Atherosclerosis in Patients With Autoimmune Disorders

Johan Frostegard

Abstract—Recent findings indicate that presence of activated immune competent cells and inflammation are typical of atherosclerosis, the main cause of cardiovascular disease (CVD). The risk of CVD is very high in a prototypic autoimmune disease, systemic lupus erythematosus (SLE), and is also raised in other autoimmune diseases such as rheumatoid arthritis. Autoimmune-related CVD and atherosclerosis are important clinical problems. They may also shed light on interactions between immune reactions and atherosclerosis development and manifestations, not least in women, who have a much higher risk of autoimmune disease than men. In general, a combination of traditional and nontraditional risk factors, including dyslipidemia (and to a varying degree, hypertension, diabetes, and smoking), inflammation, antiphospholipid antibodies (aPLs), and lipid oxidation, contribute to CVD in autoimmune diseases. Premature atherosclerosis is likely to be a major underlying mechanism, although distinctive features, if any, of autoimmune-related atherosclerosis compared with “normal” atherosclerosis are not clear. One interesting possibility is that factors such as inflammation, neoepitopes on endothelial cells, or aPLs make atherosclerotic lesions in autoimmune disease more prone to rupture than in “normal” atherosclerosis. Some cases of autoimmune-related CVD may be more related to thrombosis than atherosclerosis. Whether premature atherosclerosis is a general feature of autoimmune diseases such as SLE or only affects a subgroup of patients whereas others do not have an increased risk remains to be demonstrated. Treatment of patients with autoimmune disease should also include CVD aspects and be focused on traditional risk factors as well as on disease-related factors. Hopefully novel therapeutic principles will be developed that target the causes of the inflammation present in atherosclerotic lesions. (Arterioscler Thromb Vasc Biol. 2005;25:0-0.)

Key Words:

It is now well established that atherosclerosis has many characteristics in common with an inflammatory disease, characterized by infiltration in the intima of activated monocytes/macrophages and T cells.1–4 Proinflammatory cytokines are produced by cells in the lesions.4,5 The inflammatory nature of atherosclerosis is now well recognized, but the causes of this inflammatory reaction are still only partly known. Furthermore, the exact nature of putative antigens causing immune activation is not well characterized.

During recent years, it has become clear that atherosclerosis is not, as was often assumed previously, a slow and irreversible process, eventually causing disease by narrowing of the arterial lumen. Instead, the inflammation typical of atherosclerotic lesions like other inflammatory diseases such as rheumatoid arthritis (RA) can be ameliorated and also regress.6 Furthermore, cardiovascular disease (CVD) such as stroke or myocardial infarction (MI) is related more to plaque rupture and atherothrombosis than to a passive thickening of the vessel wall.7 Typical of atherosclerotic lesions prone to rupture is an activated immune response with increased expression of proinflammatory cytokines such as tumor necrosis factor (TNF) and interferon-γ.5 Immune mechanisms in atherosclerosis are therefore implicated at all stages of disease development, including later stages when plaque rupture and atherothrombosis are prominent manifestations of atherosclerosis.

Also, atherosclerosis, per se, has been suggested to be an autoimmune disease, with a crucial role played by autoantigens such as heat shock proteins (HSPs).8,9 This notion is also supported by recent experiments demonstrating that adoptive transfer of β2-glycoprotein I–reactive lymphocytes reactive with a plasma protein enhances early atherosclerosis in low-density lipoprotein (LDL) receptor–deficient mice.10 Animal studies indicate interesting connections between atherosclerosis and autoimmune diseases. The interaction of CD40 with CD40L plays an important role in humoral and cell-mediated immune responses, and ligation of this interaction ameliorates atherosclerosis and autoimmune disease in animal models.6,11 Furthermore, intravenous immunoglobulin, often used for treatment of severe autoimmune manifestations, protects against atherosclerosis in an animal disease model.12 Another example from a recent study indicates that abrogation of transforming growth factor-β (TGF-β) signaling in T cells increases atherosclerosis.13

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In addition to being an important clinical problem, atherosclerosis and CVD in patients with autoimmune disease could shed light on the role played by immune reactions in human atherosclerosis, not least in women because autoimmune diseases mainly afflict women.

