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Cardiovascular disease in lupus: insights and updates

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Abstract

Purpose of review—With improved management of the classical disease manifestations of systemic lupus erythematosus (SLE), cardiovascular disease (CVD) has emerged as one of the most important causes of morbidity and mortality. This review in particular focuses on progress over the past year in clinical and basic aspects of SLE-driven accelerated atherosclerosis.

Recent findings—Both subclinical CVD and CV events continue to be recognized at increased frequency in previously unstudied lupus cohorts and populations. Novel associations have been identified between lupus CVD and cognitive impairment, depression, and low income status. In terms of pathogenesis, there is an ever-increasing focus on the innate immune system and, in particular, type I interferons (IFNs). Recent studies have drawn connections in both human and murine models between neutrophils, plasmacytoid dendritic cells, type I IFNs, and endothelial dysfunction. Whether treatments such as mycophenolate mofetil or statins have a role in prevention of lupus CVD is an area of intensive study.

Summary—CVD is a major complication of lupus and is now a leading cause of death among people living with this disease. As such, additional studies are needed in order to identify the most effective preventive strategies and most predictive vascular risk biomarkers. Type I IFNs may play a critical role in lupus CVD pathogenesis, and it is recommended that vascular outcomes be included in ongoing trials testing the efficacy of anti-IFN biologics.

Keywords

systemic lupus erythematosus; cardiovascular disease; atherosclerosis; type I interferons; neutrophil extracellular traps

INTRODUCTION

The prevalence of premature CVD, especially in young women with SLE, is striking, and may be as high as 50-fold depending on the study and outcome measure [1,2]. A significant percentage of patients with SLE have evidence of subclinical vascular disease, such as increased carotid intima-media thickness (CIMT) [1,3,4] and myocardial perfusion abnormalities [5], findings which are not explained by traditional risk factors [4,6]. While all-cause mortality in SLE has improved significantly with improved monitoring and immunosuppressive treatments, CVD remains a leading cause of death [7]. The interplay between SLE and CVD is a rapidly expanding area of study and has recently been comprehensively reviewed [8,9]. Here, we will focus on those areas that have seen

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substantial progress over the past year, primarily focusing on the clinical and basic science of CVD attributable to accelerated atherosclerosis.

EPIDEMIOLOGY, RISK FACTORS, AND BIOMARKERS

Investigators of lupus CVD have characterized novel populations, correlations, and biomarkers within the past year.

Epidemiology of CVD in SLE

A nationwide study from Sweden considered whether hospitalization for immune-mediated diseases such as SLE and rheumatoid arthritis was predictive of a subsequent hospitalization for coronary artery disease (CAD). Indeed, the standardized incidence ratio (SIR) for a CAD-related hospitalization in lupus patients was 4.94, making SLE (albeit the subset of patients with enough disease activity to require hospitalization) the second highest-risk condition of 32 immune-mediated diseases considered [10]*. A recent population survey considered death certificates for lupus patients in São Paulo, Brazil, and found that renal failure and infectious diseases were still the most frequent causes of death [11]; the authors contrasted this to the higher proportion of deaths attributable to CVD in North American and European countries. Another interesting study assessed patients with at least two years of serologically active but clinically quiescent (SACQ) SLE [12]**. Treatment with antimalarials was permitted, but corticosteroid and immunosuppressive medications were not. SACQ patients acquired less lupus-related damage after three and 10 years, including renal damage in just 3.6% of SACQ patients versus 23.6% of clinically-active patients at 10 years [12]**. There was also a strong trend toward a reduction in new coronary events (1.8% vs. 7.3%; $p=0.06$) after 10 years [12]**.

