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REVIEW

# Where the immune response meets the vessel wall

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## ABSTRACT

**Immune-mediated inflammatory diseases (IMIDs), including rheumatoid arthritis and spondyloarthritis, are associated with increased cardiovascular morbidity and mortality, independent of the established cardiovascular risk factors. The chronic inflammatory state, a hallmark of IMIDs, is considered to be a driving force for accelerated atherogenesis. Consequently, aggressive control of disease activity has been suggested to be instrumental for cardiovascular risk reduction. Specific guidelines for cardiovascular risk reduction in patients with IMIDs, particularly rheumatoid arthritis, are lacking, largely due to the absence of randomised clinical trial data. In this review, we focus on pathophysiology and observational evidence of cardiovascular risk in different prototypes of IMIDs.**

## KEYWORDS

Atherosclerosis, cardiovascular disease, immune-mediated inflammatory disease

## INTRODUCTION

Immune-mediated inflammatory diseases (IMID), including atherosclerosis, Sjögren's syndrome, systemic lupus erythematosus (SLE), spondyloarthritis (e.g. ankylosing spondylitis (AS) and psoriatic arthritis (PsA)), and rheumatoid arthritis (RA), are characterised by common inflammatory pathways leading to inflammation and accompanied by increased cardiovascular morbidity and mortality. Chronic activation of innate and adaptive inflammatory pathways that provide an essential defence against 'foreign' substances, ranging from bacterial products to endogenous oxidised lipids, may contribute to atherosclerotic plaque progression, destabilisation, and ultimately rupture with subsequent clinical sequelae such as myocardial infarction or stroke. In fact, both localised and systemic infections involving respiratory or urinary tract transiently increase the risk of cardiovascular events.[1,2] A marked association has been reported between poor dental health and myocardial infarction, regardless of traditional cardiovascular risk factors,[3] which may be ascribed to bacterial components from the dental cavity, which directly affect endothelial integrity, blood coagulation and platelet function.[3] Thus, a wide array of infectious diseases may trigger manifestations of atherosclerosis and contribute to the onset of acute cardiovascular events. During the last decade, the role of chronic inflammatory disorders in the onset of cardiovascular events has increasingly been recognised. The nature of the inflammatory response preceding vascular events may have a profound impact on the final outcome.[4]

In this review, we address the impact of chronic inflammation on the cardiovascular risk profile by focussing on highly prevalent IMIDs, such as RA and SLE. Identifying critical inflammatory pathways involved in progression and destabilisation of pre-existing atherosclerotic plaques may help to define novel therapeutic strategies to further reduce cardiovascular disease burden, particularly in patients with chronic inflammatory disorders.

## RHEUMATOID ARTHRITIS

For many years, RA has been recognised to increase cardiovascular morbidity and mortality, irrespective of established cardiovascular risk factors.[5-7] In the early 1990s, it was shown that having RA may shorten overall survival with mortality rates exceeding a twofold increase.[8] This increased cardiovascular event rate was largely restricted to patients with marked disease activity. At that time, the five-year survival in RA patients with the highest disease activity proved comparable to that of individuals with three-vessel coronary artery disease or stage 4 Hodgkin's

disease.[9] Subsequently, the increased cardiovascular disease among RA patients has been corroborated in a large number of studies.[5,9-17] In recent years, tighter control of the inflammatory process in RA has been held accountable for a significant reduction in atherosclerosis-related death rates, as elegantly demonstrated in a cohort of nearly 3900 patients, followed from 1980 to 1997.[18] Determinants that probably have beneficial effects on the cardiovascular risk profile involve potent suppression of inflammation, diminished use of non-steroidal anti-inflammatory drugs, higher functional status and increased physical activity.[19,20]

**Vascular function changes and atherogenesis**

One of the earliest changes in the onset of atherosclerosis pertains to loss of vascular protection against 'atherosclerotic insults' (≈endothelial dysfunction). The severity of endothelial dysfunction has been shown to predict future cardiovascular events.[21] Active RA has been consistently associated with endothelial dysfunction, which can be reversed by retraction of the inflammatory insult.[22] Thus, acetylcholine-mediated vasodilation, as measured by venous plethysmography, was reduced in newly diagnosed RA patients, indicative of decreased vascular nitric oxide (NO) bioavailibility.[23] Six months of routine anti-inflammatory therapy effectively mitigated clinical and biochemical markers of inflammation in these patients, with ensuing improvement of endothelial vasomotor function. Similar findings have been confirmed in small-scale studies, where improvement of endothelial function paralleled the reduction in systemic inflammation and disease activity scores (DAS28) upon tumour-necrosis factor α (TNFα) blockade or treatment with the anti-CD20 monoclonal antibody rituximab.[24-26] Taken together, these data imply that endothelial dysfunction is an integral part of the early disease process in RA.