**Systemic Lupus Erythematosus**

**Background of Systemic Lupus Erythematosus and CVD**

Systemic lupus erythematosus (SLE) is often characterized as a prototypic autoimmune systemic disease, with a plethora of disease manifestations. These may affect many different organ systems and include manifestations as various as nephritis, arthritis, pleuritis, pericarditis, and vasculitis. Typical of SLE is the production of autoantibodies of different specificities and, possibly related to this, disturbed apoptosis.

The relationship between SLE and CVD has been discussed further in a recent review article. Before immunosuppressive treatment was implemented, more acute SLE manifestations were often fatal disease. In the 1970s, it also became evident that later complications caused by CVD were important clinical problems in SLE, and this bimodal mortality pattern of SLE was described in an important early article by Urowitz et al.

Several groups have confirmed these early studies demonstrating an association between SLE and CVD. In middle-aged women, the risk could be as high as 50-fold. However, it is not clearly established that the increased risk is present in most if not all patients, as is likely to be the case in diabetes and hypertension, or only affects a smaller subgroup of SLE patients.

**SLE and Atherosclerosis**

Early autopsy as well as angiographic studies indicated that the prevalence of atherosclerotic lesions is high in SLE, and also, the role of the then relatively recent introduction of corticosteroids in SLE was discussed as a possible underlying cause.

In a nested case-control study, we recently compared SLE women with a history of CVD (SLE cases) with age-matched SLE women without CVD (SLE controls) and age-matched women from the general population (controls). By use of B-mode ultrasound, we measured the intima-media thickness (IMT) of the carotid artery as a surrogate measurement of atherosclerosis. IMT and presence of atherosclerotic plaques (defined as IMT >1 mm) were higher among SLE cases compared with controls. These findings argue against the possibility that thrombosis or other types of vascular dysfunction in the absence of atherosclerosis are common causes of CVD in SLE. However, angiographic studies indicate that the occlusive disease in SLE is heterogeneous, and it is possible that some SLE patients indeed develop CVD in the absence of apparent atherosclerosis as determined by angiography.

Thrombosis and atherosclerosis could act in concert. It may also be the case that small lesions with high inflammatory activity are common in SLE but difficult to detect.

Another finding in our study was that IMT of SLE controls was not increased compared with population controls, despite that plaques were nonsignificantly more common among SLE controls than population controls.

Interestingly, in a subsequent larger case-control study of nonhospitalized SLE patients without signs of renal failure, it was demonstrated that presence of plaques was much more common among SLE patients than controls, a finding that was confirmed recently. Another surprising finding in the study by Roman et al was that SLE patients actually had decreased IMT and thus decreased general atherosclerosis. Furthermore, presence of atherosclerotic plaques was less common in patients with autoantibodies against cardiolipin (CL), Smith antigen, and RNP. Prednisone treatment was even associated with lower prevalence of plaques, and blood pressure was decreased rather than raised compared with the control group, which, to some extent, was recruited from a hypertension study, and the SLE cohort was not selected randomly.

In another recent case-control study, coronary artery calcification, another atherosclerosis-related measurement, was more frequent in patients with lupus without manifest CVD than in control subjects. The findings from this study thus suggest that early-onset atherosclerotic disease is a feature of SLE.

These findings emphasize the need for a controlled prospective study to determine which role more diffuse and generalized atherosclerosis, compared with localized plaques or atherothrombotic factors or even general arterial dysfunction without signs of macroscopic disease, plays in development of CVD in SLE. In such a study, it also appears important with randomly selected SLE patients and population-based controls. Other methods such as intravascular ultrasound or vascular stiffness determined by pulse-wave velocity could also add information about atherosclerosis in SLE.

**Risk Factors for CVD in SLE**

Because it may be debated which of all measurements of atherosclerosis is optimal in SLE and reflective of risk and disease, it is of importance to establish which are the risk factors and underlying mechanisms for CVD (and atherosclerosis). Our recent studies indicated that a combination of traditional and nontraditional risk factors for CVD characterize SLE patients, including markers of inflammation (raised levels of acute phase reactants and TNF-α), dyslipidemia, enhanced LDL oxidation, antiphospholipid antibodies (aPLs; lupus anticoagulants and antibodies to oxidized LDL [Ox-LDL]), and high levels of homocysteine. A somewhat surprising finding was that disease duration was not associated with CVD in SLE.

