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Review

# Atherogenesis in rheumatoid arthritis: the "rheumatoid vasculopathy"?

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**Abstract.** *Background and aim*: Rheumatoid Arthritis (RA) is associated with accelerated atherogenesis. RA patients have a reduced life expectancy compared to the general population, and cardiovascular (CV) disease (CVD) is recognized as a strong contributor to the excess of morbidity and mortality. Our aim was to review and discuss the recent advances in the knowledge of the RA-associated atherogenesis. *Methods:* A detailed search of the available literature was performed in the PubMed (U.S. National Library of Medicine) database. *Results*: Atherosclerosis is an early and common finding in RA patients, positively correlating to the disease duration and severity. Both traditional CV risk factors and disease-related mechanisms may contribute to the RA atherogenesis, however, clinical and epidemiological studies suggest that the systemic inflammation is the major determinant of the RA vascular comorbidity. Patients with RA show an increased risk for CV events compared with the general population, and CVD accounts for nearly 50% of death causes. CV morbidity and mortality strongly correlate with disease activity, whereas the successful pharmacological control of the chronic inflammation decreases the risk of CV complications. *Conclusions*: Atherogenesis is a precocious feature in RA, as extraarticular manifestation of the syndrome, and might be defined the "rheumatoid vasculopathy". The better understanding of molecular mechanisms leading to the RA accelerated atherogenesis, the development of effective screening methods, and the identification of successful strategies to control both systemic inflammation and concomitant CV risk factors will allow to minimize the rheumatoid vasculopathy impact on the patients' morbidity and mortality. (www.actabiomedica.it)

**Key words:** Rheumatoid arthritis, inflammation, endothelial dysfunction, atherogenesis, atherosclerosis, vascular involvement, vascular comorbidity, cardiovascular disease

## Introduction

Atherosclerosis is a disorder affecting over time the arterial tree. Traditionally considered a passive process resulting from the lipid accumulation in the arterial wall, atherogenesis is presently defined as a substantially multifactorial event, and growing evidence supports the fundamental role of inflammation since the initial phase of endothelial cell (EC) activation/dysfunction (1, 2).

Established cardiovascular (CV) risk factors (so called "traditional" risk factors) may trigger atherogenesis inducing alterations of EC constitutive functions, such as changes in permeability (increased transcytosis and subendothelial deposition of lipoproteins) and biosynthetic activity (enhanced synthesis of the basement membrane and extracellular matrix), as well as enhancement in adhesion molecule expression (3).

In the athero-prone areas, the progression of the endothelial dysfunction is characterized by reduction in EC net negative surface charge, decreased nitric oxide (NO) production, loss of EC non-thrombogenic ability, load with lipids and turn into foam cells, that progressively undergo apoptosis (3). Meanwhile, adhesion molecules increasingly expressed by activated ECs induce leukocyte adhesion and diapedesis,

monocyte recruitment, and their residence within the subendothelium as macrophages (4). During atherogenesis, macrophages interact with vascular ECs, medial smooth muscle cells, and infiltrated inflammatory cells, ultimately causing both the vessel compliance reduction and the atherosclerotic plaque development (1, 4). Moreover, the macrophage production of various enzymes and bioactive mediators may condition the plaque destabilization and rupture, as well as disorders of local blood coagulation and fibrinolysis (4).

The relevance of inflammation in atherogenesis is underlined not only by histological findings, but also by epidemiological studies showing that elevated serum levels of inflammatory markers, such as C-reactive protein (CRP), may define the risk of atherosclerotic complications (2) and predict CV events (5).

Rheumatoid Arthritis (RA) is a prototypical chronic inflammatory disease, affecting ~1% of the adult general population (6). RA has been associated with precocious and accelerated atherosclerosis (7-13) and with increased CV morbidity and mortality (14). Notably, atherosclerosis has been proposed as extraarticular manifestation of the disease (9).

Our aim was to review and discuss the recent advances in the knowledge of the RA-associated atherogenesis.