A final group of epidemiologic studies in 2012 drew our attention to patient-centric associations that we might less commonly consider in lupus CVD. One longitudinal study asked whether CV risk factors and outcomes were associated with cognitive impairment [13]. Indeed, the prevalence of cognitive impairment was 15% in lupus patients with CVD, correlating with history of stroke, hypertension, and antiphospholipid (aPL) Abs [13]. A separate cross-sectional analysis considered the association between depression and subclinical CVD in lupus patients, and found a significant odds ratio of 3.85 in a multivariable model regarding the ability of depression to predict CVD [14]. Finally, in white, but not African American, patients with SLE, low income increased the risk of myocardial infarction (MI) and stroke, with significant odds ratios of 3.24 and 2.85, respectively [15]*.

Risk factors

Historically, lupus activity, disease duration, and corticosteroid use have emerged as the most reproducible nontraditional risk factors for CVD in lupus patients; these observations have been supported by recent analyses [16–18]. Lupus patients also have a higher burden of traditional risk factors [19,20] as compared to patients without lupus, with one study suggesting a particular role for smoking as a predictor of CV mortality [21].

The genetics of CVD in lupus patients has yet to be extensively assessed, although a recent study asked whether single nucleotide polymorphisms (SNPs) associated with thrombosis in the general population might also predict thrombosis in lupus [22]. In a large lupus cohort, 23% experienced a thrombotic event, and predictive SNPs were identified in genes that included factor V and methylenetetrahydrofolate reductase [22]. Circulating levels of both matrix metalloproteinase (MMP)-2 and MMP-9 have previously been reported as elevated in lupus patients [23]. Given the role of MMP-2 in the breakdown of the endothelial basement membrane, along with its recognized role in CVD [24], a recent study asked whether a

MMP-2 promoter polymorphism that affects circulating protein levels would predict risk of CVD in an Iranian cohort of lupus patients [25]. Indeed, the promoter genotype associated with higher MMP-2 activity was associated with both lupus CVD and a higher-risk cholesterol profile [25]. Such genetic analyses will almost surely be applied with increasing frequency to lupus CVD in the future.

Biomarkers

The role of autoAbs in the accelerated atherosclerosis of SLE is a complex topic, without a clear consensus [26]. Antiphospholipid (aPL) Abs are frequently found in patients with SLE and have been considered as possible predictors of atherosclerosis, albeit with mixed results [27–31]; a recent review of the topic did suggest a significant increase in the subclinical marker CIMT in patients with primary aPL Ab syndrome as compared to controls [32]. Other autoAbs with suggested roles in lupus CVD are directed against apolipoprotein A1 [33,34], high-density lipoprotein (HDL) [34], and heat-shock protein 60 [35].

Some updates from 2012 include the description of aPL Abs as stimulators of tissue factor (TF) expression on the surface of lupus peripheral blood mononuclear cells, correlating with risk of peripheral vascular disease [36]*. Given the postulated role for TF in atherogenesis [37], as well as in aPL Ab-induced thrombosis [38,39], the authors speculate that TF may play a mechanistic role in lupus CVD [36]*.

HDL normally serves a protective role in atherosclerosis, mediating reverse cholesterol transport and protecting LDL from oxidation. However, in SLE, so-called proinflammatory HDL (piHDL) can be detected in as many as 45% of patients, correlating with increased oxLDL formation, carotid plaque, and CIMT [40,41]. Further, a piHDL phenotype, including the detection of oxidized forms of HDL, has been appreciated in murine models of SLE [42,43]**, where treatment with apoA1 mimetics has shown promise [44]. In general, interplay between oxidative stress and lupus CVD will surely receive increased attention in the coming years [45–47].

In addition to autoAb and lipid profiles, some novel biomarkers of CVD in SLE have recently been considered. In a prospective cohort study, both high-sensitivity C-reactive protein (hsCRP) and higher 10-year Framingham risk scores were predictive of future CV events (MI or angina) in lupus patients, with hsCRP levels greater than 1.6 mg/liter giving a statistically-significant hazard ratio of 3.37 [48]. The authors argue for measuring hsCRP to predict CVD risk, as one might do for selected patients in the general population [48]. Defensins activate monocyte-lineage cells to release proinflammatory cytokines, while also serving as chemokines and regulating activation of the complement cascade [49,50]. Both defensin-specific autoAbs [51] and elevated circulating defensin levels [52,53] have been described in SLE. A recent report showed that levels of human beta defensin 2 (hBD2) and human neutrophil peptide (HNP) were predictive of future CV events, as well as progression of subclinical disease [54]*. This result is especially interesting given the presence of defensins in neutrophil extracellular traps (NETs), which will be discussed in more detail below, and which we have speculated on previously with regards to CVD [55]. In general, none of the biomarkers described to date clearly differentiate CVD risk from lupus disease activity, and this will surely be a focus of future clinical studies

