Atherosclerosis in rheumatoid arthritis and systemic lupus erythematosus

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Introduction

Cardiovascular disease is recognized as a significant cause of premature mortality in patients with rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). Furthermore, inflammation has been recognized as important in the pathogenesis of atherosclerosis. These observations have led to considerable interest in elucidating mechanisms associated with traditional cardiovascular risk factors, as well as those associated with inflammation and disease severity, in the pathogenesis of atherosclerosis in patients with inflammatory rheumatic diseases.

This review summarizes information concerning accelerated atherosclerosis in patients with RA and SLE, including characterization of traditional, inflammatory, and rheumatic disease-related cardiovascular risk markers, as well as approaches to early detection of atherosclerosis. Insight into the pathogenesis of atherosclerosis in rheumatic diseases may allow better definition of risk factors in patients with RA or SLE, identification of asymptomatic high-risk patients, and thereby implementation of interventions that will minimize or prevent cardiovascular disease and improve mortality outcomes. This information might also provide new mechanistic insights into the role of inflammation in the pathogenesis of cardiovascular disease in the general population.

A. Atherosclerosis in rheumatoid arthritis

Prevalence of cardiovascular mortality in RA

As described in detail in chapter B-1, page S35, patients with rheumatoid arthritis (RA) experience premature mortality, with the most prominent cause of death being cardiovascular disease. Virtually every study indicates that cardiovascular disease is the most prominent cause of death in patients with RA, accounting for 40-50% of deaths in most series (1, 2).

Among 111, 432 women followed in the Nurses' Health Study, the adjusted risk of myocardial infarction was 2.0 (95% CI 1.23-3.29) in 527 women with RA compared to those without (3). Information concerning the risk of stroke is not as clear-cut. In the Nurses' Health Study the risk of stroke was not increased significantly in women with RA (RR=1.48, 95% CI 0.70-3.12) (3). In some studies (4, 5), the overall risk of cerebral events was increased, but when specifically assessed for cerebrovascular events, the findings have been conflicting (6, 7).

Traditional cardiovascular risk factors in patients with RA

Both traditional and non-traditional cardiovascular risk factors contribute to development of atherosclerosis in RA. The prevalence of traditional cardiovascular risk factors such as hypertension, hyperlipidemia, diabetes, and smoking is increased in several cohorts of patients with RA (5, 8). However, these risk factors account only in part for the accelerated atherosclerosis seen in these patients.

Del Rincon *et al*. (9) also found that the risk of cardiovascular mortality was increased in patients with RA, even after controlling for traditional risk factors. Not all reports indicate that traditional risk factors are increased in patients with RA (10). Gonzalez *et al*. (11) suggested that some traditional risk factors in RA may confer a significantly smaller risk for the development of cardiovascular disease compared to their contribution in a non-RA population. Combinations of cardiovascular risk factors, such as the Framingham risk score and the metabolic syndrome are better predictors of cardiovascular outcomes than individual risk factors in the general population.

The Framingham risk score is a composite model that has been used to stratify individuals in the general population into categories of low risk (<10%), intermediate risk (10-20%), and high risk (>20%) for a cardiovascular event within the next 10 years (12). The score is based on traditional cardiovascular risk factors including age, sex, smoking, blood pressure, and cholesterol concentration. In a study conducted by the authors, the Framingham risk score was higher in patients with long-standing RA than those with early RA or control subjects, and was also higher in patients with coronary calcification than those without (8). However, patients with long-standing RA also had a greater probability of having higher coronary calcium scores than control subjects, independent of Framingham score (8).

The metabolic syndrome is a cluster of cardiovascular risk factors that includes central obesity, dyslipidemia, hypertension, and impaired glucose metabolism, and is an independent predictor of cardiovascular morbidity and mortality in women (13). The modified World Health Organization definition requires the presence of insulin resistance, which can be defined by a homeostasis model assessment (HOMA) index [fasting blood glucose concentration (mmol/l) × fasting insulin concentration (μU/ml)/22.5] in the top quartile of a population without diabetes (14-16).

