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Cardiovascular disease in systemic lupus erythematosus

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Abstract

There is a well-known increased risk for cardiovascular disease that contributes to morbidity and mortality in systemic lupus erythematosus (SLE). Major adverse cardiovascular events and subclinical atherosclerosis are both increased in this patient population. While traditional cardiac risk factors do contribute to the increased risk that is seen, lupus disease-related factors, medications, and genetic factors also impact the overall risk. SLE-specific inflammation, including oxidized lipids, cytokines, and altered immune cell subtypes all are likely to play a role in the pathogenesis of atherosclerotic plaques. Research is ongoing to identify biomarkers that can help clinicians to predict which SLE patients are at the greatest risk for cardiovascular disease (CVD). While SLE-specific treatment regimens for the prevention of cardiovascular events have not been identified, current strategies include minimization of traditional cardiac risk factors and lowering of overall lupus disease activity.

Keywords

atherosclerosis • biomarkers • cardiovascular disease • myocardial infarction • prevention • stroke

Although overall mortality for lupus patients has improved in recent decades, cardiovascular disease (CVD) has been recognized as a major cause of morbidity and mortality.[1] The bimodal pattern of mortality in lupus was first recognized by Urowitz *et al*. in 1976, who found that although deaths within 1 year of diagnosis were largely due to active systemic lupus erythematosus (SLE) disease, another peak of mortality 8.6 years into the disease course could be attributed to cardiovascular events.[1–4] The increased risk of CVD seen in lupus probably results from as-yet-unknown relationships between autoimmune inflammation and traditional CVD risk factors.

Epidemiology (Prevalence/Incidence) of CVD in SLE

Major adverse cardiovascular events

Multiple epidemiologic studies have identified a significantly elevated risk of death due to CVD in SLE patients. In one recent meta-analysis of 15 reports, the standardized all-cause mortality rate for death due to CVD events was 2.2.[5]

Nonfatal CVD events in SLE patients are also elevated. In an examination of the Medicaid Analytic eXtract, SLE patients had a 27% higher risk of nonfatal cardiovascular events compared to age- and sex-matched patients with diabetes, and more than twice the risk compared to the general population.[6] Even when looked at as separate outcomes, there is an increased risk of myocardial infarction (MI) and stroke in SLE patients. The hazard ratio (HR) for MI in SLE patients has ranged in various studies from 2.6 [7] to 5.1,[8] while the HR for stroke ranges from 2.1 to 3.3.[9] In the Medicaid population, the HR for MI in SLE compared to the general population was 2.9 after accounting for socioeconomic factors, Charlson comorbidity index score, CVD risk factors, and total medications.[6] Annual rates of MI and strokes in younger patients with SLE were also increased. Among 18–39-year-olds, SLE patients had an incidence rate (IR) per 1,000 person years for stroke of 4.97, compared to the general population of 0.37. MI was also increased in this group,

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Review • DOI: 10.2478/rir-2021-0022 • 2(3) • 2021 • 157–172

with an IR of 2.32, compared to 1.67 in the general population. This gap narrows as the population ages, although SLE patients continue to have higher IRs.[6] CVD events in SLE patients also correlate with greater in hospital morbidity and mortality. Both in-hospital mortality and length of hospitalizations are longer compared to non-SLE patients, diabetics, and non-diabetic patients.[3]

Subclinical atherosclerosis

In addition to major cardiovascular events, subclinical atherosclerosis is also increased in lupus patients. Necropsy studies have found atherosclerotic plaques in 25%–56% of young SLE patients, with narrowing in 76%–100%.[10, 11] In comparison, in non-SLE patients of a similar age range atherosclerosis was found in 17%–70% of individuals, but with an average area of stenosis of 32.7%.[12] The detection of subclinical atherosclerosis by several different methods can predict cardiovascular morbidity and mortality in the general population.[13, 14] Similarly, detection of subclinical atherosclerosis can also predict future cardiovascular events in SLE patients.[15] Most studies have found higher rates of atherosclerotic plaque in SLE patients compared to controls. For example, one cross-sectional study using carotid ultrasound found that plaques were more prevalent in SLE patients, with 37.1% of SLE patients examined having increased carotid atherosclerosis compared to 15.2% of controls.[16] A follow-up study showed an average of 10% per year increase in atherosclerosis, compared to <5% in the general population.[17] An alternative method of determining subclinical atherosclerosis by measuring coronary artery calcium (CAC) using multidetector CT showed a prevalence ratio of 1.5–2.8, with the greatest disparity seen in the youngest age group.[18] Another study demonstrated that the odds of having a significant CAC score were 12.6 times higher in SLE than in controls.[19]