PATHOGENESIS: THE CRITICAL ROLE OF INNATE IMMUNITY

Although T and B cells are indispensable for lupus pathogenesis, they have not been definitively linked to lupus CVD. In contrast, links between innate immunity, SLE, and CVD are myriad. In our opinion, the most compelling of these suggests a critical role for

type I interferons (IFNs) (Table 1). Recently described roles for cellular mediators of innate immunity such as neutrophils and platelets also exist.

Type I IFNs

Type I IFNs (including 15 subtypes of IFN- α , one IFN- β , and several other less-studied forms) share a single receptor, and represent an important group of cytokines in host defense, especially against viral infection [68]. Type I IFNs have received considerable attention as mediators of lupus pathogenesis in human and murine systems [43,69–73], and drugs targeting type I IFNs are currently in clinical trials for management of SLE in humans [74,75]. Plasmacytoid dendritic cells (pDCs) are well-recognized secretors of IFN- α in SLE [76], while myeloid-lineage cells may also play a role in type I IFN production [77]. The antiangiogenic properties of type I IFNs have been recognized for decades in the cancer literature [78], but investigators have only more recently considered their role in lupus CVD (Table 1), where endothelial injury, and failed repair, during lupus disease flares could lead to initiation and expansion of vascular lesions, ultimately challenging endothelial integrity and predisposing to atheroma formation.

Lessons from animal models

With the exception of the hypercholesterolemia-inducing knockout models of apolipoprotein E [apoE(–/–)] and the LDL receptor [LDLR(–/–)], mice do not develop atherosclerotic lesions *a priori* [79]. Therefore, in the absence of spontaneous atherosclerosis in lupus models, investigators have either crossed lupus-prone genotypes with the aforementioned proatherogenic backgrounds, or have focused on subclinical markers of endothelial dysfunction. The combined lupus/atherosclerosis models have generally shown acceleration of both the lupus and atherosclerosis phenotypes [80–84], although the role of type I IFNs in these lupus/atherosclerosis models has not been examined.

In an interesting 2012 study, LDLR(–/–) mice were crossed with the lupus-prone strain Sle16 to create a new lupus/atherosclerosis model [85]**. Atherosclerosis was again accelerated by the lupus phenotype, while hypercholesterolemia enhanced both the nephritis score and C3 deposition in kidneys [85]**. Intriguingly, despite more C3 in the kidneys, there was less deposition in atherosclerotic lesions [85]**. Further, lesional C3 deposition was inversely correlated with the number of apoptotic cells, arguing that complement depletion by active lupus may prevent complement-mediated repair of the damaged endothelium and developing plaque [85]**. These observations are reminiscent of some of the aforementioned lupus/atherosclerosis models that also demonstrated accumulation of apoptotic debris [80,82], albeit without considering the role of complement.

In another paper from 2012, the role of type I IFNs in the subclinical vascular dysfunction of lupus-prone mice was assessed [43]**. Knockout of the type I IFN receptor in the lupus-prone model NZM2328 improved endothelium-dependent vasorelaxation, EPC numbers and function, and *in vivo* neoangiogenesis; these effects were independent of sex (male mice do not typically develop nephritis or high-titer anti-dsDNA Abs in this model) arguing against a global impact of disease activity [43]**. Further, acute administration of IFN- α worsened both endothelium-dependent vasorelaxation and EPC function in lupus-prone, as well as non-lupus-prone, mice [43]**. In the same 2012 study, the impact of type I IFNs on apoE(–/–) mice (without lupus predisposition) was also considered [43]**. Knockout of the type I IFN receptor resulted in decreased atherosclerosis severity, with decreased recruitment of F4/80-positive macrophages and CD3-positive T cells into lesions [43]**. These observations are substantiated by another recent study in which IFN- β administration to apoE(–/–) and LDLR(–/–) mice resulted in accelerated atherosclerosis as well as increased macrophage recruitment into lesions [63]. Further, specific blockade of type I IFN signaling

in myeloid cells inhibited atherosclerosis and protected against accumulation of macrophages [63].