Most SLE patients with a history of CVD are on treatment with blood pressure–lowering drugs nowadays, and previous studies indicate that hypertension is an important risk factor for CVD in SLE.

Similar results have been reported in other studies on risk factors for CVD in SLE, with some differences. For example, one study in a multiethnic US cohort found that another traditional risk factor, smoking, was important and in another, a similar combination of traditional and nontradi-
Among patients with SLE, 30% to 50% have aPLs, and the antiphospholipid syndrome (APS), characterized by fetal loss, autoimmune thrombocytopenia, and thrombosis, is referred to as secondary APS. Suggested nonmutually exclusive mechanisms causing arterial and also venous thrombosis include interference with coagulation mechanism and a direct activating or even damaging effect on endothelial cells.

Previous studies have indicated that aPLs are also associated with CVD in the general population, but their role in atherosclerosis development is not clear and may also vary depending on type of aPLs.

We described recently that inhibition of binding of anti-thrombotic plasma protein annexin V to endothelium caused by aPLs could represent a novel mechanism for CVD in SLE patients and possibly in the general population as well. We also discovered that annexin V is abundant in atherosclerotic plaques, especially at sites prone to plaque rupture, and we hypothesize that although annexin V may promote plaque growth in advanced disease, it may also stabilize plaques and inhibit plaque rupture. Some aPLs may also be induced by infectious agents. However, their significance is not clear but may also decrease annexin V binding (unpublished data). Interestingly, the risk of MI is raised after upper respiratory infections. Whether raising annexin V binding (eg, by administering neutralizing antibodies) could represent a therapeutic possibility remains to be elucidated.

Antibodies against endothelial cells (aECs) are associated with SLE-related disease activity and vasculitis and promote endothelial activation by acting directly on endothelial cells. aECs have also been described in CVD in the general population. However, aECs were only nonsignificantly raised in SLE-related CVD in our study. The capacity of aECs to promote atherogenesis in more active SLE patients remains to be evaluated.

In APS and SLE, many antibodies against CL (aCLs) recognize oxidized phospholipids, suggesting an important association between lipid peroxidation and aPLs. The role played by aOxLDL appears to be more complex compared with aPLs but also more directly related to atherosclerosis. Although not included in the definition of APS, some aOxLDL can also be regarded as aPLs that cross-react with aCLs. Recent evidence indicates that aOxLDL may also have atheroprotective properties. Active immunization with OxlDL leading to raised aOxLDL levels causes decreased atherosclerosis development in experimental animals. In humans, a growing body of evidence indicates that aOxLDL are decreased in the early stage of CVD development in nonautoimmune disease and in healthy individuals but raised at later stages and in more advanced disease. An interesting possibility is that natural antibodies against OxLDL epitopes such as phosphorylcholine (PC), mainly of IgM subclass and belonging to the B-1 lineage of B cells, function as protection factors by promoting clearance of oxidized lipids, apoptotic cells, and PC-containing bacteria. As discussed, also some other autoantibodies, including those against Smith antigen and RNP but also aCLs, have been
described to be associated negatively with atherosclerosis.26 Clearly, some autoantibodies could have atheroprotective roles, and further studies are necessary to determine these differences and underlying mechanisms in detail.

The role of antibodies against HSPs and related HSP measurements in CVD in general is likely to be complex. The proposition that aHSP65 is atherogenic is supported by animal experiments and clinical studies. One explanation for this finding could be that HSPs are conserved molecules from an evolutionary point of view, and aHSP could cross-react with HSPs present on activated endothelial cells and in bacteria, including mycobacteria.56–58

Whereas antibodies against HSP60/65 are risk factors,56,57,59 HSP70 appears to be a protection factor for atherosclerosis.60 However, available evidence does not indicate that these factors are of major importance in SLE-related CVD.24