Pathology involving microvascular cardiac function is also observed in SLE. Coronary flow reserve (CFR) is a function of microvascular perfusion and plays a role in prognosis in patients with CVD.[20] In all, 44% of SLE patients were found to have abnormal stress myocardial perfusion by cardiac MRI without evidence of coronary obstruction.[21] Endothelial dysfunction is one of the earliest indications of subclinical atherosclerosis and is correlated with the risk of future cardiovascular events in the general population.[22, 23] SLE patients have been found to have higher rates of endothelial dysfunction, shown in impaired flow-mediated dilation, even when controlled for traditional CVD risk factors.[24, 25]

Screening for subclinical atherosclerosis does have important limitations. Atherosclerosis in one vascular area, or lack thereof, may not reflect the total atherosclerotic burden. For example, one Danish study evaluated three areas commonly affected by CVD: carotid vessels using ultrasound, coronary arteries with cardiac CT, and peripheral arteries with the ankle-brachial index. A total of 41% of SLE subjects had evidence of atherosclerosis in at least one of the three sites, but only 3% showed disease in all three sites, and only 16% demonstrated two sites of involvement.[26] Thus, if a patient is deemed to be high-risk for atherosclerosis, it may be necessary to screen for atherosclerosis with multiple modalities.

Causes of Atherosclerosis in SLE

Although accelerated atherosclerosis in SLE is most likely due to increases in both traditional risk factors and SLE-driven inflammation, the exact mechanistic pathways are still not fully elucidated.

Traditional cardiac risk factors

Traditional Framingham risk factors that increase cardiovascular risk in the general population also impact risk for SLE patients. In one cohort, 53% of lupus patients had at least three traditional cardiac risk factors.[27, 28] Factors such as diabetes, hypertension, and hyperlipidemia can be exacerbated by glucocorticoids and other lupus therapies.[29] SLE disease activity can also directly influence cardiovascular risk factors; for example, patients with high lupus disease activity have high levels of very low-density lipoprotein (VLDL) and triglycerides (TG) and low levels of high-density lipoprotein (HDL) compared to patients with quiescent disease.[30]

Although there is some inconsistency across studies, hypertension,[27, 31, 32] hypercholesterolemia,[4, 27, 33] diabetes mellitus,[4, 27] older age,[27, 32, 33] tobacco use, and postmenopausal status[32, 33] have all been associated with CVD in SLE patients in several cohorts. In a recent meta-analysis the strongest traditional risk factors for major adverse cardiovascular events (MACE) in SLE were male gender (OR 6.2), hyperlipidemia (OR 3.9), familial history of cardiac disease (OR 3.6), and hypertension (OR 3.4).[34]

Other non-Framingham traditional risk factors have also been associated with increased cardiovascular risk in SLE, including both high body mass index (BMI) >30,[35] and low BMI <20,[35, 36] premature menopause, sedentary lifestyle, and increased waist-to-hip ratio.[37] Metabolic syndrome has also been associated with increased cardiovascular events and mortality.[38] Race and ethnicity may also contribute to cardiovascular risk in SLE patients. One large population-based study found that the risk of MI was the lowest in those of Asian and Hispanic descent compared to Whites, while the risk of stroke was higher in Blacks and Hispanics.[39]

Although traditional cardiac risk factors contribute to atherosclerosis in SLE, studies show that these factors do not

Review • DOI: 10.2478/rir-2021-0022 • 2(3) • 2021 • 157–172

fully explain the increased risk. For example, in a Canadian SLE cohort, Esdaile *et al.* found a tenfold increased relative risk for MI and a nearly eightfold increased risk for stroke, even after controlling for traditional Framingham risk factors and left ventricular hypertrophy.[40] In a separate cohort, 19% of SLE patients had coronary calcium on electron beam computed tomography (EBCT), even though 99% were identified as low risk using the Framingham risk calculator.[41] Another recent study found that both generic cardiac risk scores and SLE-adapted scores (such as the QRESEARCH risk estimator, version 3 (QRISK3), and the modified Framingham risk score) underestimated high cardiovascular risk.[42] Thus, although SLE patients are impacted by traditional cardiac risk factors,[40, 43, 44] these factors do not adequately account for the significantly increased level of CVD.