Additionally, several recent studies have considered the role of type I IFN-producing pDCs in the atherosclerotic lesions of non-lupus-prone apoE(−/−) mice. Although splenic and aortic pDC numbers did not differ between control and apoE(−/−) mice, pDCs from apoE(−/−) mice had a more activated phenotype [64]*. Further, when pDCs were depleted by monoclonal Ab treatment, atherosclerotic plaque area was significantly reduced, as was macrophage recruitment [64]*. In terms of pDC stimulation, another study considered the possibility that protein-DNA complexes derived from neutrophil extracellular traps (NETs) might activate pDCs and thereby accelerate atherosclerosis [86]**. As will be discussed in more detail below, NETs—consisting of chromatin, the cathelicidin-LL37 peptide, and other proteins derived from azurophilic granules—are potent stimulators of pDCs in various lupus models [87–89]. Indeed, both NETs and the murine orthologue of cathelicidin-LL37, CRAMP, were detected at the luminal surface of atherosclerotic arteries, while depletion of either pDCs or CRAMP protected against atherosclerosis and reduced anti-double-stranded DNA (dsDNA) titers [86]**. A final relevant study in 2012 considered the role of CRAMP in apoE(−/−) atherogenesis by focusing in particular on early lesions [90]. CRAMP derived from neutrophils was found especially along the luminal surface in these early lesions, where it was sufficient to enhance monocyte adhesion [90]. Although all these studies were performed in models without a predisposition toward the lupus phenotype, the intriguing link between CRAMP/NETs, pDC activation, and vascular damage seem highly relevant to lupus vasculopathy.

Neutrophils

Although historically receiving relatively little attention in lupus pathogenesis, neutrophils have emerged in the past five years as potentially indispensable players [91]. In 2004, a new form of programmed cell death, NET formation, was described [92]. As above, NETs represent extracellular chromatin decorated with neutrophil-derived proteins, and presumably function to trap and kill pathogens [93]. A subset of lupus patients have an impaired ability to degrade NETs [94,95]. Lupus neutrophils are also predisposed to enhanced NET release, with stimulatory roles for both type I IFNs and autoAbs such as anti-cathelicidin-LL37 and anti-RNP [87–89]. Further, our group has suggested that a proinflammatory subset of lupus neutrophils termed low density granulocytes (LDGs) are especially primed for NET release, with LDG-derived NETs capable of endothelial damage in vitro [89]. Our group has also shown that NETs, and especially cathelicidin-LL37, can activate the inflammasome in macrophages, resulting in an activated, and potentially pro-atherogenic, phenotype [96].

In other disease models [97,98], including atherosclerosis [90,99], NETs have emerged as mediators of vascular damage, and are also being increasingly recognized as an integral and stimulatory component of deep vein thrombi [100]. Our group has recently shown that these potentially damaging pathways may also be active in lupus models. Lupus-prone NZM2328 mice demonstrate enhanced NET formation and high titers of anti-NET autoAbs as compared to nonautoimmune controls [101]. Further, inhibition of NET formation with an inhibitor of histone deimination, mitigates the endothelial dysfunction and accelerated thrombosis characteristic of these mice [101]. These findings remain to be confirmed in other models and with other NET inhibitors.