**Table 1.** Atherogenesis in rheumatoid arthritis: traditional and disease-related risk factors

| | |
|---|---|
| **Traditional** | Age |
| | Cigarette smoking |
| | Hyperlipemia/Dyslipidemia |
| | Insulin resistance/Diabetes mellitus |
| | Hypertension |
| | Sedentary lifestyle/Physical inactivity |
| | Body mass index alterations/Obesity |
| **Disease-related** | |
| • *Inflammatory* | Proatherogenic cytokines |
| | Chemokines |
| | Increased adhesion molecule expression |
| | Autoantibodies |
| | Perturbation of T-cell subsets |
| | Genetic polymorphisms |
| | Hyperhomocysteinemia |
| | Oxidative stress |
| | Apoptosis disorders/Endotelial progenitor cell exhaustion |
| | Prothrombotic variables/Thrombocytosis |
| • *Not inflammatory* | Physical inactivity/immobilization |
| | Weight gain |
| • *Iatrogenic* | Glucocorticoid-related metabolic effects |
| | Glucocorticoid-related arterial hypertension |
| | Methotrexate-related hyperhomocysteinemia |

## Methods

A detailed search of the available literature was performed in the PubMed (U.S. National Library of Medicine) database, using the following key words: rheumatoid arthritis, systemic inflammation, endothelial dysfunction, atherogenesis, atherosclerosis, vascular involvement, vascular comorbidity, cardiovascular disease, cardiovascular events, morbidity, mortality.

## Results

### *Traditional risk factors in RA-associated atherogenesis*

The role of traditional CV risk factors (Table 1) in RA atherogenesis has been recently evaluated in a multinational cross-sectional cohort of patients (15). Conventional risk factors, except obesity and physical inactivity, have been found to be significantly associated with CV morbidity (15).

In other studies, however, physically inactive RA patients were found to have significantly worse CV Disease (CVD) risk profile compared with physically active patients (16, 17), and obesity was found to correlate with increased CVD risk independently of many confounders (18). Otherwise, low body mass index has been associated with a significantly increased risk of CV death in RA patients (19, 20).

Age and arterial hypertension have been associated with atherosclerosis and increased CV risk in RA patients (15, 21-23).

Moreover, lipid levels and cigarette smoking has been found to be significantly associated with RA atherosclerosis (12, 17, 21). Of note, smoking is presently recognized an independent risk factor for the RA

development (24), and its association with the disease activity, duration and severity (21, 25-27) has been reported.

However, subjects with RA seem to have higher absolute risks of CVD compared with controls, even independently of smoking (17). Smoking status showed weaker associations with CV events among RA subjects compared to non-RA subjects (28), and did not predict CV events or CVD-associated mortality in seropositive RA patients, suggesting that increased mortality in these patients is not simply related to the smoking effects (29).

*Disease-associated risk factors in RA-associated atherogenesis*

The accelerated atherogenesis and the increased incidence of CV events in RA patients cannot be fully explained on the basis of traditional factors alone (30), and the involvement of disease-related risk factors has been suggested, being inflammation a shared pathogenic factor (1, 2, 9, 11, 31-33).

Several disease-related mechanisms may be involved in the development of premature vascular damage in RA (Table 1), including increased synthesis of proinflammatory mediators (such as cytokines, chemokines, adhesion molecules), autoantibodies against endothelial cell components, perturbations in T-cell subsets, genetic polymorphisms, hyperhomocysteinemia, oxidative stress, and abnormal vascular repair, as well as iatrogenic factors (32, 34).

In RA, considerable evidence supports the systemic endothelial activation/dysfunction, positively correlating with markers of inflammation (32) and improving with anti-tumour necrosis factor (TNF)-α therapy (35).

Proinflammatory cytokines are potent up-regulators of cellular adhesion molecule expression on endothelial cells (32) and induce a spectrum of proatherogenic changes, including dyslipidemia, insulin resistance, oxidative stress, and prothrombotic alterations (32, 34, 36, 37).

The systemic cytokine response activates the innate and adaptive immune system cells and conditions phenotypic and functional perturbation of T-cell subsets in RA (31). In patients with RA, enhanced blood levels of $CD4^+CD28^{null}$ T cells, that are autoreactive and can cause endothelial cell cytotoxicity, have been demonstrated in positive correlation with disease severity, and their persistent expansion is associated with increased subclinical atherosclerosis (32, 38-41).

Notably, $CD4^+CD28^{null}$ T cells are clonally expanded in patients with acute coronary syndromes and have been found to invade the unstable atherosclerotic plaque (42).

Genetic polymorphisms of candidate genes encoding for β-fibrinogen (G-455A), Factor XIIIA (Val34Leu), plasminogen activator inhibitor 1 (PAI-1) (4G/5G), and TNF receptor II (M196R) have been associated with vascular damage in RA patients (43).

Hyperhomocysteinemia, which is a common finding in patients with RA, is a further contributor to the impaired endothelial function, potentiates the oxidation of lipoproteins, and has prothrombotic effects (44).