SLE-specific risk factors

SLE itself is associated with an increased risk of CVD. As previously noted, there is a bimodal pattern of mortality in lupus, with a peak of mortality due to CVD nearly 9 years into the course of disease.[4] Several cross-sectional cohort studies have also found that longer SLE disease duration is associated with subclinical atherosclerosis.[45–47] However, other studies have indicated that MACE can occur before or within the first 2 years of SLE diagnosis.[48] Early indicators of atherosclerosis such as endothelial dysfunction and vascular stiffness can also be found early in the course of SLE.[49]

Despite the association with SLE disease itself, the association between disease activity measurements and atherosclerosis has been inconsistent. Although one study found a significant association between higher mean SLE Disease Activity Index-2000 (SLEDAI-2K) and increased coronary calcium scores,[47] another study found an inverse relationship between the Systemic Lupus Activity Measure and carotid plaque.[45] Several other longitudinal studies found no association between disease activity and progression of atherosclerosis.[17, 50–52] More recently, studies have examined the impact of long-term remission on cardiovascular events. One study found that patients in prolonged remission with at least 5 years of no lupus disease activity had a reduced risk of cardiovascular events.[53] Another study by our group found that patients who achieved a lupus low disease activity state (LLDAS) during 50% of clinic visits in the year following cohort entry had decreased risk of future cardiovascular events (unpublished data).

Damage scores, measured using the SLE International Collaborating Clinics (SLICC) damage index (SDI), have been more consistently associated with CVD in lupus. In one study, SLE subjects with higher baseline SDI scores were 9.6 times more likely to develop MACE.[54] Higher SDI scores were also independent predictors of cross-sectional[16] and longitudinal carotid plaque.[17]

Renal involvement is one specific manifestation of both lupus activity and damage that has been associated with increased cardiovascular risk in lupus. For example, active renal disease, measured as proteinuria[55, 56] or elevated serum creatinine[57, 58] has been associated with early atherosclerosis in patients with SLE. End-stage renal disease (ESRD) in SLE is also associated with MACE. In a large study, lupus patients with ESRD had significantly higher cardiovascular mortality than age-matched non-SLE patients with ESRD.[59] A history of previous nephritis has also been associated with subclinical atherosclerosis in some[46, 51, 57, 60] but not all studies.[16, 61]

Glucocorticoids used to manage SLE disease activity also may impact cardiovascular risk. Glucocorticoids are known to increase blood pressure, blood glucose, cholesterol levels, and BMI.[28, 62] Several SLE cohort studies have demonstrated that longer duration of corticosteroid treatment[45, 63] and a higher accumulated corticosteroid dose,[36, 45, 51, 57, 61, 64–66] are associated with a higher incidence of cardiovascular events and atherosclerosis, although no significant association was found in others.[67–69]

Genetic risk factors

There is some evidence that SLE-specific genetic risk factors may also contribute to cardiovascular risk in SLE. An IL-19 risk allele was associated with a 2.3-fold increased risk for MI and stroke in SLE and a 2.8-fold increased risk in RA, but not in the general population. SLE patients with the risk allele had increased plasma levels of IL-10 and aPL antibodies.[70] The presence of one or more apolipoprotein L1 risk alleles was associated with a sevenfold increased odds for atherosclerosis in a cohort of African-American SLE patients.[71] Another study found that the H131R variant of Fcγ receptor IIA is associated with carotid plaque, markers of endothelial dysfunction, and platelet activity in SLE patients.[72]

General Mechanisms of Atherosclerosis

As in the pathogenesis of SLE, the interplay of multiple inflammatory mediators—including cytokines, chemokines, adhesion molecules, leukocytes, complement, and antibodies—contribute to the formation of atherosclerotic plaques.[73] Endothelial cell (EC) activation can occur in response to hemodynamic stresses such as hypertension[22] or exposure to cytokines such as TNFα or IL1β.[73] In response to endothelial cell activation, the expression of leukocyte adhesion molecules and chemokines is upregulated,[22] inducing a cascade that results in monocyte and T-cell migration into the subendothelial space.[73]

Review • DOI: 10.2478/rir-2021-0022 • 2(3) • 2021 • 157–172

Low-density lipoproteins (LDL) are also transported into artery walls. Once there, LDL is trapped and oxidized by reactive oxygen species (ROS) produced by nearby artery wall cells.[74] These oxidized low-density lipoproteins (oxLDLs) in turn stimulate further EC activation and monocyte recruitment.[73] The OxLDL are phagocytized by infiltrating monocytes/macrophages, which ultimately become foam cells around which atherosclerotic lesions are built.[74] HDLs are generally protective and can inhibit this cascade in several ways: HDL inhibit the migration of leukocytes in response to oxLDL,[75] inhibit the expression of cell surface adhesion molecules,[76] and can also prevent and reverse LDL oxidation.[76]

Circulating monocytes and T cells then transmigrate through the foam cell plaque as arterial smooth muscle cells infiltrate the lumen, leading to fibrosis. Cardiovascular events are ultimately caused by the occlusion of platelets in the narrowed artery and/or rupturing of the brittle fibrotic plaque.[73]

SLE-Specific Inflammation and Mechanisms of Atherosclerosis

Inflammation and immune dysregulation are hallmarks of the pathophysiology of SLE. Many of these same mechanisms may also contribute to the formation of atherosclerotic plaques in SLE patients. Greater insights into the pathogenesis of CVD may provide clues to potential biomarkers of risk in this population and may ultimately identify strategies for treatment.