Patients with RA had a higher prevalence of the metabolic syndrome than control subjects, particularly if defined according to the WHO-criteria that include a direct measure of insulin resistance (17). Furthermore, the presence of the WHO-defined metabolic syndrome was associated with increased risk of having higher coronary calcification scores, independent of age and sex (17).

These observations indicate that patients with RA require aggressive treatment of classic cardiovascular risk factors such as hypertension and dyslipidemia (18), and attention to the metabolic syndrome. However, these observations also indicate that increases in the prevalence of traditional risk factors only partly explain accelerated atherosclerosis in patients with RA. Further investigation of potential additional risk factors related to inflammation and disease severity, and possible interactions between traditional and disease-associated risk factors has been undertaken. Given the association between low levels of inflammation and coronary heart disease in the general population (19, 20), the relationships between inflammation and atherosclerosis in RA are of interest to general research concerning the pathogenesis of atherosclerosis.

Sub-clinical atherosclerosis in patients with RA

The pathogenesis of atherosclerosis in RA has been studied through identification of sub-clinical atherosclerosis, which precedes cardiovascular events due to ischemic heart disease. The two primary measurements used to detect sub-clinical atherosclerosis are ultrasound to detect carotid intima-media thickness (IMT), and electron beam computed tomography (EBCT) to detect coronary calcium (21). Ultrasonography is more widely available, and more reports characterize carotid IMT (21). EBCT is a non-invasive technique that quantifies the amount of calcification in coronary arteries, a measure that is correlated significantly with the degree of atherosclerosis. Coronary calcification by EBCT, quantified according to a method described by Agatson *et al.* (22), provides prognostic information independent of that provided by traditional cardiovascular risk factors in the general population.

Kumeda *et al.* found that 138 patients with RA had a higher IMT than 94 healthy controls matched for age and sex (23). IMT was associated with increased disease duration and severity. Similarly, Park *et al.* (24) found that carotid IMT was increased in 53 postmenopausal women with RA compared with 53 age-matched female controls. Neither study found an association between corticosteroid treatment and IMT. Roman *et al.* (25) found a 3-fold increase in carotid atherosclerotic plaques in 98 patients with RA compared to matched controls (44% *vs.* 15%, $p<0.001$); hypertension, smoking and the use of TNF-α inhibitors were significantly associated with the presence of atherosclerotic plaque in this study.

Chung *et al.* (26) measured coronary calcium in 141 subjects with RA (70 with shorter disease duration of <6 years, and 71 with long-standing RA of ≥6 years) compared to 86 age- and sex-matched control subjects. The amount and severity of coronary calcium (measured as the Agatston score) was significantly higher (OR=3.42, 95%CI (1.55-7.53)) in patients with longstanding RA compared to control subjects, even after adjusting for traditional cardiovascular risk factors. Finally, smoking and higher ESR were associated with higher levels of coronary calcium in patients with RA after adjusting for age and sex, again indicating roles for both traditional cardiovascular risk factors and inflammation in atherosclerosis.

Associations of sub-clinical atherosclerosis with inflammation

Inflammation appears to contribute to the evolution of atherosclerotic lesions from a fatty streak to an organized plaque, and to the final process of plaque rupture and occlusion of coronary arteries (27, 28). Measurement of carotid IMT or coronary calcium and inflammatory mediators that may be associated with the pathogenesis of atherosclerosis has been used to study the relationship between inflammation and atherosclerosis (Table I). It is possible that if the inflammatory processes of RA and atherosclerosis share similar mediators (29), aggressive control of disease activity may abrogate increased cardiovascular risk in RA.