**Vascular structure changes and atherogenesis**

Morphological changes in the carotid artery wall, visualised as increased intima-media thickening (IMT) by B-mode ultrasonography, are reported to precede the development of overt atherosclerotic lesions by at least one to two decades.[21] In this regard, carotid IMT proved thicker in RA patients, compared with controls[29] and smoking inclined towards higher carotid IMT compared with non-smokers.[27] Additional studies revealed increased prevalence and severity of coronary-artery calcification in RA patients.[28,29] Furthermore, the prevalence of carotid atherosclerotic plaques was threefold higher in 94 RA patients compared with matched controls, and was associated with age, hypertension and TNFα-blocking therapy, most likely confounded by a more severe subgroup of patients.[30] Once cardiovascular disease becomes manifest, RA patients exhibit a higher prevalence of multivessel disease and greater need for revascularisation than age- and sex-matched controls.[31] Consistent with this notion, angiographic scores indicate that RA patients have an increased risk for multivessel disease compared with matched controls.[32,33] Taken together, it seems safe to assume that RA can be considered a high-risk condition for cardiovascular events; once cardiovascular disease is present it may carry a poorer prognosis in the post-event period.

## PSORIATIC ARTHRITIS

Hitherto, several studies provide support for augmented cardiovascular risk, represented by both functional and structural arterial wall changes in association with PsA. Flow-mediated dilation (FMD) was significantly impaired in 50 PsA patients without traditional cardiovascular risk factors or cardiovascular disease compared with matched controls (mean, [range] 6.3%, [0.3-13.4%] *vs* 8.2%, [0.0-21.2%]). In this report, a significant correlation between inflammation indices (i.e. C-reactive protein and erythrocyte sedimentation rate) at the time of diagnosis and FMD was found.[34] In addition, a cohort of 59 PsA patients showed increased carotid IMT compared with healthy controls.[35] Another study also showed a higher prevalence of subclinical atherosclerosis, as measured by carotid IMT, among 82 PsA patients compared with matched controls, even after adjusting for traditional cardiovascular risk factors.[36] In this report, independent variables that significantly correlated with subclinical atherosclerosis include increased glucose and triglyceride levels. In accordance with these data, a recent case control study showed higher carotid IMT and carotid plaque index in 40 patients with PsA than in matched controls, whereas PsA status as well as age and triglyceride levels correlated with carotid plaque presence.[37] There was a trend suggesting that other traditional risk factors were also more prevalent among patients with PsA. As in RA, cardiovascular diseases and their risk factors including hyperlipidaemia, diabetes mellitus and hypertension were more common in patients PsA than in matched controls.[38] Taken together, having PsA is associated with increased cardiovascular risk, particularly in the presence of risk factors that relate to the metabolic syndrome.

## ANKYLOSING SPONDYLITIS

A recent study demonstrated impairment of endothelial function, as measured by FMD, in 54 patients with AS compared with healthy controls. FMD did not correlate with known risk markers such as age, serum lipids, smoking habits or inflammatory indices and disease activity scores.[39] The findings of a recent study show that coronary flow reserve, reflecting coronary microvascular function, and left ventricular diastolic function are impaired in AS, possibly pointing at an early manifestation of cardiac involvement in patients with AS.[40]

The severity of these impairments correlated with inflammation indices, including C-reactive protein. Referring to structural changes, another study found significantly increased carotid IMT in 60 AS patients compared with healthy controls, whereas carotid IMT was positively correlated with smoking habits, waist-hip-ratio and blood pressure.[41]

Other studies, however, failed to demonstrate increased cardiovascular risk among AS patients. A cross-sectional study in 28 AS patients showed that carotid IMT and parameters related to arterial elastic properties in young AS patients free of traditional cardiovascular risk factors were not different from those in healthy controls.[42] Two additional studies also failed to observe difference in subclinical atherosclerosis, as detected by carotid IMT, between AS patients compared with matched controls,[39,43] although there was a higher prevalence of metabolic syndrome among AS patients. Based on the foregoing, the evidence for increased cardiovascular risk in AS is still inconclusive and needs further clarification.