The role of altered immune cell subtypes in SLE atherosclerosis

Lymphocyte and leukocyte population subtypes are commonly altered both in SLE and in CVD. General white blood cell numbers observed in routine clinical laboratory measurements would most likely not accurately identify patients with increased risk of CVD. Flow cytometry measurements of specific immune cell subtypes, however, might provide a biomarker panel to assist in predicting risk.

Monocytes/macrophages

Foam cells—cholesterol-rich macrophages (and, to a lesser extent, smooth muscle cells) that lose their ability to migrate and dispose of lipids—are generally considered as the main cell type that contributes to plaque. As macrophages mainly reside in tissues, **monocytes**—circulating macrophage precursors—are often examined in laboratory settings to approximate macrophage populations. Aberrant endothelial cell activation recruits circulating monocytes to transmigrate into the subendothelial space, where monocytes differentiate into macrophages and initiate atherogenesis via a complex interplay between endothelial cells, cytokines and chemokines, and other immune cells.[77, 78] About 90% of circulating human monocytes are $CD14^{hi}CD16^{-}$ and are often referred to as M1, inflammatory, or “classical” monocytes. $CD14^{lo}CD16^{+}$ monocytes, termed as M2, anti-inflammatory, or “non-classical” monocytes make up most of the last 10%. Although these monocyte classifications have proven to be controversial and somewhat misleading, as intermediate CD14+CD16+ populations exist and each kind of monocyte can behave with the opposite phenotype depending on the environment,[79] the M1/M2 characterization is useful to broadly characterize circulating monocytes.

Circulating monocyte subpopulations have been associated with atherosclerosis in SLE. The $CD14^{lo}CD16^{+}$ M2 monocyte population positively correlated with intima-media thickness (IMT) in a Polish SLE cohort.[80] Conversely, transcript analysis of *ex vivo* monocyte-derived macrophages in a small number of SLE patients with atherosclerosis suggested increased M1 skewing, including downregulation of Jak2 and STAT6, signaling molecules known to differentiate monocytes to the M2 macrophage phenotype.[81] In another study, intermediate $CD14^{+}CD16^{+}$ monocyte numbers were significantly higher in SLE patients with high IMT compared with healthy controls, although total monocyte numbers appeared to also be significantly higher in SLE patients.[82]

T cell subsets

T cells also play a major role in atherosclerosis initiation and progression. How *$CD4^{+}$ Treg cells* contribute to SLE is still debated, although multiple sets of data suggest that $CD4^{+}Foxp3^{+}$Treg numbers are significantly decreased in SLE patients.[83, 84] Treg cells appear to be atheroprotective in murine models[85, 86] and in some studies in humans if they continue to stably express Foxp3 and secrete IL-10.[87–89] One study suggests that $CD4^{+}CD25^{+}$Treg numbers are decreased in SLE patients with coronary artery disease,[90] yet another publication states that $CD4^{+}CD25^{+}Foxp3^{+}$ Treg numbers are lower in SLE patients with low HDL—but not with carotid atherosclerosis.[91] More studies on Treg numbers and markers in atherosclerosis in SLE, therefore, must be conducted before definitive conclusions are reached as to whether Treg would be a reliable biomarker for CVD risk.

IFNγ/CCR5-expressing *$CD4^{+}$ Th1* cells are generally accepted as the most abundant T cell subtype found in atherosclerotic plaques.[92–94] Multiple studies suggest $CD4^{+}$ T cell numbers are increased in non-autoimmune disease patients with atherosclerosis,[95] and several CD4+ T cell subsets have correlated with carotid IMT in SLE cohort studies. Increased senescent $CD4^{+}CD28^{null}$ T cell numbers correlated with carotid IMT in a Spanish SLE cohort,[96] and this atherogenic $CD4^{+}$ subtype is only found in primates[89] (greater numbers of $CD4^{+}CXCR3^{+}$ T cells correlated with higher carotid IMT in SLE patients in a French cohort[97]). Cytotoxic IFNγ-secreting Th1 cells that

Review • DOI: 10.2478/rir-2021-0022 • 2(3) • 2021 • 157–172

specifically recognize β_2-glycoprotein I (GPI) were isolated from human SLE plaque in an Italian cohort.[98, 99] $CD4^+$ T cells also expressing IL-17 were also increased in the former study and isolated from plaque in the latter, suggesting that *Th17* cells also contribute to plaque formation in SLE.