Dyslipidemia and Inflammation

Dyslipidemia with low high-density lipoprotein (HDL) raised triglycerides (TGs), unchanged or only slightly elevated LDL; and raised lipoprotein(a) (Lp(a)) is typical of SLE and, especially in active disease, this lipid pattern has been described as the “lupus pattern of dyslipoproteinemia,” but the underlying mechanisms are not well known.24,61,62 Previous studies by Ilowite et al demonstrated that children with active SLE have elevated TGs and Lp(a) and that TGs are elevated in patients with inactive disease but even higher among patients with newly diagnosed active SLE.63

We recently described a strong correlation between blood lipids, especially elevated TGs but also low levels of HDL, and active SLE disease. We also demonstrated that cumulative disease damage is associated with high cholesterol and TG levels, further supporting a putative role of blood lipids as potential disease markers in SLE.24,29,30

Another finding in our SLE-CVD study was that activity in the TNF-α system and raised TNF-α levels are strongly associated with high TGs and low HDL in SLE patients.24,29,30 Likewise, TNF-α levels are raised and occur together with similar lipoprotein derangement as seen in SLE during infections,64 and TNF-α given to humans causes an increase in TG and very low-density lipoprotein (VLDL) levels.65 In rats, TNF-α administration induces an increase in circulating TG-rich VLDL particles,66 suggested to be caused by de novo hepatic synthesis of VLDL.66 Indeed, one of the first effects attributed to TNF-α was its ability to inhibit lipoprotein lipase (LPL).67 The major enzyme that degrades VLDL particles in the circulation, LPL activity is reduced by ~50% compared with healthy individuals in SLE.68 Induction of de novo hepatic lipogenesis and inhibition of LPL are thus 2 known mechanisms through which TNF-α can induce lipoprotein changes of the kind seen in SLE. Therefore, it is possible that TNF-α (or other inflammatory cytokines) can play an important role in SLE-related dyslipoproteinemia.

HDL may be atheroprotective not only through reverse cholesterol transport but also by functioning as an antioxidant and anti-inflammatory agent, decreasing endothelial adhesivity.69,70 and HDL-associated apolipoprotein A-1 has been shown to decrease TNF-α production through inhibiting contact-mediated activation of monocytes by binding to stimulated T cells.71 Low HDL levels may thus be caused by SLE but may also indirectly contribute to enhanced inflammation in SLE.

It should be noted that the exact nature of lipid composition in SLE remains to be demonstrated. We recently addressed this question by NMR measurement of lipids in SLE, and preliminary data indicate that a typical atherogenic lipid pattern, with small dense LDL (and HDL), was not present in SLE-related CVD (unpublished observation). It is not yet clear how dyslipidemia in SLE is best treated.

Lipid Oxidation

As a result of oxidation, a variety of immunogenic neoepitopes are formed on OxLDL. For example, oxidation of the PC-containing phospholipids in LDL renders them antigenic and also recognized by macrophage scavenger receptors, leading to enhanced uptake of OxLDL and foam cell formation.72 OxLDL is also chemotactic, proinflammatory, and has toxic properties,73 and antibodies to oxidation-specific epitopes of OxLDL (aOxLDL) are common in the population.7 These antibodies include those of IgG subclass, usually T-cell dependent, and OxLDL has been reported to promote T-cell activation.74,75

SLE patients have enhanced urinary excretion of isoprostanes, indicative of enhanced lipid peroxidation, and increased oxidative stress and lipid peroxidation is raised in SLE.76,77 We demonstrated that LDL oxidation as determined by recognition of phospholipid oxidation epitopes on LDL is raised in SLE-related CVD.24,78

We have shown previously that lyso phosphatidylcholine (LPC) is an important antigen for aOxLDL and also an important mediator of many OxLDL-related effects.79 Antibodies against LPC recognize PC and participate in clearance of apoptotic cells and possibly of OxLDL as well.80 A considerable proportion of exposed oxidized phospholipid epitopes are present on Lp(a), which is raised in patients with SLE and CVD.81

Renal Function and Hypertension

Hypertension is most likely an important risk factor for CVD in SLE, although difficult to document because many SLE-CVD patients are treated with drugs that, among other properties, decrease blood pressure (eg, β-blockers). Renal disease and renal failure are well known as risk factors for CVD. We demonstrated recently that OxLDL levels in the circulation are associated with renal manifestations in SLE.78 OxLDL has also been implicated in renal disease in the general population,82 and OxLDL was demonstrated in sclerotic and mesangial regions of biopsies from patients with chronic renal disease.83 Furthermore, expression of macrophage scavenger receptors can be induced in human mesangial cells.84 Enhanced LDL oxidation may in principle play a role in the development of renal manifestations in SLE but may also be a secondary phenomenon to nephritis.