## SYSTEMIC LUPUS ERYTHEMATOSUS

Epidemiological reports from the early 1970s unambiguously showed that cardiovascular disease contributes significantly to morbidity and (premature) mortality in SLE.[44-49] In a retrospective study on a cohort of 498 women with SLE that was followed for 14 years, the age-specific incident rates of cardiovascular events, including myocardial infarction and angina pectoris, was 50-fold higher compared with age-matched controls.[50] Combining data from 263 participants in two SLE registries, retrospective assessment demonstrated a relative risk of 10.1 for nonfatal myocardial infarction (95% CI 5.8-15.6), 17.0 for death due to coronary heart disease (95% CI 8.1-29.7), 7.5 for overall coronary heart disease (5.1-10.4), and 7.9 for stroke (4.0-13.6) after a mean follow-up of 8.6 years.[51] These findings could only partially be attributed to traditional Framingham risk factors. Accordingly, a population-based estimation of the relative prevalence of myocardial infarction, congestive heart failure, or cerebrovascular accident among young women with SLE, using the California Hospital Discharge Database, revealed that the frequencies of hospitalisation due to these cardiovascular 'entities' was increased by 2.3 times (95% CI 1.1-3.5), 3.8 times (2.4-5.2), and 2.1 times (1.2-2.9), respectively, compared with controls.[52]

### Vascular function changes and atherogenesis

FMD was impaired in 62 SLE patients compared with controls (median, 3.6 *vs* 6.9%; p<0.01).[53] In a study comprising 111 SLE patients, lupus was associated with significant endothelial dysfunction compared with healthy controls.[54] Recent studies have corroborated these findings, showing endothelial dysfunction and increased arterial stiffness in patients with SLE compared with matched controls,[55] which correlates with disease activity.[56,57]

### Vascular structure changes and atherogenesis

A large case-control study showed that preclinical carotid atherosclerosis was more prevalent among SLE patients than in the controls (37.1 *vs* 15.2%, p<0.001), whereas older age, the presence of SLE (odds ratio 4.8; 95% CI 2.6-8.7), and higher serum cholesterol were independently related to the presence of plaque.[58] Similar findings were achieved in other studies, where a higher prevalence of carotid plaques was observed among patients with SLE compared with controls, and carotid IMT was higher in the former.[54,59] Additional studies revealed increased carotid IMT in patients with SLE,[55,60,61] particularly among those with a history of cardiovascular disease[62] and in the presence of nephrotic-range proteinuria.[50] Last, a longitudinal study of 217 women with SLE from the Pittsburgh Lupus Registry showed that carotid plaque progression rate was higher than the control group, whereas the IMT progression rate was similar.[63] Noticeably, SLE patients showed a higher prevalence of coronary-artery atherosclerosis (calcification), as measured by electron-beam computed tomography, compared with controls, whereas the age at onset was reduced.[64]

Despite a few studies that failed to show evidence for early carotid atherosclerosis,[65] available data clearly indicates that SLE similar to RA potentiates the risk of cardiovascular disease in a young, predominantly female population without common risk factors.

## MECHANISMS CONTRIBUTING TO ACCELERATED ATHEROGENESIS

Accelerated atherogenesis in IMID may involve many inflammation-related and non-inflammatory factors. Due to space limitations, we forego a detailed discussion of all factors described and provide the reader with a brief insight into the most common mechanisms involved.

### Innate immunity

Monocytes have been firmly implicated in the pathogenesis of atherosclerosis, starting from adhesion to the endothelium and their migration into the intima early in atherogenesis, followed by differentiation into macrophages. Macrophages that are crucial to all IMIDs[66-68] are phenotypically polarised by specific signals and secrete a variety of proinflammatory cytokines, and proteinases that may accelerate atherosclerosis progression. Among many proatherosclerotic activities TNFα, a key inflammatory mediator, induces potent atherogenic effects on the arterial wall, involving cell apoptosis, upregulation of adhesion molecules[69] and endothelial cells adopting

a more procoagulant[70] and vasoconstrictor phenotype.[71] Matrix metalloproteinases are proteolytic enzymes that can degrade collagen and render the growing plaque's cap thin and susceptible to rupture.[72] Neutrophils that infiltrate the atherosclerotic plaque and express destabilising factors such as myeloperoxidase, gelatinase-associated lipocalin, proteolytic enzymes and tissue factor, have been increasingly linked to accelerated atherogenesis, as has been shown elegantly in experimental atherosclerosis.[73,74] With regard to inflammatory proteins, the acute phase reactant CRP has emerged as a direct partaker in atherosclerosis, and we have shown that infusion of CRP in humans renders the endothelium dysfunctional with ensuing procoagulant responses, particularly under hypercholesterolaemic conditions.[75] The atherogenic role of the terminal complement has been confirmed recently by showing that the absence of CD59, a key regulator of the complement membrane attack complex assembly, accelerated and a neutralising anti-mouse C5 antibody attenuated atherosclerosis in experimental atherosclerosis.[76]