Several studies suggest that persistent inflammation is associated with increased atherosclerosis in RA. Maradit-Kremers *et al.* showed that an ESR value that was elevated repeatedly over the course of a patient's illness was associated with increased cardiovascular risk (30). The US Veterans study found that major cardiovascular events were associated with higher DAS28 scores (4). Increased disease activity has been also associated with increased mortality (31, 32), and studies have shown that mortality is reduced by aggressive treatment of RA (33, 34).

Table I. Representative studies of biomarkers and mediators implicated in atherosclerosis in RA.

Author	Biomarker/Mediator	Study population	Outcome variable
Wallberg-Jonsson *et al*. (35)	Chol, LDL, LDL/HDL ratio, TG, tPA Ag, ICAM	RA (n=39) and controls (n=39)*	IMT and plaque
Del Rincon *et al*. (109)	ESR, CRP	RA (n=204) and controls (n=102)*	IMT and plaque
Wallberg-Jonsson *et al*. (36)	Chol, ICAM (IMT), Chol, E-selectin, LDL (Plaque)	RA (n=39) and controls (n=39)*	IMT and plaque
Gonzalez-Gay *et al*. (110)	CRP (in highest quantile)	RA (n=47)	IMT
Del Rincon *et al*. (111)	ESR	RA (n=631)	IMT
Chung *et al*. (26)	ESR	RA (n=141)and controls(n=86)*	Coronary Calcium
Dessein *et al*. (37)	VCAM	RA (n=74) and controls (n=80)	IMT and Plaque
Roman *et al*. (25)	TNF-α blocker usage	RA (n= 98) and controls (n=98)*	Carotid Plaque
Pahor *et al*. *(*112)	CRP (IMT), Apo B (Plaque)	RA (n=70) and controls (n=40)*	IMT and Plaque
Dessein *et al*. (39)	TG, Insulin resistance	RA (n=74)	IMT and Plaque
Daza *et al*. (38)	Von Willebrand factor (vWF), AST	RA (n=55) and controls(n=20)*	IMT
Surdacki *et al*. (40)	ADMA, endothelial progenitor cell count	RA (n=30) and controls (n=20)*	IMT and Plaque
Dessein *et al*. (41)	PMN cell count, thyroid status	RA(n=91)	Carotid Plaque
Asanuma *et al*. (42)	Osteoprotegrin	RA (n=157) and controls (n=87)*	Coronary Calcium
Hannawi *et al*. (113)	CRP	RA (n=40) and controls (n=40)*	IMT

Studies are listed in chronological order. For each study only the biomarkers significantly associated with the outcome are shown.
AST: Aspartate aminotransferase; ADMA: Asymmetric dimethyl-L-arginine; Chol: Total cholesterol; HDL: High density lipoprotein; ICAM: Intercellular adhesion molecule; IMT: Carotid intima media thickness; LDL: Low density lipoprotein; PMN cell: Polymorphonuclear cell; tPA Ag: tissue plasminogen activator antigen; TG: Triglycerides; VCAM: Vascular cell adhesion molecule.
*Groups are sex and age matched.

Several biomarkers have been associated with carotid IMT and plaque, including ICAM (35, 36), VCAM (37), von Willebrand factor (38), aspartate aminotransferase (AST) (38), triglycerides (39), indices of insulin resistance (39), endothelial progenitor cell count (40), and polymorphonucelar cell count (41). In the case of coronary calcium, osteoprotegrin (OPG) was associated with increased coronary calcification (42), and the authors have found that concentrations of several inflammatory mediators were higher in patients with RA than controls, although only TNF-α and IL-6 were associated with coronary calcium (unpublished data). That finding suggests that selective targeting of specific cytokines may be beneficial in the prevention and treatment of cardiovascular disease in RA, but further research will be needed to determine whether these biomarkers are in fact causally associated mediators of atherosclerosis (43, 44).