The role of *$CD8^+$ T cells* in SLE-mediated CVD is not as well understood. $CD8^+$ T cell numbers in human plaque are generally higher than $CD4^+$ cells.[100] Contradictory data in non-autoimmune mouse models and human studies suggest that $CD8^+$ T cells can act in both pro- and anti-atherogenic ways, possibly due to differing murine genetic backgrounds and as-yet nondelineated $CD8^+$ subtypes.[89] Greater numbers of atherogenic $CD8^+CD31^+CXCR4^+$ cells were noted in SLE patients versus healthy controls,[101] although their correlation to plaque or events was not examined.

B cells

Specific **B cell** populations also appear to distinctly influence atherosclerosis. *B2 cells* (follicular and marginal zone B cells) are thought to be atherogenic, based on murine depletion and adoptive transfer experiments.[102, 103] Murine *B1 cells*, through production and release of natural IgM that target oxidized lipids and other pro-inflammatory epitopes (discussed below), are believed to be protective, although dysregulated B1 cells have been reported to contribute to SLE progression through mechanisms that could include autoantibody production or declining function/numbers due to aging.[104, 105] Human studies that address B cell subtypes in atherosclerosis, however, are lacking and, in the case of B1 cells, controversial.

NETs and LDGs

Recent studies have found that **neutrophils** and neutrophil extracellular traps (NETs) are involved both in the progression of SLE disease activity[106–108] and atherosclerosis.[109, 110] NET formation occurs after neutrophils release nuclear DNA and associated proteins and enzymes, such as histones, myeloperoxidase (MPO), and neutrophil elastase (NE).[111] NET formation can be induced by multiple stimuli, including activation of Toll-like receptors 2/4, ROS, and multiple bacterial and viral antigens. Once formed, NETs can immobilize and kill pathogens through simple physical immobilization and enzymatic action of NE and cathepsin G.[112] Low-density granulocytes (LDGs), a neutrophil subtype that is found in patients with autoimmune diseases, produce high levels of pro-inflammatory cytokines and are much more easily induced to make NETs when compared with normal neutrophils/granulocytes.[108] Increased NET formation most likely leads to a "feed-forward" loop of increased oxidation, cytokine production, and citrullination resulting in excess thrombosis, coagulation, and endothelial damage.[108, 113, 114] Recent transcript analysis suggests that multiple subpopulations of SLE LDGs (distinguished by CD10 expression) express a pro-atherogenic and pro-vasculopathic phenotype that contributes to accelerated CVD in SLE patients.[115, 116]

Other potential mechanisms of and biomarkers for atherosclerosis in SLE

Interferon alpha

Interferon alpha and the "interferome"—the one thousand-plus genes IFNα regulates—are now considered to drive SLE disease activity. It is reasonable to suggest that high IFNα levels in SLE also influence accelerated atherosclerosis, as high IFNα levels are noted in plaque in non-autoimmune patients.[117] Indeed, activation of the interferon correlates with multiple mechanisms of dysregulated vascular cells. Smooth muscle cell progenitor differentiation is halted in IFNα-high mice, possibly leading to increased macrophage/foam cell generation,[118] and IFNα-activated endothelial cells increase.[119] Multiple studies in humans[120] and mice[121] also suggest that vitamin D might be able to ameliorate IFNα-driven endothelial dysfunction, possibly through activation of eNOS.[120] High IFNα levels have in fact been associated with endothelial dysfunction in patients with SLE.[122]

Oxidized Low-Density Lipoproteins (oxLDLs)

The oxidation of LDL is an important event in early atherosclerosis, and elevated levels of circulating oxLDL are strongly associated with coronary artery disease in the general population.[123] There is some speculation that oxLDL may contribute to increased atherosclerosis and thrombosis risk due in part to cross-reactivity between autoantibodies and oxLDL. Cardiolipin is a component of LDL, and anticardiolipin antibodies have been shown to bind oxLDL.[124] β_2-GPI also binds directly and stably to oxLDL, leading to antiphospholipid antibody recruitment to oxLDL.[125]