**Adaptive immunity**

Peripheral blood $CD4^+$ T-cell subsets that lack expression of the CD28 molecule may contribute to increased cardiovascular risk.[77] Individuals with RA, in whom expansion of this T-cell subset with a proinflammatory phenotype and tissue damaging potential[78, 79] is detected, show impairment of FMD and increased IMT compared with those without, and TNFα-blockade induces CD28 reappearance on the $CD4^+$ cell surface.[77] Additional T-cell activities that have been linked to atherogenesis involve IL-17 production with interferon-γ by coronary artery-infiltrating T cells, inducing proinflammatory responses in vascular smooth muscle cells.[80] Further, CXCR6, a chemokine receptor expressed on a subset of $CD4^+$ T helper 1 cells and natural killer T cells, has been implicated in lymphocyte homing and the local immune response within the vessel wall.[81] Furthermore, dendritic cells at the media-adventitia junction were identified to have an important role in immune-sensing and T-cell-stimulatory functions, modulating wall-infiltrating T cells to display vessel-specific activation profiles including that of atherosclerosis with differential production of CD40L, lymphotoxin-α, and interferon-γ in medium and large human arteries.[82]

**Non-inflammatory factors**

Referring to non-inflammation-related factors, few IMIDs such as RA have been associated with an atherogenic lipid profile, i.e. elevated levels of apolipoprotein-B containing lipoproteins and low HDL, which is reversible upon effective treatment and correlates significantly with clinical scores and inflammatory activity.[83-85] Improvement of lipid profile is accompanied by atheroprotective alterations in high-density lipoprotein composition upon tumour necrosis factor blockade. As indicated above, IMID patients exhibit a higher prevalence of the metabolic syndrome, a cluster of cardiovascular risk factors including dyslipidaemia, insulin resistance, elevated blood pressure and abdominal obesity.[86] Another mechanism focuses on endothelial progenitor cells (EPC), of which the numbers inversely correlate with cardiovascular risk factors, and thus constitute a biomarker for vascular malfunction.[87] In RA, peripheral numbers of EPCs have been found to correlate inversely with disease activity.[88] Statin therapy, at least in the experimental adjuvant-induced arthritis model of RA, appears to have favourable effects on the presence of EPCs.[89]

Collectively, the mechanisms by which chronic inflammation in IMIDs may contribute to the pathogenesis of atherosclerosis are multifactorial by nature. High disease activity promotes an inflammatory endothelial and leucocyte phenotype combined with a proatherogenic lipid profile that in conjunction stimulates plaque growth and destabilisation, ultimately culminating into an acute clinical event.

## CONCLUSION

Over the past two decades it has become increasingly clear that chronic inflammation is an independent risk factor for cardiovascular events, with an impact over and above established risk factors. Since IMIDs are protracted disorders, the focus on adequate cardiovascular prevention in these patients is long overdue. Pathophysiologically, chronic inflammation provides a direct link between IMIDs and accelerated atherogenesis. Therefore, proper management of cardiovascular risk, first and foremost, requires aggressive control of disease activity. Yet, guidelines for optimal cardiovascular risk reduction in patients with IMIDs are lacking, largely due to the absence of randomised clinical trial data. As implicated by this review, the need to adapt cardiovascular risk calculators is growing to better accommodate the impact of chronic inflammatory disease over and above established risk factors to predict cardiovascular risk in the individual patient with an IMID.

## REFERENCES

1 Smeeth L, Thomas SL, Hall AJ, Hubbard R, Farrington P, Vallance P. Risk of myocardial infarction and stroke after acute infection or vaccination. N Engl J Med. 2004;351:2611-8.

2 Meier CR, Jick SS, Derby LE, Vasilakis C, Jick H. Acute respiratory-tract infections and risk of first-time acute myocardial infarction. Lancet. 1998;351:1467-71.

3 Mattila KJ, Nieminen MS, Valtonen VV, et al. Association between dental health and acute myocardial infarction. BMJ. 1989;298:779-81.

4 Maier W, Altwegg LA, Corti R, et al. Inflammatory markers at the site of ruptured plaque in acute myocardial infarction: locally increased interleukin-6 and serum amyloid a but decreased C-reactive protein. Circulation. 2005;111:1355-61.

5 Wallberg-Jonsson S, Ohman ML, Dahlqvist SR. Cardiovascular morbidity and mortality in patients with seropositive rheumatoid arthritis in Northern Sweden. J Rheumatol. 1997;24:445-51.