Platelets

Activated platelets have a recognized role in atherothrombosis [102], and as mediators of immunity and inflammation. They not only release cytokines, but also express CD40 ligand

(CD40L/CD154), FcγRIIa, and TLRs—among other immunologically relevant molecules—on their surface [103]. Patients with SLE have increased platelet activation compared to controls [104,105], and, recently, interplay between type I IFNs, platelets, and vascular damage has been suggested. A type I-IFN signature has been described in the transcriptome of lupus platelets, extending to the protein level for selected type I IFN-regulated genes [106]. This type I-IFN signature, as well as platelet activation, were more likely to be found in lupus patients with a history of vascular events, compared to lupus patients without [106]. Platelets may also play a role in the vicious cycle of type I IFN production, given that they upregulate CD40L on their surface in response to circulating ICs, and activate pDCs to release more type I IFNs via a CD40L-CD40 interaction [107]. Further, either platelet depletion or inhibition of platelets with clopidogrel can improve nephritis and disease activity in murine models [107]. Whether, antiplatelet agents have a unique role in protecting against lupus CVD in experimental models remains to be determined. Potential interplay between NETs and platelets in lupus CVD, as has been seen in other models of vascular damage [97,108], also remains to be defined.

LUPUS THERAPEUTICS

Corticosteroids, widely used as adjuvant treatment in SLE, likely have mixed effects on CVD. While there has long been evidence that duration of prednisone use can independently predict risk of CVD events [109], there is also evidence that, over time, more aggressive treatment with drugs like cyclophosphamide and corticosteroids, will correlate with reduced CVD burden [4]. In terms of drugs with a specific role in the treatment of the disease manifestations of SLE, two—the antimalarials and mycophenolate mofetil—have received the most attention for their potential cardioprotective benefits. In recent years, there has also been increasing interest in whether drugs with defined roles in diseases like hypercholesterolemia and diabetes might have particular benefit in patients with SLE.

Antimalarials

In general, antimalarials are probably vasculoprotective, and, indeed, antimalarial use in SLE correlates with reduced vascular stiffness [110], decreased prevalence of carotid plaque [4], and lower total cholesterol levels, especially in patients taking corticosteroids [111]. Further, in a nested case-control study, antimalarials were the only protective factor against thrombovascular events in a multivariate analysis [112], consistent with the antithrombotic effect of these drugs in relevant murine models [113]. One recent study did suggest a counter to the generally vasculoprotective data for antimalarials, showing that chloroquine impairs cholesterol efflux from macrophage foam cells [114], a phenomenon that will require further investigation in the context of SLE.

Mycophenolate mofetil

In patients without SLE, a short course of mycophenolate mofetil (MMF) decreases T cell activation and increases regulatory T cells in carotid artery plaques [115], and may also protect against cardiovascular mortality in renal transplant patients with pretransplant diabetes [116]. Further, recent murine data showed a promising effect of MMF on atherogenesis in a combined model of lupus and atherosclerosis [117]*. When LDLr(−/−) mice were transplanted with bone marrow from a lupus-prone strain, MMF, but not atorvastatin, attenuated atherosclerosis and the recruitment of CD4-positive T cells into lesions; this was without an effect on markers of lupus activity, such as kidney pathology [117]*. Despite this interesting experimental data, in another 2012 study, MMF did not improve either CIMT or CAC over a two-year period in a prospectively-followed lupus cohort [118]**. However, an important caveat of this study is that a relatively small number

of patients, 25 out of 187, were treated with MMF at any point during the two years, and the question will therefore need to be reconsidered in larger cohorts.

Statins

In lupus-prone NZB/W F₁ mice, atorvastatin treatment reduced anti-dsDNA Ab levels and also improved both proteinuria and kidney histology; the clinical changes were accompanied by reduced expression of MHC class II and CD80/86 on B cells [119]. Further, in a combined lupus/atherosclerosis model, simvastatin therapy not only reduced atherosclerotic lesion area, but also reduced lymphadenopathy and nephritis, while shifting the inflammatory pattern from T_H1- to T_H2-predominant [120]. In patients, anecdotal reports suggest that statins may reduce proteinuria in lupus nephritis, at least in the short term [121], while an eight-week course of atorvastatin improved flow-mediated dilation in young, female lupus patients [122]. However, a two-year trial of atorvastatin in adult patients with SLE, but without clinical CVD, showed no difference in CAC, CIMT, or disease activity [123]. In addition, the recently published APPLE trial, which administered atorvastatin to pediatric lupus patients over 36 months, reported no difference in CIMT, although hsCRP and lipid profiles did improve [124]*. An important, although understandable, caveat to the clinical trials published to date is their relatively small size and power [125]. Nevertheless, despite interesting experimental and shortterm clinical data, there is no evidence at present to support the use of statins in lupus patients who do not meet criteria for their use based on standard CVD guidelines.