Higher levels of circulating oxLDL in SLE patients associate with a history of CVD[64, 126] and with thickened IMT on carotid ultrasound.[57] Risk of arterial thrombosis increases in the presence of detectable oxLDL/β_2-GPI complexes.[127] Interestingly, SLE glomerulonephritis has been associated with both higher levels of circulating oxLDL[126] and circulating oxLDL/β_2-GPI) complexes.[128]

Circulating "natural" IgM antibodies to oxLDL (anti-oxLDL) have also been described, although the relationship to the development and progression of atherosclerosis is unclear. Although anti-oxLDL is generally considered to be protective against atherosclerosis in murine models,[73] one human study demonstrated a positive association between anti-oxLDL and a history of CVD in SLE patients.[64] Conversely, one study demonstrated that antibody titers to phosphorylcholine (anti-PC antibodies), one phospholipid component of oxLDL, were inversely correlated with the presence of vulnerable carotid

Review • DOI: 10.2478/rir-2021-0022 • 2(3) • 2021 • 157–172

plaques in SLE.[129] In two other studies, anti-oxLDL and arterial disease were not associated.[130, 131] Additional experiments illustrated that anti-PC and malondialdehyde (MDA) IgM production was enhanced by B cell–T cell interactions, illustrating a possible link between innate and adaptive immunity that might be disrupted in SLE-mediated atherosclerosis.[132] Subsequent experiments by the same group suggest that anti-PC IgM activates and polarize Treg in an atheroprotective manner.[133] Titers of anti-oxLDL have also been associated with SLE disease activity.[134]

HDL structure and function

Higher amounts of circulating HDL are generally believed to be cardioprotective, yet HDL function might be equally or more important in evaluating HDL-associated atherosclerotic risk.[76] Both acute and chronic inflammations alter HDL function from anti-inflammatory to pro-inflammatory (piHDL). piHDL is made up of higher concentrations of pro-inflammatory protein components like serum amyloid A while protective protein concentrations of apolipoproteins A-I/M and paraoxonase are reduced.[135–139] Lipids and proteins in HDL can also be oxidized by multiple mechanisms, such as NETosis, leading to piHDL formation;[115, 140] piHDL effectively increases atherosclerosis because piHDL cannot carry out the normal antioxidant functions of HDL, like effective cholesterol efflux or removing oxidation from LDL.[141]

HDL function is abnormal in approximately 10 times more SLE patients than controls.[142] piHDL associates with both presence [61] and progression [52] of subclinical carotid artery plaque and associates with cardiovascular events in SLE.[143] The ability of HDL to effectively flux cholesterol was reduced in SLE patients versus controls and inversely correlated with carotid plaque.[141] HDL from women with primary antiphospholipid syndrome exhibited reduced beneficial effects on endothelial cell activation.[144] Anti-HDL and anti-paraoxonase antibodies are also associated with subclinical CVD[145] in SLE. Lower paraoxonase activity associates with higher carotid artery IMT and abnormal flow-mediated dilation in primary APS patients [144] and also associates with atherosclerotic events in patients with SLE.[146]

B-cell activating factor (BAFF)/B lymphocyte stimulator (BLyS)

Soluble B-cell activating factor (BAFF)/B lymphocyte stimulator (BLyS) is the target of belimumab, and its inhibition is believed to suppress autoimmunity by ultimately depleting B cells by blocking class-switch recombination. Unexpectedly, multiple groups have found that in multiple (non-autoimmune) mouse models of CVD, BAFF blockade utilizing a murine-optimized belimumab actually led to significant increases in atherosclerosis.[147, 148] Recent data in a mouse model of lupus and atherosclerosis found that BAFF inhibition improved atherosclerosis lesions in mice with low plasma cholesterol levels but worsened the lesions in mice with high cholesterol levels.[149]

Human data also suggest a complicated scenario where high serum BAFF levels positively correlate with subclinical atherosclerosis, although multiple BAFF genetic variants might positively and negatively affect plaque formation.[150, 151] Endothelial progenitor cells (EPCs) also express receptors for all BAFF family members; functionally deficient EPCs isolated from SLE patient PBMC return to normal with co-incubation of BAFF and belimumab.[152] Subclinical atherosclerosis and cardiovascular event data in patients taking belimumab are not available, although no abnormal event data was noted in clinical trials. More characterization of the role of BAFF in SLE CVD will take place as longitudinal belimumab therapy data accumulates in the near future.