6 van Leuven SI, Franssen R, Kastelein JJ, Levi M, Stroes ES, Tak PP. Systemic inflammation as a risk factor for atherothrombosis. Rheumatology (Oxford). 2008;47:3-7.

7 Cobbs S, Anderson F, Bauer W. Length of life and cause of death in rheumatoid arthritis. N Engl J Med. 1953;249:553-6.

8 Wolfe F, Mitchell DM, Sibley JT, et al. The mortality of rheumatoid arthritis. Arthritis Rheum. 1994;37:481-94.

9 Pincus T, Brooks RH, Callahan LF. Prediction of long-term mortality in patients with rheumatoid arthritis according to simple questionnaire and joint count measures. Ann Intern Med. 1994;120:26-34.

10 Del Rincon I, Williams K, Stern MP, Freeman GL, Escalante A. High incidence of cardiovascular events in a rheumatoid arthritis cohort not explained by traditional cardiac risk factors. Arthritis Rheum. 2001;44:2737-45.

11 Solomon DH, Karlson EW, Rimm EB, et al. Cardiovascular morbidity and mortality in women diagnosed with rheumatoid arthritis. Circulation. 2003;107:1303-7.

12 Reilly PA, Cosh JA, Maddison PJ, Rasker JJ, Silman AJ. Mortality and survival in rheumatoid arthritis: a 25 year prospective study of 100 patients. Ann Rheum Dis. 1990;49:363-9.

13 Kvalvik AG, Jones MA, Symmons DP. Mortality in a cohort of Norwegian patients with rheumatoid arthritis followed from 1977 to 1992. Scand J Rheumatol. 2000;29:29-37.

14 Mikuls TR, Saag KG, Criswell LA, et al. Mortality risk associated with rheumatoid arthritis in a prospective cohort of older women: results from the Iowa Women's Health Study. Ann Rheum Dis. 2002;61:994-9.

15 Gabriel SE, Crowson CS, Kremers HM, et al. Survival in rheumatoid arthritis: a population-based analysis of trends over 40 years. Arthritis Rheum. 2003;48:54-8.

16 Bjornadal L, Baecklund E, Yin L, Granath F, Klareskog L, Ekbom A. Decreasing mortality in patients with rheumatoid arthritis: results from a large population based cohort in Sweden, 1964-95. J Rheumatol. 2002;29:906-12.

17 Krishnan E, Lingala VB, Singh G. Declines in mortality from acute myocardial infarction in successive incidence and birth cohorts of patients with rheumatoid arthritis. Circulation. 2004;110:1774-9.

18 Krishnan E, Lingala VB, Singh G. Declines in mortality from acute myocardial infarction in successive incidence and birth cohorts of patients with rheumatoid arthritis. Circulation. 2004;110:1774-9.

19 Choi HK, Hernan MA, Seeger JD, Robins JM, Wolfe F. Methotrexate and mortality in patients with rheumatoid arthritis: a prospective study. Lancet. 2002;359:1173-7.

20 Kremer JM. Safety, efficacy, and mortality in a long-term cohort of patients with rheumatoid arthritis taking methotrexate: followup after a mean of 13.3 years. Arthritis Rheum. 1997;40:984-5.

21 Bisoendial RJ, Hovingh GK, de GE, Kastelein JJ, Lansberg PJ, Stroes ES. Measurement of subclinical atherosclerosis: beyond risk factor assessment. Curr Opin Lipidol. 2002;13:595-603.

22 Tonetti MS, D'Aiuto F, Nibali L, et al. Treatment of periodontitis and endothelial function. N Engl J Med. 2007;356:911-20.

23 Bergholm R, Leirisalo-Repo M, Vehkavaara S, Makimattila S, Taskinen MR, Yki-Jarvinen H. Impaired responsiveness to NO in newly diagnosed patients with rheumatoid arthritis. Arterioscler Thromb Vasc Biol. 2002;22:1637-41.

24 Bosello S, Santoliquido A, Zoli A, et al. TNF-alpha blockade induces a reversible but transient effect on endothelial dysfunction in patients with long-standing severe rheumatoid arthritis. Clin Rheumatol. 2008;27(7):833-9.

25 Hurlimann D, Forster A, Noll G, et al. Anti-tumor necrosis factor-alpha treatment improves endothelial function in patients with rheumatoid arthritis. Circulation. 2002;106:2184-7.

26 Gonzalez-Juanatey C, Llorca J, Vazquez-Rodriguez TR, Diaz-Varela N, Garcia-Quiroga H, Gonzalez-Gay MA. Short-term improvement of endothelial function in rituximab-treated rheumatoid arthritis patients refractory to tumor necrosis factor alpha blocker therapy. Arthritis Rheum. 2008;59:1821-4.