The involvement of both apoptosis disorders and decrease in circulating endothelial progenitor cells, that have been demonstrated in patients, has been suggested in RA-associated atherosclerosis and enhanced CV risk (32, 34, 45).

Moreover, prothrombotic variables, including elevated fibrinogen, von Willebrand factor, PAI-1, and thrombocytosis, that reflect the inflammatory response, may contribute to the development of CV complications in RA (9, 32).

The role of glucocorticoid (GC) treatment in the RA-associated atherogenesis is controversial. GCs display beneficial anti-inflammatory activity, but may favor atherosclerosis through their metabolic side effects and by inducing arterial hypertension. However, in RA patients, the long-term GC administration was not found to be associated with a higher prevalence of the metabolic syndrome, a cluster of classical CV risk factors, including hypertension, obesity, glucose intolerance, and dyslipidemia (46).

The long-term GC treatment of RA patients was found to be associated with significantly increased frequency of carotid plaque and lower-limb arterial incompressibility, independent of CV risk factors and RA clinical manifestations (47). Otherwise, in another study, no significant association was found between

GC therapy and atherosclerosis in patients with RA (8).

Low dose prednisolone administration for at least 4 years did not influence endothelial functions and atherogenesis in RA patients, although total cholesterol levels were found to be increased (48). GC pulse therapy was shown to induce an early and progressive decrease in homocysteine plasma levels, that stabilise in RA patients continuing oral treatment with GC low dose (49).

Following exposure to GCs, rheumatoid factor (RF)-positive but not RF-negative patients were shown to be at increased risk of CV events. This finding suggests that GCs may interact with RF status to modulate the occurrence of CV events in RA (50).

Methotrexate (MTX), a commonly used disease modifying antirheumatic drug (DMARD) inhibiting dihydrofolate reductase and reducing folate levels, may cause hyperhomocysteinemia which can be prevented by folic acid supplementation. However, in an 18-year follow-up of 1240 RA patients, MTX reduced the overall mortality by 60%, primarily decreasing CV mortality by 70%, compared with patients not receiving DMARD therapy (51).

*RA-associated atherosclerosis assessment*

Several studies evaluating vascular function by direct measures, including flow-mediated vasodilation (40, 52, 53), pulse wave analysis (54) or venous occlusion plethysmyography (55), confirmed endothelial dysfunction in RA patients.

Significantly decreased endothelium-dependent vasodilatation was observed in RA patients compared with controls, especially in those carrying HLA-DRB1*04 allele (52).

Endothelial dysfunction was present in patients with newly diagnosed RA (55), as well as in young to middle-aged patients with low disease activity, in a strong association with average CRP levels (40). Moreover, in RA patients, endothelial dysfunction was found to be significantly associated with RF seropositivity (53).

Significantly reduced small and large artery elasticity, as well as increased systemic vascular resistance were found in RA patients, independently of traditional risk factors, and arterial elasticity was inversely associated with measures of inflammation, such as CRP (54).

Assessment of subclinical atherogenesis in RA has been performed by ultrasonography, measuring intima-media wall thickness (IMT) usually of carotid arteries (cIMT), that is regarded as a useful and sensitive index of early-stage generalized atherosclerosis (7, 8, 21, 22, 25, 26, 53, 56-58).

Increased prevalence of atherosclerosis was evidenced in RA patients, compared with age-, sex-, and established CV risk factors-matched controls (7, 8, 53, 56-58). The increased arterial wall thickness was independently correlated with the presence, duration and severity of RA (8, 21, 53, 56, 58). Moreover, cIMT was found to be significantly higher even in patients with recent onset RA than in controls matched for age, sex and CV risk factors (57).

In RA patients, a significant positive association was found between cIMT/carotid plaque values and levels of serologic markers of systemic inflammation [such as erythrocyte sedimentation rate (ESR) and CRP], independently of age, sex and measured CV risk factor (25).

In RA patients, the status of coronary arteries has been investigated by angiography (41), cardiac multidetector computed tomography (CT) (59), or by electron-beam tomography (EBT), useful method to evaluate the extent of coronary arterial calcification (CAC), which is a subclinical measure associated with the atherosclerotic plaque degree and a strong predictor of CV events (60, 61).

EBT was performed in patients with early and established RA of both genders, compared with age-, sex- and race-matched controls (60). CAC significantly occurred more frequently in patients with established RA than in those with early RA or controls. Among RA patients, smoking and elevated ESR were significantly associated with more severe CAC after adjustment for age and sex (60).