Impact of treatment of RA on atherosclerosis

Since RA is an inflammatory disease and inflammation contributes to accelerated atherosclerosis, controlling disease activity may lead to decreased cardiovascular mortality. Krause *et al*. (33) reported better mortality outcomes among RA patients who were "good responders" to methotrexate. Choi *et al*. (34) found that treatment with methotrexate in patients with RA was associated with decreased mortality rates. In the international QUEST-RA (45) database of 4,363 patients (100 patients each from 48 sites in 15 countries at the time of publication), exposure to not only methotrexate, but also leflunomide, sulfasalazine, glucocorticoids and biologic agents was associated with a reduced likelihood of cardiovascular morbidity, including after adjustment for traditional cardiovascular risk factors. Aggressive use of DMARDs, including biologic agents, to control inflammation may be beneficial in preventing cardiovascular events in RA (45). Possible effects of corticosteroids and biologic agents on atherosclerosis in patients with RA are important considerations.

Glucocorticoids

Glucocorticoids are widely used in the treatment of RA, and although effective in treating inflammation, their use is limited by significant toxicities (46). Corticosteroids increase triglyceride concentrations and can induce hypertension and diabetes, all established cardiovascular risk factors.

The possible contribution of corticosteroid therapy to the process of accelerated atherosclerosis in RA has been explored in several studies with inconclusive results. Kumeda (23), Park (24) and Roman *et al*. (25) did not find a significant association between corticosteroid treatment and carotid IMT or plaque but del Rincon *et al*. (47) did. In the QUEST-RA study, corticosteroid use was associated with a decreased risk of cardiovascular morbidity (HR 0.95, 95%CI 0.92-0.98), but the beneficial effect was smaller than that of other DMARDs.

These findings highlight the dual effects of corticosteroids as both potentially beneficial (anti-inflammatory) or deleterious (dyslipidemia, hypertension, hyperglycemia). Dosage may be an important consideration, with a greater risk of deleterious effects at high doses, confounded by the possibility that patients with more severe clinical status receive higher doses. Furthermore, the effect of glucocorticoids on the atherosclerotic process in RA may vary in individual patients.

Biologic agents

TNF-α is an inflammatory cytokine central to the pathogenesis of RA. TNF-α is also associated with atherosclerosis and cardiovascular mortality in the general population (48, 49). Therefore, the possibility that inhibition of TNF-α may

be beneficial in the treatment of both RA and atherosclerosis is attractive.

Treatment with a TNF-α antagonist has been found to improve endothelial function (50, 51) and lead to regression of carotid IMT (52). Among the DMARDs studied in the QUEST-RA study, TNF-α antagonist use was associated with the lowest risk of cardiovascular events (HR 0.42, 95%CI 0.21-0.81). Thus, further evaluation of the effects of TNF-α antagonists on the pathogenesis and progression of atherosclerosis will be important.

In addition to TNF-α antagonists, an IL-6 receptor antagonist (tocilizumab) has been studied more recently in patients with RA (53, 54). Limited information is available concerning effects of tocilizumab on cardiovascular risk factors. In clinical trials performed in patients with RA, serum lipid concentrations were increased in patients treated with tocilizumab (53, 54), particularly total and LDL cholesterol. Such effects may be of concern, but could be offset by beneficial effects resulting from decreased ability of IL-6 to promote atherosclerosis. Further research to address these questions will be required.

B. Atherosclerosis in SLE

Prevalence of cardiovascular disease in SLE

Atherosclerotic cardiovascular disease has been recognized in patients with SLE for decades. As early as 1975, subclinical atherosclerosis was reported in many patients with SLE at autopsy (55). In 1976, Urowitz *et al*. described a bimodal pattern of mortality in systemic lupus erythematosus (SLE) (56). The majority of the deaths within the first year after diagnosis were attributed to active disease and infections, whereas the majority of deaths in patients with longer disease duration were attributed to cardiovascular disease.