Cytokines and Inflammatory Factors

Several studies demonstrate that interleukin-10 (IL-10), a T-helper 2 cytokine, is raised in SLE patients and has been
implicated as one of the causative factors in SLE by induction of autoantibodies and apoptosis. IL-10 has also anti-inflammatory effects on the proinflammatory function of T-helper 1 cells, endothelial cells, and monocytes/macrophages. IL-10 can also be immune stimulatory, promoting B-cell activation and antibody production.85–87

Recent findings from animal models of atherosclerosis indicate that IL-10 is an antiatherogenic cytokine, possibly because of the anti-inflammatory properties of this cytokine.88,89

IL-10 production is known to be influenced by a functional polymorphism (-1087) and the A-1087 IL-10 allele has been reported to be associated with a lower capacity for IL-10 production.90–93

We reported recently that the A allele frequency of -1087IL-10 gene was positively associated with CVD in SLE and that the IL-10 AA genotype is associated with reduced ratio of atheroprotective to atherogenic cytokines in SLE/CVD patients.94 Both IL-10 and TNF-levels were raised in SLE-CVD patients, but lower IL-10:TNF ratio was observed in those with the -1087IL10 AA genotype. Our findings indicate that the A-1087IL-10 allele may be an underlying factor contributing to the high risk of CVD in SLE. Developing SLE in spite of low capacity for IL-10 production could thus increase the risk of CVD in SLE. Whether IL-10 could protect some SLE patients from atherosclerosis remains to be elucidated. The role played by other cytokines such as anti-inflammatory TGF-β or chemokines in SLE-related CVD is not well described.

We recently compared other nontraditional and inflammation-related risk factors for SLE-related CVD, including platelet-activating factor (PAF)--acylhydrolase (PAF-AH), secretory phospholipase A2 (PLA2) aECs as well as HSPs and aHSPs, but among these, only PAF-AH was significantly associated with CVD in SLE.95

PAF-AH and secretory PLA2 (sPLA2) are important in the degradation of PAF and PAF-like lipids and in the generation of LPC. PAF, PAF-like lipids, and LPC are major proinflammatory components of OxLDL that could induce and promote the inflammatory reaction in the vessel wall.95–99 Inhibition of PAF activity decreases the development of atherosclerosis in animal models,100 and antibodies against PAF are associated with CVD independent from other aPLs.101,102

Recent evidence suggests that PAF-AH is a risk marker for CVD in general, including stroke and coronary artery disease.103–105 Our data support this possibility, one of which is that PAF-AH may promote atherogenesis by increasing LPC concentration in the arterial wall. Although PLA2 levels were not raised in the circulation of SLE cases in our study, this negative finding does not necessarily rule out the possibility that sPLA2 plays a role in the artery wall in SLE.

Derangements in apoptotic mechanisms are typical in SLE and may be of importance in CVD development, but the role of apoptosis in atherosclerosis and CVD is not clear. For example, increased apoptosis could theoretically ameliorate plaque growth but also decrease the strength of the fibrous cap and thus the risk for plaque rupture. Furthermore, apoptotic blebs could be antigenic for some aPLs.106

The complement system has been long known to play a role in SLE, in which dysfunctional complement function can lead to defective clearance of immune complexes, inflammation, and vasculitis.107 The role of complement in atherosclerosis is much less well defined, although the presence of complement in atherosclerotic lesions has been known for ~3 decades.108 Although complement activation at a late stage has been implicated in MI and plaque rupture, it is not clear whether complement is detrimental or protective at earlier stages of disease development. C-reactive protein activates complement and avidly binds modified LDL, and such complexes could well be of importance in atherogenesis (eg, mediated through vasculitis).109

Corticosteroids and Other Treatment in SLE-Related CVD

The role of corticosteroids in atherosclerosis and CVD has been much discussed since introduced several decades ago in the treatment arsenal in rheumatic disease. Clearly, randomized prospective studies, albeit relatively difficult to accomplish, are implicated if this issue is to be completely clarified, and available literature does not give any certain information as to whether corticosteroids are protective or damaging agents.