In a cross-sectional study, female patients with RA duration of at least 2 years and no clinical CVD completed EBT scans and were evaluated for concomitant CV risk factor. Patients with long-standing RA show more extensive subclinical atherosclerosis or CAC compared to the referent group, matched for age, race, and traditional CV risk factors (61).

Recently, a large compared study was performed in RA patients of both sexes and without clinical CVD, using the Multi-Ethnic Study of Atherosclerosis cohort as a control group (59). CAC prevalence and extent were assessed by cardiac multidetector CT. A higher prevalence and extent of CAC in RA patients was observed, compared with geographically compatible control population after CV risk and sociodemographic adjustments, and was associated with increasing overall disease severity, suggesting that RA disease process contributes to atherogenesis independently of traditional CV risk factors. Moreover, age and gender heterogeneities were observed, being the largest percentage difference in CAC between RA and control groups in the youngest age category and in male patients. These gender and age differences suggest that preventive measures should be emphasized particularly in male patients, and have to be considered even in young RA patients with low levels of traditional CV risk factors (59).

In addition, male sex and increased age at disease onset were found to be predictors of CV events (15, 29).

*Cardiovascular morbidity and mortality in RA*

A significant proportion of RA patients has comorbid CVD, with heavy impact on annual healthcare costs (62).

The absolute CV risk in RA patients was found to be similar to that in non-RA individuals who were 5-10 years older (20). More than half of the newly diagnosed RA patients who were 50-59 years of age and all of those >60 years of age had a >10% risk of CVD within 10 years of their RA incidence (20).

Patients with RA show a significantly higher prevalence of angina pectoris (63), have increased risk for multi-vessel coronary artery disease (CAD), and display more advanced coronary atherosclerosis at the time of CAD diagnosis, compared to patients without RA and independently of traditional CVD risk factors (41).

Disease severity has been reported to be a major determinant of CV morbidity in RA. Extraarticular disease was associated with the occurrence of myocardial infraction (MI) in patients with RA (15). Severe extraarticular manifestations were found to be associated with excess risk of all forms of noncardiac vascular disease, except cerebrovascular disease alone (64). Extraarticular RA was associated with a significantly increased risk of first ever CVD events, and also with an increased risk of new-onset CAD, adjusted for age, sex, and smoking (65). Moreover, the association between CVD and seropositive and erosive RA has been reported (66).

Most studies report that survival in RA is poorer than in general population, being mortality rates of patients 1.5-1.6 fold higher (14). CVD is the main attributed cause of excess morbidity and mortality in RA (11-14, 67-74).

A recent meta-analysis of observational studies evidenced a 50% increased risk of CVD death in RA patients, being the risk of death from ischemic heart disease or cerebrovascular disease similarly elevated (75). RA severity and duration are strongly related with the increased CV mortality (68,74). The contribution of rheumatoid factor positivity on both overall mortality trends and CV mortality has been underlined (29,76).

*Management of cardiovascular risk in RA*

Despite growing evidence of precocious atherosclerosis and increased CV risk in RA patients, specific guidelines for both prevention and management are lacking. The interventions should be targeted to identify and control the concurrence of both traditional and disease-related risk factors, and preventive strategies should be carefully tailored to the personal patient risk profile.

Owing to cigarette smoking represents an important risk factor not only for CVD, but also for RA development and severity (24, 27), counseling and assisting in smoking cessation can be particularly beneficial in RA patients.

Optimal blood pressure levels should be achieved and kept by physical activity, weight control, and antihypertensive therapy, when required (34).

Weight control and increased exercise are useful in reducing hyperglycemia and insulin resistance. Moreover, thiazolinediones, a new class of insulin-sensitizing agents that functions as peroxisome proliferator-activated receptor-α agonists, could represent a

potential option in RA, due to their anti-inflammatory properties (77). Of note, thiazolidinediones have been found to reduce CRP serum concentrations and expression of matrix metalloproteinase-9, which has been implicated in the pathogenesis of the atherosclerotic plaque rupture (77).

Specific guidelines for lipemic disorder management in RA patients are presently lacking, however, dietary control, exercise, and statins, when indicated, are the first line interventions to achieve ideal levels. Statins may produce beneficial pleiotropic effects on CV risk reduction, including improvement of endothelial dysfunction, increased NO bioavailability, antioxidant properties, inhibition of inflammatory responses, and stabilization of atherosclerotic plaque, in concert with their potent low-density lipoprotein cholesterol-lowering effects (78). Notably, *in vitro* statins inhibit interferon-γ release from mononuclear cells from peripheral blood and synovial fluid, suppress proinflammatory cytokine production by T-cell contact-activated macrophages, and modulate T-cell costimulation (79). In an animal model of arthritis, statins have been found to display significant disease-modifying effects (79).