27 Gerli R, Sherer Y, Vaudo G, et al. Early atherosclerosis in rheumatoid arthritis: effects of smoking on thickness of the carotid artery intima media. Ann N Y Acad Sci. 2005;1051:281-90.

28 Chung CP, Oeser A, Raggi P, et al. Increased coronary-artery atherosclerosis in rheumatoid arthritis: relationship to disease duration and cardiovascular risk factors. Arthritis Rheum. 2005;52:3045-53.

29 Kao AH, Krishnaswami S, Cunningham A, et al. Subclinical coronary artery calcification and relationship to disease duration in women with rheumatoid arthritis. J Rheumatol. 2008;35:61-9.

30 Roman MJ, Moeller E, Davis A, et al. Preclinical carotid atherosclerosis in patients with rheumatoid arthritis. Ann Intern Med. 2006;144:249-56.

31 Yalamanchili K, Aronow WS, Kilaru R, et al. Coronary artery disease is more severe in older persons with rheumatoid arthritis than in older persons without rheumatoid arthritis. Cardiol Rev. 2006;14:55-6.

32 Yalamanchili K, Aronow WS, Kilaru R, et al. Coronary artery disease is more severe in older persons with rheumatoid arthritis than in older persons without rheumatoid arthritis. Cardiol Rev. 2006;14:55-6.

33 Warrington KJ, Kent PD, Frye RL, et al. Rheumatoid arthritis is an independent risk factor for multi-vessel coronary artery disease: a case control study. Arthritis Res Ther. 2005;7:R984-R991.

34 Gonzalez-Juanatey C, Llorca J, Miranda-Filloy JA, et al. Endothelial dysfunction in psoriatic arthritis patients without clinically evident cardiovascular disease or classic atherosclerosis risk factors. Arthritis Rheum. 2007;57:287-93.

35 Gonzalez-Juanatey C, Llorca J, Amigo-Diaz E, Dierssen T, Martin J, Gonzalez-Gay MA. High prevalence of subclinical atherosclerosis in psoriatic arthritis patients without clinically evident cardiovascular disease or classic atherosclerosis risk factors. Arthritis Rheum. 2007;57:1074-80.

36 Tam LS, Shang Q, Li EK, et al. Subclinical carotid atherosclerosis in patients with psoriatic arthritis. Arthritis Rheum. 2008;59:1322-31.

37 Eder L, Zisman D, Barzilai M, et al. Subclinical atherosclerosis in psoriatic arthritis: a case-control study. J Rheumatol. 2008;35:877-82.

38 Han C, Robinson DW, Jr., Hackett MV, Paramore LC, Fraeman KH, Bala MV. Cardiovascular disease and risk factors in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. J Rheumatol. 2006;33:2167-72.

39 Sari I, Okan T, Akar S, et al. Impaired endothelial function in patients with ankylosing spondylitis. Rheumatology (Oxford). 2006;45:283-6.

40 Caliskan M, Erdogan D, Gullu H, et al. Impaired coronary microvascular and left ventricular diastolic functions in patients with ankylosing spondylitis. Atherosclerosis 2008;196:306-12.

41 Mathieu S, Joly H, Baron G, et al. Trend towards increased arterial stiffness or intima-media thickness in ankylosing spondylitis patients without clinically evident cardiovascular disease. Rheumatology (Oxford). 2008;47:1203-7.

42 Choe JY, Lee MY, Rheem I, Rhee MY, Park SH, Kim SK. No differences of carotid intima-media thickness between young patients with ankylosing spondylitis and healthy controls. Joint Bone Spine. 2008;75:548-53.

43 Malesci D, Niglio A, Mennillo GA, Buono R, Valentini G, La MG. High prevalence of metabolic syndrome in patients with ankylosing spondylitis. Clin Rheumatol. 2007;26:710-4.

44 Shome GP, Sakauchi M, Yamane K, Takemura H, Kashiwagi H. Ischemic heart disease in systemic lupus erythematosus. A retrospective study of 65 patients treated with prednisolone. Jpn J Med. 1989;28:599-603.

45 Tsakraklides VG, Blieden LC, Edwards JE. Coronary atherosclerosis and myocardial infarction associated with systemic lupus erythematosus. Am Heart J. 1974;87(5):637-41.

46 Gladman DD, Urowitz MB. Morbidity in systemic lupus erythematosus. J Rheumatol Suppl. 1987;14( Suppl 13):223-6.

47 Petri M, Perez-Gutthann S, Spence D, Hochberg MC. Risk factors for coronary artery disease in patients with systemic lupus erythematosus. Am J Med. 1992;93:513-9.