Because atherosclerosis is an inflammatory disease, corticosteroids could be expected to have an antiatherogenic effect, a possibility supported by animal experiments.110 On the other hand, corticosteroids have well-known metabolic effects that could in theory be proatherogenic. It should be noted that treatment is implemented because of higher inflammatory reactivity, and a history of steroid treatment could also simply reflect a higher inflammatory activity, which, per se, could be an important risk factor.24

Relatively little is known about the role of other treatments in SLE in relation to atherosclerosis, including nonsteroidal anti-inflammatory drugs. We did not find any association between medications other than steroids commonly used in SLE and CVD.24 Interestingly, Roman et al even described a negative association between immunosuppression other than corticosteroids and atherosclerosis,25 and in this study, corticosteroid use was nonsignificantly lower in SLE patients with CVD.

RA and Other Autoimmune Conditions in Relation to Atherosclerosis

During recent years, an increased risk of CVD has been reported in RA.111–114 For example, in young women, a 3.6-fold increased risk of death in coronary artery disease has been demonstrated, and in a population-based cohort of RA patients compared with controls matched for age and sex, the incidence of MI and coronary heart disease was 50% higher in RA.115 Albeit raised, the risk of CVD in RA thus appears to be lower than in SLE and has also been reported to be decreasing.115

As in SLE, the underlying mechanisms causing this increased risk are not wholly clarified, but a combination of traditional and nontypical risk factors including inflammation appear to be of importance.115–117 Also, complications such as extra-articular manifestations, which are
usually related to systemic inflammation, have been demonstrated to cause increased mortality from CVD.\textsuperscript{120}

The presence of rheumatoid factor in RA has been known for many decades, but little is known how these or immune complexes in general affect large vessels in RA and what role, if any, activation of different complement pathways may play in development of atherosclerosis and CVD in RA.

In a recent interesting article, Swanberg et al reported that functional polymorphisms relating to MHC molecule expression are associated with susceptibility to RA, multiple sclerosis, and MI.\textsuperscript{122} This finding clearly opens up intriguing possibilities regarding common underlying genetic causes and contributions to major chronic inflammatory diseases. Whether such genetic factors may contribute to the increased prevalence of CVD (and atherosclerosis) in RA and SLE and other rheumatic diseases is an interesting possibility that most certainly merits further study.

Although some recent studies support an increased prevalence of atherosclerosis as determined by ultrasound of carotid arteries,\textsuperscript{117,119,123} there is also a relatively large recent study in which such an increase was not detected, neither as IMT nor as determined by prevalence of plaque.\textsuperscript{116}

It is important to note that in SLE and RA, it may well be the case that although differences in the appearance of atherosclerosis as determined by macroscopic methods such as ultrasound are difficult to discern, there may still be important immunopathological differences. If the local inflammatory process is more accentuated, for example, this may lead to an increased risk of plaque rupture and ensuing CVD, even though differences are not detected by radiological methods. It is also possible that patients with autoimmune disease such as SLE and RA have less tolerance to atherosclerosis compared with the normal population (eg, through mechanisms such as aPLs), causing decreased annexin V binding and thus raised proneness to arterial thrombosis.\textsuperscript{40}

In favor of arterial changes in RA (as in SLE) are studies in which endothelial dysfunction has been determined.\textsuperscript{124} aPLs as well as antibodies against OxLDL are raised in RA, but their clinical importance for CVD and atherosclerosis is not clear in this context and is likely to be complex.\textsuperscript{125} Also in RA, lipid peroxidation may play a role, and interestingly, OxLDL-containing foam cells have been detected in synovia from RA patients.\textsuperscript{126} Also interesting, HSPs are implicated in RA and atherosclerosis, although immune reactivity to HSPs in RA appears to play a somewhat different role, being protective in many cases.\textsuperscript{127}