Ten years later, a review of 51 patients who died indicated that coronary atherosclerosis was the major cause of death in almost half of the cohort of patients who had disease duration longer than 5 years. Autopsy results available in 27 patients indicated moderate to severe atherosclerosis in 11 cases (41%); 6 (22% of all autopsy cases) were females under the age of 55 (57). Furthermore, atherosclerotic heart disease also caused death in patients who had shorter disease duration, including many who had long periods of clinically quiescent or inactive disease (57).

Subsequent studies have further characterized risk of cardiovascular disease in SLE. In one study, female SLE patients between the ages of 35 and 44 years were estimated to have a 50-fold increased risk of myocardial infarction (MI) compared to age- and sex-matched control subjects (58). Patients with SLE aged 18-44 years were also found to be 2.3 times as likely to be hospitalized for an acute MI, 3.8 times as likely to have congestive heart failure, and twice as likely to be hospitalized for cerebrovascular events, compared with age-matched controls (59). It appears that the relative risk is highest in younger patients, while the absolute risk of cardiovascular disease in patients with SLE of any age is increased more than 2-fold (58).

Traditional cardiovascular risk markers in SLE

Hypercholesterolemia (60, 61), sedentary lifestyle (60, 62) and obesity (60, 63) have been reported to be more prevalent in patients with SLE than in age-matched control subjects. Hypercholesterolemia and older age at the time of diagnosis have been identified as factors associated with increased risk of clinical coronary heart disease in SLE (58, 64, 65). However, results of some of these studies may be confounded by glucocorticoid use (longer duration (58) and higher cumulative dose (65)) as well as underlying renal disease (65). A longitudinal study indicated that 24% of patients with SLE who had persistently elevated total cholesterol developed a new cardiovascular event over a 12-14 year follow-up period, compared to 3% of patients who had normal concentrations of cholesterol (66). By contrast, neither cholesterol nor lipid subclasses measured by nuclear magnetic resonance spectroscopy were associated with coronary calcification in a group of patients with SLE with no history of atherosclerotic cardiovascular disease (67).

The Framingham risk score did not differ from that of control subjects in patients with SLE (62, 68), indicating that an increase in traditional cardiovascular risk factors detected by this index did not account for the excess cardiovascular risk observed (62, 68). In contrast to the Framingham risk score, the metabolic syndrome (13) was more frequent in patients with SLE compared to control subjects, after adjusting for age, sex, race, and body mass index (69). The presence of metabolic syndrome also was associated with higher concentrations of C-reactive protein, homocysteine, lipoprotein a, and cholesterol. However, in patients with SLE, decreased insulin sensitivity, measured by the HOMA index, was not associated with coronary calcification; this finding is in contrast to the association between insulin resistance and coronary calcification found in patients with RA (70).

These observations indicate that other "non-classical" inflammatory and/or disease-specific cardiovascular risk factors may contribute to the excess risk of cardiovascular disease in SLE.

Sub-clinical atherosclerosis in SLE

The pathogenesis of atherosclerosis in SLE has been investigated using ultrasound to assess carotid artery IMT and the presence of plaque, and electron beam computed tomography (EBCT) to estimate coronary artery calcification, as in RA. In addition, atherosclerosis in patients with SLE has been studied using direct measurement of myocardial perfusion imaging, flow-mediated dilatation, and pulse wave analysis (a non-invasive method that calculates central arterial pressure from measurements obtained at the radial and carotid arteries).

