk factors might also induce arterial stiffness. In the general population and in hypertensive subjects, CRP was an independent predictor of PWV and AIx (163, 173, 174). Low adiponectin levels were also independently associated with increased arterial stiffness in hypertensive patients (173).

MMP and TIMP are involved in vascular remodeling and might also affect arterial elasticity (175-177). In hypertensive patients, the fall in PWV with antihypertensive treatment correlated with a decrease in MMP-3 levels (175). In both hypertensive patients and healthy subjects, MMP-9 levels correlated with PWV (176). In patients with aortic stenosis, MMP-9, MMP-3 and TIMP correlated with PWV (177). Arterial stiffness correlates with the presence and severity of atherosclerosis (178, 179). More importantly, increased arterial stiffness appears to represent an independent risk factor for vascular morbidity and mortality in the general population (29). The predictive value of arterial stiffness was also shown in specific populations, including patients with hypertension, T2DM, end-stage renal disease and established CVD (29). It appears that evaluation of arterial stiffness could represent a useful tool in risk stratification in both primary and secondary prevention setting (29).

Arterial stiffness could lead to left ventricular hypertrophy (LVH) in hypertensive patients (180, 181). Increased left ventricular mass is an independent predictor of vascular and all-cause mortality (182, 183). A recent study showed that patients with SLE had increased left ventricular mass and a higher prevalence of LVH compared with age- and gender-matched subjects (184). In the same study, arterial stiffness was an independent determinant of LVH in SLE patients (184).

Arterial stiffness in SLE

Several studies compared arterial stiffness between SLE patients and age-matched healthy subjects and are summarized in Table I (11, 43, 185-187). Most reported increased arterial stiffness

Table I. Studies comparing arterial stiffness in patients with systemic lupus erythematosus (SLE) and age-matched healthy controls.

Study	No (SLE/controls)	Index of arterial stiffness	Results	Parameters correlating with arterial stiffness in SLE
Brodszki *et al*. (185)	39/55	Stiffness index β in the abdominal aorta, the common carotid artery and the popliteal artery	Stiffness in the popliteal artery significantly (p=0.02) higher in SLE; non-significant differences in the other arteries	Mean arterial pressure
Roman *et al*. (11)	101/105	Stiffness index β, Young's modulus and Petersons' elastic modulus	All parameters significantly (p<0.001, p=0.004 and p<0.001, respectively) higher in SLE	Duration of disease, hs-CRP and cholesterol levels
Lee *et al*. (43)	35/35	C1 and C2	C2 significantly (p<0.001) lower in SLE; non-significant differences in C1	Older age and oxidized LDL levels
Bjarnegård *et al*. (186)	27/27	Carotid-femoral and carotid-radial PWV and pulse wave analysis (including AIx)	Carotid-femoral PWV significantly (p<0.05) higher in SLE; non-significant differences in the other indices of arterial stiffness	C3
Wright *et al*. (187)	30/19	C1 and C2	Both C1 and C2 significantly (p=0.003 and p< 0.001, respectively) reduced in SLE	Systolic and diastolic blood pressure

hs-CRP: high-sensitivity C-reactive protein; LDL: low-density lipoprotein; PWV: pulse wave velocity; Aix: augmentation index; C1: large artery elasticity; C2: small artery elasticity.

Table II. Established, emerging and disease-specific vascular risk factors in patients with systemic lupus erythematosus (SLE).

Vascular risk factors	Comments
Established	
Gender	Even though most patients are female, there is an earlier occurrence of menopause
↑ prevalence of smoking	
↓ HDL-C levels	Impaired antioxidative ability of HDL-C has also been reported
↑ TG levels	↓ total cholesterol and LDL-C levels in SLE
Shift towards small dense LDL particles and increased LDL oxidation	The difference in the prevalence of MetS depended on the MetS definition used
↑ prevalence of visceral adiposity, insulin resistance, MetS and T2DM	
↓ physical activity	
Emerging	
↑ prevalence of CKD*	Prospective studies support its role in the increased prevalence of CVD in SLE
↑ plasma homocysteine levels*	Prospective studies support their role in the increased prevalence of CVD in SLE
↑ inflammation*	
↑ oxidative stress and ↓ PON-1 activity	
↑ Lp(a) levels	
↑ plasma fibrinogen levels	
↑ PAF-AH levels	
↓ TGF-β1 activity	
↑ leptin levels	
↑ MMP-3 and TIMP-1 levels and ↑ MMP-9 activity	
SLE-specific	
Antiphospholipid antibodies*	Prospective studies support its role in the increased prevalence of CVD in SLE
↑ levels of other autoantibodies (against oxidized LDL and endothelial cells)	
Treatment with azathioprine	
Treatment with corticosteroids*	
Treatment with NSAIDs	
Reduced use of antimalarial drugs*	Prospective studies support their protective role against CVD in patients with SLE

*Most important emerging and disease-specific vascular risk factors in SLE.
HDL-C: high-density lipoprotein cholesterol; TG: triglyceride; LDL: low-density lipoprotein; LDL-C: low-density lipoprotein cholesterol; MetS: metabolic syndrome; T2DM: type 2 diabetes mellitus; CKD: chronic kidney disease; CVD: cardiovascular disease; PON: paraoxonase; Lp(a): lipoprotein (a); PAF-AH: platelet-activating factor-acetylhydrolase; TGF: transforming growth factor; MMP: matrix metalloproteinase; TIMP: tissue inhibitor of metalloproteinase; NSAIDs: non-steroidal anti-inflammatory drugs.

in SLE despite the use of different methodologies to assess arterial elasticity (11, 187). In contrast, other studies did not identify differences between SLE patients and controls in some markers of stiffness or in some arteries (43, 185, 186).