48 Urowitz MB, Bookman AA, Koehler BE, Gordon DA, Smythe HA, Ogryzlo MA. The bimodal mortality pattern of systemic lupus erythematosus. Am J Med. 1976;60:221-5.

49 Spiera H, Rothenberg RR. Myocardial infarction in four young patients with SLE. J Rheumatol. 1983;10:464-6.

50 Manzi S, Meilahn EN, Rairie JE, et al. Age-specific incidence rates of myocardial infarction and angina in women with systemic lupus erythematosus: comparison with the Framingham Study. Am J Epidemiol. 1997;145:408-15.

51 Esdaile JM, Abrahamowicz M, Grodzicky T, et al. Traditional Framingham risk factors fail to fully account for accelerated atherosclerosis in systemic lupus erythematosus. Arthritis Rheum. 2001;44:2331-7.

52 Ward MM. Premature morbidity from cardiovascular and cerebrovascular diseases in women with systemic lupus erythematosus. Arthritis Rheum. 1999;42:338-46.

53 El-Magadmi M, Bodill H, Ahmad Y, et al. Systemic lupus erythematosus: an independent risk factor for endothelial dysfunction in women. Circulation. 2004;110:399-404.

54 Zhang CY, Lu LJ, Li FH, et al. Evaluation of risk factors that contribute to high prevalence of premature atherosclerosis in Chinese premenopausal systemic lupus erythematosus patients. J Clin Rheumatol. 2009;Mar 18.

55 Cacciapaglia F, Zardi E, Coppolino G, et al. Stiffness parameters, intima-media thickness and early atherosclerosis in systemic lupus erythematosus patients. Lupus. 2009;18:249-56.

56 Shang Q, Tam LS, Li EK, Yip GW, Yu CM. Increased arterial stiffness correlated with disease activity in systemic lupus erythematosus. Lupus. 2008;17:1096-102.

57 Valdivielso P, Gomez-Doblas JJ, Macias M, et al. Lupus-associated endothelial dysfunction, disease activity and arteriosclerosis. Clin Exp Rheumatol. 2008;26:827-33.

58 Roman MJ, Shanker BA, Davis A, et al. Prevalence and correlates of accelerated atherosclerosis in systemic lupus erythematosus. N Engl J Med. 2003;349:2399-406.

59 Falaschi F, Ravelli A, Martignoni A, et al. Nephrotic-range proteinuria, the major risk factor for early atherosclerosis in juvenile-onset systemic lupus erythematosus. Arthritis Rheum. 2000;43:1405-9.

60 Keser G, Aksu K, Tamsel S, et al. Increased thickness of the carotid artery intima-media assessed by ultrasonography in Behcet's disease. Clin Exp Rheumatol. 2005;23(4 Suppl 38):S71-S76.

61 Colombo BM, Murdaca G, Caiti M, et al. Intima-media thickness: a marker of accelerated atherosclerosis in women with systemic lupus erythematosus. Ann N Y Acad Sci. 2007;1108:121-6.

62 Svenungsson E, Jensen-Urstad K, Heimburger M, et al. Risk factors for cardiovascular disease in systemic lupus erythematosus. Circulation. 2001;104:1887-93.

63 Thompson T, Sutton-Tyrrell K, Wildman RP, et al. Progression of carotid intima-media thickness and plaque in women with systemic lupus erythematosus. Arthritis Rheum. 2008;58:835-42.

64 Asanuma Y, Oeser A, Shintani AK, et al. Premature coronary-artery atherosclerosis in systemic lupus erythematosus. N Engl J Med. 2003;349:2407-15.

65 Rossi M, Mosca M, Tani C, Franzoni F, Santoro G, Bombardieri S. Integrated backscatter analysis of carotid intima-media complex in patients with systemic lupus erythematosus. Clin Rheumatol. 2008;27:1485-8.

66 Gordon S. The macrophage: past, present and future. Eur J Immunol. 2007;37(Suppl 1):S9-17.

67 Martinez FO, Sica A, Mantovani A, Locati M. Macrophage activation and polarization. Front Biosci. 2008;13:453-61.

68 Hamilton JA, Tak PP. The dynamics of macrophage lineage populations in inflammatory and autoimmune diseases. Arthritis Rheum. 2009;60:1210-21.

69 Tracey D, Klareskog L, Sasso EH, Salfeld JG, Tak PP. Tumor necrosis factor antagonist mechanisms of action: a comprehensive review. Pharmacol Ther. 2008;117:244-79.