Sub-clinical atherosclerosis detected by EBCT has been reported in several cohorts of patients with SLE (71-73), and the prevalence and severity of coronary artery calcification is increased markedly compared to matched control subjects (71). A higher prevalence of carotid atherosclerotic plaque was also found in patients with SLE compared to control subjects in three cross-sectional studies (74-76); plaque was present in

37.1% of patients with SLE *vs*. 15.2% of control subjects in one study (74) and 50% of SLE patients *vs*. 29% of control subjects in a second study (76). A third study evaluated presence of carotid artery plaque and found that in premenopausal women 36% of SLE patients compared to 0% of control subjects had carotid plaque. Moreover, there was a five fold increased prevalence of plaque in postmenopausal patients compared to matched controls (75). Furthermore, longitudinal studies using carotid ultrasonography indicated that 28% of SLE patients had progressive atherosclerosis after a mean duration of 34 months; progression was associated independently with older age at diagnosis, longer disease duration, and higher homocysteine concentrations (77). Another study indicated that 27% of patients with SLE compared to 10% of control subjects (p<0.001) experienced plaque progression, as seen by ultrasonography, although progression of IMT was similar in the two groups (78).

Doppler ultrasound of the brachial artery is used to measure flow-mediated dilation (FMD), a response that reflects endothelial function. Endothelial dysfunction is present in patients with cardiovascular risk factors or early atherosclerosis (79). An increased prevalence of endothelial dysfunction has been found in patients with SLE compared to healthy control subjects (80, 81). For example, a study evaluating FMD in 69 pre-menopausal patients with SLE and 35 age and sex matched controls, found that FMD was significantly impaired in patients with SLE (5.0±5.0%) compared to control subjects (12.0±6.0%) (p<0.001) (81).

In summary, extensive evidence based on several imaging methods indicates that the prevalence of sub-clinical atherosclerosis is increased substantially among patients with SLE compared to control subjects.

Association of sub-clinical atherosclerosis and inflammation in SLE

Several pro-inflammatory cytokines, including interleukin-6 (IL-6) and monocyte chemoattractant protein-1 (MCP-1), are higher in SLE patients compared to controls (82). Such cytokines in patients with SLE were found to be associated with inflammation, disease activity measured by the systemic lupus erythematosus disease activity index (SLEDAI) (83), and an adverse lipid profile. Moreover, higher concentrations of IL-6 were associated with coronary calcification in SLE (OR=1.07, p=0.035) (82), further suggesting a role of active inflammation in the development of atherosclerosis in SLE.

The authors have compared concentrations of inflammatory mediators associated with atherosclerosis in patients with SLE and control subjects (84). Concentrations of the adhesion molecules E-selectin and intercellular adhesion molecule (ICAM), the inflammatory enzyme myeloperoxidase (MPO), the cytokines vascular endothelial growth factor (VEGF) and TNF-α, and the acute phase reactant serum amyloid A (SAA) were higher in patients with SLE than in control subjects. Moreover, concentrations of these adhesion molecules, as well as TNF-α, were associated with sub-clinical atherosclerosis detected by EBCT, independent of Framingham risk score (84). In another study, concentrations of TNF-α also were found to be higher in patients with SLE who had a history of cardiovascular disease, and were correlated positively with triglycerides and VLDL cholesterol (85).

Recent evidence suggests co-stimulatory molecules also may be involved in associations of inflammation and atherosclerosis. The co-stimulatory molecule CD40 ligand (CD40L, also called sCD154) is a member of the TNF family and participates in B cell differentiation and proliferation (86) as well as in antibody isotype switching (87). The binding of CD40L to its receptor, CD40, is thought to also be involved in atherogenesis and atherosclerotic plaque rupture (88-90). CD40L has been found to be over expressed in T cells of patients with SLE (91), and elevated concentrations of CD40 and CD40L have been found in atherosclerotic plaques in SLE patients (88). Some reports indicate elevated serum concentrations of CD40L in patients with SLE compared to matched control subjects (92, 93). However, in other studies there was no association between serum CD40L and coronary calcium or carotid atherosclerosis (74, 94).

Pro-inflammatory oxidized low-density lipoprotein (OxLDL) is formed as part of the atherosclerotic process. It is phagocytized by monocytes or macrophages in the subendothelial space, which then develop into foam cells, early components of the atherosclerotic lesion. Patients with SLE, particularly those who have a history of cardiovascular disease, have elevated concentrations of circulating OxLDL(95). However, concentrations of another measure of oxidant stress, F_2-isoprostanes, were not elevated in patients with SLE, nor were they associated with the presence of atherosclerosis (96).