Dyslipidemia is often present in RA but appears to be somewhat different from the lupus pattern of dyslipidemia, with a low LDL and not high or unchanged as in SLE. However, as in SLE, low HDL and high TGs are present in a similar way as in inflammatory and infectious diseases in general. In an interesting article, an increased prevalence of atherogenic small dense LDL particles were determined in RA, and LDL from RA patients also had an increased capacity to bind proteoglycans, which is considered an important early step in atherogenesis.\textsuperscript{128}

As in SLE, the role played by corticosteroid and other treatment must be taken into account, and prospective treatment studies can hopefully help to settle the question whether corticosteroids are antiatherogenic or proatherogenic. A previous report indicates that methotrexate treatment is associated with an increased risk of CVD;\textsuperscript{129} one mechanism may be raised homocysteine levels caused by this medication, but recent investigations suggest such treatment could influence CVD risk factors in a beneficial way.\textsuperscript{130} During recent years, folate substitution has been implemented, which may be beneficial. Also, the large-scale introduction of inhibitors of cytokines, especially of TNF, may influence risk of CVD. Theoretically, TNF inhibition could be expected to be anti-atherogenic because TNF has proinflammatory and metabolic effects that may be atherogenic.\textsuperscript{24} Indeed, a recent article demonstrates that in a mice model of atherosclerosis, TNF inhibition decreases atherosclerosis development.\textsuperscript{131} However, side effects such as heart failure have been implicated.\textsuperscript{132} The effects of TNF and other cytokine inhibitors on CVD and mortality is an important area of future research.

Except for type I diabetes, often considered an autoimmune disease, information about atherosclerosis in patients with other autoimmune diseases than RA and SLE is relatively scarce. In type I diabetes, an increased risk of vascular disease is a known feature, and increased atherosclerosis as determined by IMT measurements has been reported, in addition to the well-known microvascular complications.\textsuperscript{133} Risk factors include hyperglycemia, and intensive treatment is reported to decrease progression rate.\textsuperscript{134} Other risk factors except age include male gender, TGs, and nephropathy.\textsuperscript{135} Endothelial function is impaired in children with diabetes mellitus within the first decade of its onset and precedes an increase in carotid IMT.\textsuperscript{136}

Relatively little is known about atherosclerosis in patients with a history of vasculitis, although in Kawasaki’s disease, increased atherosclerosis has been reported,\textsuperscript{137} which is also the case in Takayasu’s arteritis.\textsuperscript{138} And in patients with autoimmune disease, a close relationship between vasculitis and atherosclerosis has been noted in early studies.\textsuperscript{139} Also in Behcets disease, in which vasculitis is a common feature, and in another more typical form of vasculitis, Wegener’s granulomatosis, raised IMT has been reported.\textsuperscript{140,141} Allergies and asthma are important and increasing problems in many parts of the world, but also in this group of immune-related diseases, the knowledge of influence on atherosclerosis or CVD is rather limited, although recent studies indeed indicate a possible positive association with atherosclerosis.\textsuperscript{142} Presently, the knowledge is scarce on putative associations and common causes between atherosclerosis and other rheumatic or autoimmune diseases, but hopefully, further research will add to our knowledge in this area.

**Summary and Conclusions**

The risk of CVD is very high in SLE and also increased in RA and most likely to a varying degree in other autoimmune disease. The exact nature of the underlying vascular pathology causing CVD is not clear but is likely to be related to atherothrombosis and increased prevalence of atherosclerotic plaques in many if not most cases. Of note, there are also negative studies in which IMT is not increased: in SLE and RA. It could also be the case that in some patients, CVD occurs through thrombotic mechanisms and not atheroscler-
rotic. However, also in this case, it is possible that early vascular dysfunction or atherosclerotic changes that are difficult to detect could still play a role. Further studies are needed to determine whether atherosclerotic plaques in autoimmune disease have special features or whether systemic factors such as aPLs trigger atherothrombosis more easily than in “normal” atherosclerosis. When treating patients with these autoimmune diseases, it is important to pay attention to the increased risk of CVD. Traditional risk factors should be monitored closely, and disease symptoms including inflammation should be treated. Hopefully, novel therapeutic principles will be developed that target the causes of the inflammation present in atherosclerotic lesions.

References


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