Thiazolidinediones

Thiazolidinediones (TZDs), such as rosiglitazone and pioglitazone, modify gene expression as agonists of peroxisome proliferator-activated receptor gamma (PPAR γ), a regulator of adipocyte differentiation, lipid and carbohydrate metabolism, and inflammation. Given the anti-inflammatory properties of TZDs, there has been interest in their impact on both SLE in general and lupus CVD. In a combined lupus/atherosclerosis model, rosiglitazone mitigated autoAb production, renal disease, and atherosclerosis [126], with the beneficial effect mediated by the anti-inflammatory adipocytokine adiponectin. Both rosiglitazone and pioglitazone are also renal-protective in NZB/W F₁ mice [127,128], while pioglitazone additionally was shown to have a positive impact on endothelial regeneration and function [128]. Recently, for the first time, the impact of pioglitazone on the CV risk profile of lupus patients was considered [129]. In a small group of young, female lupus patients, pioglitazone administration over three months improved HDL levels, insulin resistance, and HDL size, while decreasing markers of inflammation such as CRP and serum amyloid A; specific markers of endothelial function were not considered [129]. It also remains to be determined whether TZDs (or other non-TZD PPAR γ agonists) might improve disease activity in lupus patients.

CONCLUSIONS

Evidence indicates that the rheumatologist can help mitigate CV risk by effectively controlling lupus disease activity. The treatment of traditional CV risk factors should also be attempted, and further education of rheumatologists regarding the need to identify, monitor, and treat these factors is required. We propose an important role for type I IFNs in lupus CVD, a hypothesis that has gained support in the field of CVD in general. Going forward, there should be continued focus on understanding the extent to which specific therapeutic regimens—whether already available, like antimalarials and MMF, or novel, like anti-IFN—might be particularly effective against this significant cause of morbidity and mortality in patients with SLE.

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KEY POINTS

- SLE—and especially active SLE—is a risk factor for subclinical endothelial dysfunction and CV events, an observation which continues to be supported by the most recent epidemiologic studies.
- Type I IFNs likely play a critical role in both endothelial dysfunction and atherogenesis in lupus patients, patients with other autoimmune diseases, and, potentially, in the general population.
- NET formation—a process by which neutrophils externalize chromatin and granule-derived proteins—is a likely cause of endothelial damage in SLE, which may be one of the first steps in atherogenesis.
- Further study is needed to better understand the impact of lupus-specific medications such as antimalarials and mycophenolate mofetil, as well as cholesterol-lowering and anti-platelet agents, on lupus CVD.

Table 1

Impact of type I IFNs on the vasculature and atherosclerotic lesions

Endothelial cells (ECs)	
Increased EC apoptosis	[3]
Decreased levels and function of reparative EC progenitors	[43,56–61]
Inhibition of proangiogenic pathways, including VEGF and IL-1 β	[58]
Upregulation of IL-18 which interferes with normal EC progenitor differentiation	[62]
Macrophages	
Increased macrophage recruitment into atherosclerotic lesions	[43,63,64]
Upregulation of TLR4, with increased TNF- α , IL-12, and MMP-9 production	[65]
Upregulation of scavenger receptor A, thereby priming for foam cell formation	[66]
T cells	
Increased T cell recruitment into atherosclerotic lesions	[43]
Promotion of T cell-mediated smooth muscle cell death and plaque instability	[67]