High density lipoprotein (HDL) is usually anti-inflammatory, but under some circumstances it may become pro-inflammatory, and lose capacity to prevent LDL from undergoing oxidation. This decreased ability to prevent oxidation of LDL negates a cardio-protective effect of HDL, and has been proposed as a potential risk factor for atherosclerosis (97). In the general population, people with CAD frequently may have pro-inflammatory HDL, despite normal cholesterol concentrations by standard measurements (98). A recent study in patients with SLE and RA found significantly more pro-inflammatory HDL than in control subjects (99). In the cohort of 154 SLE patients studied, 14 had documented clinical atherosclerosis, including CAD, cerebrovascular disease, or both. Out of these 14 patients, the 4 patients with CAD all had pro-inflammatory HDL (mean±SD 1.11±0.07, compared to 0.08±0.43 in patients without CAD (p<0.0001)) (99).

Homocysteine

Hyperhomocysteinemia is associated with increased cardiovascular risk in the general population (100) and has been identified as a risk factor for coronary heart disease in patients with SLE (62, 101). Moreover, an independent association was seen between homocysteine concentrations and coronary artery calcification measured by EBCT in patients with SLE, suggesting that

increased homocysteine concentrations may help identify patients who are at high risk for developing premature atherosclerosis (102), and also those with a higher risk of progression of atherosclerosis (77). It should be noted, however, that in patients with vascular disease, strategies to lower homocysteine generally have not reduced the risk of cardiovascular events (103). No information is available concerning such strategies in patients with SLE.

Renal impairment

Patients with chronic renal insufficiency have a higher risk of atherosclerosis compared to age-matched controls (104). An association between proteinuria and sub-clinical atherosclerosis has been described in patients with SLE (72, 105). Nephrotic range proteinuria was a major risk factor for a significantly higher carotid intima media thickness in patients with juvenile SLE (105), and proteinuria and impaired renal function were among disease-related variables associated with coronary calcification (72).

Glucocorticoid therapy and atherosclerosis in SLE

As in RA, glucocorticoid use has been described as a "double-edged" sword in terms of cardiovascular risk in SLE (106). Glucocorticoids in high doses accelerate atherosclerosis in experimental animals and humans and could affect cardiovascular risk adversely by worsening or inducing hypertension, obesity, hypercholesterolemia, and diabetes. A higher cumulative dose of prednisone was found to be associated with the presence of carotid artery plaque in patients with SLE (107), although the higher glucocorticoid dose may be a surrogate for more severe clinical status.

Glucocorticoid therapy could also reduce cardiovascular risk through anti-inflammatory effects. In studies of carotid artery plaque in patients with SLE, those who had plaque detected by ultrasound had received less glucocorticoids or cyclophosphamide, suggesting that aggressive control of inflammation may lead to a lower atherosclerotic risk (74). The dose of corticosteroid also may be important in alterations in cardiovascular risk factors. For example, some studies have found that a dose higher than 10 mg/day of prednisolone or prednisone is associated with higher triglyceride (108) and cholesterol concentrations (60), respectively.

Conclusion

This review summarizes evidence showing that both RA and SLE are associated with an increased risk of subclinical atherosclerosis and cardiovascular events. Some traditional risk factors identified in atherogenesis in the general population are elevated in patients with these inflammatory diseases. However, additional disease-related risk factors associated with disease severity and inflammation have been identified as increasing cardiovascular risk in these patient populations. Current evidence suggests that better control of disease activity and thus inflammation in patients with RA and SLE may result in better cardiovascular outcomes. Identification of specific mediators in rheumatic diseases and atherosclerosis will advance therapies directed to both atherosclerosis and complications of the rheumatic disease.

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