Anti-platelet agents could be an attractive approach in RA patients, however, their use has to be targeted (34).

Owing to systemic inflammation emerged as the major contributor of RA-associated atherosclerosis, early and lasting suppression of the systemic inflammatory response can lessen CV comorbidity in RA patients.

The role of nonsteroidal anti-inflammatory drugs in the prevention or development of CVD is debated. An increased CV risk has been associated with cyclooxygenase-2 inhibitors, that should be administered with particular caution in subjects already at enhanced risk (34).

GCs may display dual effects in RA-associated atherogenesis, being beneficial as anti-inflammatories, but potentially deleterious on metabolic parameters and blood pressure (34). However, the effects of GC treatment on the vasculature likely depend on dose and duration, and further investigations are needed in this regard.

RA patients' exposure to DMARDs, such as sulfasalazine (SSZ), hydroxychloroquine (HCQ) or MTX, is associated with both decreased CV morbidity, even after adjustment for traditional CV risk factors (66), and reduced hospitalisation for heart failure (80). MTX and, to a lesser extent, SSZ were associated with significantly lower CVD rate, and it has been suggested that DMARD use, in particular MTX use, might reduce the development of atherosclerosis and subsequently clinically overt CVD (66). MTX treatment has been also associated with a significantly reduced CV mortality (51).

Cyclosporine frequently leads to adverse lipid changes and hypertension (9), whereas HCQ appears to have vasculoprotective and hypoglycemic activity, as well as beneficial effects on lipid profiles, and treated patients with RA were found to have a decreased risk of developing diabetes mellitus, being the risk of incident diabetes significantly reduced with increased duration of HCQ use (81).

A role of anti-TNF agents in the prevention of RA-associated CVD has been suggested. TNF inhibition may improve endothelial function (82), and has been associated with decreased CV risk and mortality (83).

In RA patients refractory to TNF-α blockers, rituximab therapy was found to improve endothelial function, which was associated with a significant decrease in CRP levels and disease activity (84).

## Discussion

Accelerated atherosclerosis and related clinical sequelae are more prevalent than expected in both early and long-standing RA. The traditional CV risk factors cannot fully explain the increased propensity to the premature atherogenesis in RA, and the disease is presently thought to be a significant independent risk factor.

The RA immune dysregulation and persistent inflammation are considered the main drivers of RA-associated atherosclerosis. Proinflammatory cytokines, such as interleukin (IL)-1, IL-6, and TNF-α, directly induce endothelial activation and also promote both traditional (*i.e.* dyslipidemia, insulin resistance) and non traditional (*i.e.* prooxidative and procoagulative effects) systemic CV risk factors (10, 12, 13, 33, 63),

generating a spectrum of proatherogenic changes. Moreover, the contribution of $CD4^+$ $CD28^{null}$ T lymphocytes in the early development of RA atherosclerosis has been suggested (38-41).

Inflammation severity was found to be associated with functional and structural arterial wall changes in patients with recent RA onset, and early control of inflammation is associated with improved arterial function that may reduce atherosclerosis progression (85). Not only the magnitude, but also the chronicity of systemic inflammation have been reported to be particularly relevant in RA-associated atherogenesis (32), thus, an early and long-term effective suppression of disease activity must be achieved.

All physicians who provide care to patients with RA should be aware of their increased risk of atherosclerosis and CVD, and the screening for subclinical vascular involvement, along with the careful identification of concomitant traditional CV risk factors, should be systematically performed.

It has been emphasized that preventive measures should be carried out even in younger patients with low levels of traditional CV risk factors, and particularly in male RA patients.

## Conclusions

Atherosclerosis is a common and early RA feature, proposed as extraarticular manifestation of the disease, so it might be defined the "rheumatoid vasculopathy". The rheumatoid vasculopathy was found to condition excess of morbidity and mortality in patients, being CVD the most prominent cause of death.

The better understanding of precise molecular mechanisms that lead to premature vascular damage in RA, the development of effective screening methods, and the identification of strategies addressed to control both systemic inflammation and concomitant CV risk factors will allow to minimize the rheumatoid vasculopathy impact on patients' morbidity and mortality.

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