70 Speiser W, Kapiotis S, Kopp CW, et al. Effect of intradermal tumor necrosis factor-alpha-induced inflammation on coagulation factors in dermal vessel endothelium. An in vivo study of human skin biopsies. Thromb Haemost. 2001;85:362-7.

71 Patel JN, Jager A, Schalkwijk C, et al. Effects of tumour necrosis factor-alpha in the human forearm: blood flow and endothelin-1 release. Clin Sci (Lond). 2002;103:409-15.

72 Liang J, Liu E, Yu Y, et al. Macrophage metalloelastase accelerates the progression of atherosclerosis in transgenic rabbits. Circulation. 2006;113:1993-2001.

73 Yvan-Charvet L, Welch C, Pagler TA, et al. Increased inflammatory gene expression in ABC transporter-deficient macrophages: free cholesterol accumulation, increased signaling via toll-like receptors, and neutrophil infiltration of atherosclerotic lesions. Circulation. 2008;118:1837-47.

74 Zernecke A, Bot I, Djalali-Talab Y, et al. Protective role of CXC receptor 4/CXC ligand 12 unveils the importance of neutrophils in atherosclerosis. Circ Res. 2008;102:209-17.

75 Bisoendial RJ, Kastelein JJ, Peters SL, et al. Effects of CRP infusion on endothelial function and coagulation in normocholesterolemic and hypercholesterolemic subjects. J Lipid Res. 2007;48:952-60.

76 Wu G, Hu W, Shahsafaei A, et al. Complement regulator CD59 protects against atherosclerosis by restricting the formation of complement membrane attack complex. Circ Res. 2009;104:550-8.

77 Gerli R, Schillaci G, Giordano A, et al. CD4+CD28- T lymphocytes contribute to early atherosclerotic damage in rheumatoid arthritis patients. Circulation. 2004;109:2744-8.

78 Namekawa T, Wagner UG, Goronzy JJ, Weyand CM. Functional subsets of CD4 T cells in rheumatoid synovitis. Arthritis Rheum. 1998;41:2108-16.

79 Warrington KJ, Takemura S, Goronzy JJ, Weyand CM. CD4+,CD28- T cells in rheumatoid arthritis patients combine features of the innate and adaptive immune systems. Arthritis Rheum. 2001;44:13-20.

80 Eid RE, Rao DA, Zhou J, Lo SF, et al. Interleukin-17 and interferon-gamma are produced concomitantly by human coronary artery-infiltrating T cells and act synergistically on vascular smooth muscle cells. Circulation. 2009;119:1424-32.

81 Galkina E, Harry BL, Ludwig A, et al. CXCR6 promotes atherosclerosis by supporting T-cell homing, interferon-gamma production, and macrophage accumulation in the aortic wall. Circulation. 2007;116:1801-11.

82 Pryshchep O, Ma-Krupa W, Younge BR, Goronzy JJ, Weyand CM. Vessel-specific Toll-like receptor profiles in human medium and large arteries. Circulation. 2008;118:1276-84.

83 Park YB, Choi HK, Kim MY, et al. Effects of antirheumatic therapy on serum lipid levels in patients with rheumatoid arthritis: a prospective study. Am J Med. 2002;113:188-93.

84 Wijbrandts CA, van Leuven SI, Boom HD, et al. Sustained changes in lipid profile and macrophage migration inhibitory factor (MIF) levels after anti-TNF therapy in rheumatoid arthritis. Ann Rheum Dis. 2009;68(8):1316-21.

85 Van Eijck IC, de Vries MK, Levels JH, et al. Improvement of lipid profile is accompanied by atheroprotective alterations in high-density lipoprotein composition upon tumor necrosis factor blockade: A prospective cohort study in ankylosing spondylitis. Arthritis Rheum. 2009;60:1324-30.

86 Chung CP, Oeser A, Solus JF, et al. Prevalence of the metabolic syndrome is increased in rheumatoid arthritis and is associated with coronary atherosclerosis. Atherosclerosis. 2008;196:756-63.

87 Hill JM, Zalos G, Halcox JP, et al. Circulating endothelial progenitor cells, vascular function, and cardiovascular risk. N Engl J Med. 2003;348:593-600.

88 Grisar J, Aletaha D, Steiner CW, et al. Depletion of endothelial progenitor cells in the peripheral blood of patients with rheumatoid arthritis. Circulation. 2005;111:204-11.

89 Haruna Y, Morita Y, Yada T, Satoh M, Fox DA, Kashihara N. Fluvastatin reverses endothelial dysfunction and increased vascular oxidative stress in rat adjuvant-induced arthritis. Arthritis Rheum. 2007;56:1827-35.