Adipocytokines

White adipose tissue has recently been recognized as an endocrine organ that secretes adipokines that regulate energy homeostasis and metabolism. The adipokine leptin is an anorectic peptide that acts on the hypothalamus to modulate food intake, body weight, and fat stores.[153] Obese patients have high circulating leptin levels, but they develop resistance to leptin similar to insulin resistance in type II diabetes.[153] Hyperleptinemia in the general population associates with hypertension, metabolic syndrome, and atherosclerosis.[153] In addition, leptin has been linked to increased oxLDL levels and increased oxidative stress in endothelial cells and cardiomyocytes.[154] Conversely, adiponectin is the most abundant adipocytokine in human plasma, and levels are inversely correlated with adipose tissue mass.[155] Adiponectin levels are reduced in type II diabetes and CVD.[155]

Several small cohort studies have shown elevated leptin levels in adult [156–158] and pediatric [159] SLE patients. In our cohort, mean leptin levels were significantly higher in the SLE patients with carotid plaque than in those without plaque, and also weakly correlated with carotid IMT.[160] In another cohort, adiponectin levels were significantly and independently associated with carotid plaque in SLE.[161] However, Chung *et al.* found no significant relationship between leptin or adiponectin levels and coronary calcification.[162]

Homocysteine

Homocysteine is a predictor of atherosclerosis in the general population. Homocysteine may contribute to the pathogenesis of atherosclerosis through several mechanisms, as it is prothrombotic,[163] can enhance foam cell formation in vessel walls, and has toxic effects on endothelial cells.[164–166] Hyperhomocysteinemia can result from increased age, renal

Review • DOI: 10.2478/rir-2021-0022 • 2(3) • 2021 • 157–172

insufficiency, medications such as methotrexate, genetic factors, and dietary factors.[167, 168]

In SLE, elevated homocysteine correlated with cross-sectional[37, 46, 63, 64, 169] and longitudinal[17, 52, 170] progression of subclinical atherosclerosis in multiple studies, and with cardiovascular events.[143, 171] However, homocysteine did not correlate with atherosclerosis in SLE in all studies.[16, 56, 172]

The PREDICTS model

Homocysteine, along with other biomarkers such as piHDL, leptin, and soluble tumor necrosis factor-like weak inducer of apoptosis (sTWEAK), plus clinical variables such as increased age and diabetes were combined into a risk prediction panel, *PREDICTS*. When patients in a longitudinal cohort study had a high-risk *PREDICTS* score at cohort entry, they were significantly more likely to have future progression of carotid plaque[52] and major adverse cardiovascular events.[143, 171]

Other potential biomarkers

Increased osteopontin (OPN) levels are used as biomarkers of increased risk of multiple neurological and CVDs.[173] Lupus nephritis severity, neuropsychiatric SLE manifestations, and possibly SLE disease activity correlate with high plasma OPN levels.[174–177] In addition, OPN levels correlated with IMT in SLE patients, in contrast to the inverse correlation observed in the healthy control subgroup of the same study.[178]

Plasma levels of β2 microglobulin (B2M), an essential component of MHC class I, predicted multiple cardiovascular morbidity and mortality better than hs-CRP in non-autoimmune patients.[179] B2M also positively correlated with carotid plaque and CAC in SLE patients.[180] Multiple apoptosis markers, including plasma IL-8, Matrix metalloproteinase 7 (MMP-7), and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) receptor-2, are also associated with carotid plaque in SLE patients.[181]

Strategies to Prevent and Treat CVD In SLE

Unfortunately, few randomized clinical trials exist exploring the prevention of CVD in SLE patients. In addition, recruitment and retention difficulties are barriers to carrying out such trials.[182] This leaves physicians with little evidence-based guidance for reducing CVD risk. Therefore, current recommendations are similar to general strategies to manage CVD risk in the general population and include strategies such as smoking cessation, controlled diabetes mellitus, and exercise.[183] There is also some evidence of the benefit of aspirin use in SLE patients, especially if they have at least one traditional CVD risk factor.[184]

Statins

Statins utilize multiple mechanisms to provide benefits in reducing CVD risk. The most well-known is the lipid-lowering property. Other potential mechanisms include anti-inflammatory and immunomodulatory effects, carried out via inhibition of adhesion molecules, T-cell activation, secretion of pro-atherosclerotic cytokines and chemokines, and ROS formation.[185–190] Further studies are required to confirm whether these mechanisms are beneficial in SLE.