A number of independent risk factors for arterial stiffness were reported in SLE patients. Established vascular risk factors, including older age, higher blood pressure (24, 43, 99, 185, 187, 188), elevated cholesterol levels (11), T2DM and higher insulin levels reduced arterial elasticity (99, 184). Emerging vascular risk factors, including renal disease (99, 188), oxidized LDL (43), plasma homocysteine (71) and hs-CRP levels (11) also correlated with arterial stiffness in some studies. Disease activity and duration were other independent predictors of arterial stiffness in SLE patients (11, 184). A low leukocyte count ($<5x10^3/mm^3$), which might also reflect disease activity, was also a risk factor (188). Non-use of hydroxychloroquine was also associated with arterial stiffness (188).

Some studies reported a positive correlation of PWV with serum C3 levels in SLE patients (99, 186, 188). In animals, C3 stimulated the growth of VSMC and this might impair arterial elasticity (189). Complement activation might also play a role in the development of atherosclerosis in humans (190). Indeed, elevated C3 levels were independently associated with a greater risk of carotid atherosclerosis and CAC in SLE (126, 146). However, lower C3 levels are observed in active SLE; therefore, the positive association of C3 with atherosclerosis and PWV is difficult to explain and requires further study (186).

Arterial stiffness and endothelial function in SLE

The endothelium plays an important role in the regulation of arterial elasticity, mainly through the production of the potent VSMC-relaxing agent NO (29, 191, 192). Endothelial dysfunction represents the initial step of atherosclerosis and correlates with arterial stiffness (29, 193, 194). Patients with SLE have reduced flow-mediated dilatation (an index of endothelial function) compared with healthy individuals (195-200). This difference persisted after adjustment for established vascular risk factors (196). Circulating markers of endothelial dysfunction, including soluble vascular cell adhesion molecule 1 (sVCAM-1), soluble intercellular adhesion molecule 1 (sICAM-1), soluble thrombomodulin (sTM) and von Willebrand factor levels were also higher in SLE patients (12, 43, 143, 201-203). sICAM-1, sVCAM-1 and sTM levels also correlated with disease activity (201-203). It is possible that impaired endothelial function in SLE might contribute to the reduced arterial elasticity.

Endothelial dysfunction is also characterized by increased production of endothelin-1 (ET-1), which induces vasoconstriction and stimulates the proliferation of VSMC (204). Intravenous infusion of ET-1 increased PWV and AIx in healthy men (205) and ET-1 levels directly correlated with arterial stiffness (172). ET-1 levels were higher in SLE patients (206) and *in vitro* studies showed that endothelial cells release greater amounts of ET-1 when exposed

to serum from patients with SLE than in the presence of serum from healthy subjects (207).

Endothelial progenitor cells (EPC) are reduced in SLE patients and this was attributed to an increased apoptosis of haematopoietic stem cells, the precursors of EPC (208). EPC play an important role in endothelial repair and regeneration and their reduced number in SLE might contribute to the impaired endothelial function and increased atherogenesis in lupus patients (209, 210).

Conclusions

SLE patients have an excessive vascular risk that appears to be related to a higher prevalence of established and emerging vascular risk factors. Disease-specific factors also play a role in the increased atherogenesis in SLE.

Arterial stiffness is more prevalent in SLE patients reflecting the increased burden of vascular risk factors in this population. In cross-sectional studies, arterial stiffness is associated with the presence of carotid atherosclerosis in SLE (99, 184, 188). Therefore, arterial stiffness could represent a barometer of vascular risk in this population. SLE patients with increased arterial stiffness could also be potential candidates for more proactive vascular risk management. In the general population, antihypertensive and lipid-lowering treatment improves arterial elasticity and this might reduce vascular risk (29). It is therefore possible that measurement of arterial stiffness could also be used to guide therapeutic decisions in SLE. Given the significance of disease-specific factors in the pathogenesis of arterial stiffness and CVD in SLE, this subgroup of patients might also require more aggressive immunosuppressive therapy. Finally, since reduced arterial elasticity was reported in other autoimmune inflammatory diseases, including rheumatoid arthritis and active systemic vasculitis (11, 211-214), arterial stiffness might also represent a useful predictive tool in these populations. However, before using arterial stiffness measurement to guide treatment decisions in these patients, prospective studies should determine whether this promising risk factor can independently predict vascular morbidity and mortality.

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