With demonstrated effects in various anti-inflammatory pathways, it is fair to presume that statins provide SLE patients benefit. However, there is inconclusive evidence in support of statin use in SLE patients. A 2-year randomized controlled trial of atorvastatin did not show a significant difference in carotid IMT, CAC, or carotid plaque compared with controls, with the caveat that it is not expected that statins can improve these measures after only 2 years of therapy.[191] A similar outcome was observed in a 3-year study of children evaluating the effect of statin use on subclinical atherosclerosis,[192] although a follow-up study showed slowed progression of carotid IMT in the subgroups of 15.5-year-olds with a high CRP.[193] Despite the lack of evidence that statins improve measurable atherosclerotic disease, a UK-based study showed that statin use across different autoimmune rheumatic diseases was associated with all-cause mortality reduction (HR of 0.85), compared with propensity score–matched non-initiators.[194]

Statin studies in the general population involved very large cohorts with a longer follow-up,[195] while studies on SLE patients are typically smaller and shorter in duration.[196] It is possible that larger and longer randomized clinical trials may show positive results in the SLE group. Until then, statin use in SLE patients should be based on the recommendations of the American Heart Association and American College of Cardiology, with SLE considered equivalent to DM as a risk factor.[196, 197]

Antihypertensives

The current American College of Cardiology/American Heart Association Guidelines published in 2017 defines hypertension as a blood pressure ≥130/80.[198] A longitudinal study of SLE patients showed that the cohort with Stage 1 hypertension, defined as 130–139/80–89, had a greater risk of atherosclerotic events compared with the normotensive cohort.[199] The Seventh Joint National Committee recommends a blood pressure goal of 130/80 for patients with high-risk conditions such as DM or SLE [200, 201] although the Eighth Joint National Committee recommends a goal of <140/90.[202]

There exists no lupus-specific anti-hypertensive regimen guideline.[203] In the high cardiac risk general population,

Review • DOI: 10.2478/rir-2021-0022 • 2(3) • 2021 • 157–172

ACE-inhibitors (ACE-I) reduce the risk of MI, CVA, and cardiovascular death, with benefits greater than would be expected for the amount of blood pressure reduction observed.[204] In SLE patients, ACE-I has been shown to delay the onset of renal involvement as well as lower the risk of SLE disease activity.[205] European Alliance of Associations for Rheumatology (EULAR) recommends ACE-I as a first-line anti-hypertensive in inflammatory arthritis due to its beneficial effects on inflammatory markers and endothelial function in rheumatoid arthritis.[206] Angiotensin II receptor blockers are a viable alternative in patients who do not tolerate ACE-I, and can also result in a significant reduction in proteinuria.[207] Thiazide diuretics and calcium channel blockers are other first-line anti-hypertensives recommended by the AHA/ACC,[198] and there are no apparent contraindications in SLE patients. Beta-blockers should be used with caution, as they can trigger Raynaud's phenomenon and its associated complications.[208]

Hydroxychloroquine

Hydroxychloroquine, a drug used commonly to treat the clinical manifestations of SLE, also appears to have cardiovascular benefits. *In vitro* studies have shown it to reduce the synthesis of cholesterol.[209] Studies in SLE patients also demonstrate a reduction in cholesterol in patients taking hydroxychloroquine, both with and without concomitant corticosteroid use.[210] Multiple studies show that anti-malarials have an anti-thrombotic effect[211–214] and improve overall survival.[215] SLE patients not using hydroxychloroquine have been found to have increased aortic stiffness [216] and increased carotid IMT.[16] Hydroxychloroquine use had an inverse correlation with cardiac events in SLE, but not strokes.

Treatment of disease activity

There are currently no published randomized controlled trials of lupus therapies that have included cardiovascular outcomes as study endpoints. Thus, the impact of traditional disease modifying agents and newly approved biologic therapies on cardiovascular risk in SLE is still unknown. It is likely, however, that controlling disease activity while minimizing corticosteroid use will be critical for future success in preventing cardiovascular damage in SLE. Treatment targets such as LLDAS and remission have been shown to improve quality of life and protect against irreversible organ damage.[217–220] Achievement of LLDAS 50% of the time reduced the risk of MI and renal injury in one cohort study [219] and was associated with reduced mortality risk.[221]

Summary

Patients with SLE have an increased prevalence of CVD that also occurs at an earlier age. The cardiovascular risk in SLE is likely due to a complicated inflammatory process characterized by the interactions of numerous different moieties including lipids, enzymes, chemokines, and multiple peripheral blood cells. The SLE-related factors that account for this increased risk are likely numerous and related to the factors described. Future studies that enhance our understanding of the pathogenesis of SLE will hopefully allow us to identify specific treatment strategies to prevent CVD and improve the overall quality of this at-risk population.

Conflict of Interest

MM has been a consultant for Astra Zeneca, Aurinia Pharmaceuticals, Eli Lilly, and Glaxo Smith Klein. None of these entities had any input into manuscript design or content.

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