

# Risk factors and early detection of atherosclerosis in rheumatoid arthritis

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## ABSTRACT

**Background** Patients with rheumatoid arthritis (RA) have an increased morbidity and mortality due to cardiovascular disease (CVD). This cannot be explained alone by the increased prevalence of traditional cardiovascular risk factors like smoking and hypertension. Other factors therefore seem to be involved in the pathogenesis of atherosclerosis in RA.

**Methods** Literature was searched for epidemiology and pathophysiology of atherosclerosis in RA, with special focus on the role of advanced glycation end products (AGE's), endothelial activation, endothelial dysfunction and premature atherosclerosis as measured by intima media thickness (IMT). Finally, a literature search was performed on therapeutic strategies to prevent atherosclerosis in RA.

**Results** In RA increased AGE accumulation, endothelial activation, endothelial dysfunction and premature atherosclerosis can be identified. Treatment of RA activity by multiple disease modifying anti rheumatic drugs (DMARD's) has shown to be effective in reducing premature atherosclerosis in RA.

**Conclusion** Cardiovascular disease is increased in RA. Tight disease control and treatment of other risk factors is recommended to prevent morbidity and mortality due to CVD in RA.

**Keywords** Advanced glycation end products, cardiovascular diseases, endothelial activation, endothelial dysfunction, intima media thickness, rheumatoid arthritis.

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## Introduction

In the last decades, increasing evidence arose from several epidemiological surveys that patients with Rheumatoid Arthritis (RA) have an increased morbidity and mortality, mostly caused by cardio-vascular diseases (CVD) [1]. This excess morbidity and mortality cannot be explained by traditional risk factors alone [2]. In this review, on the basis of leading publications (because of limited word and reference count, a systematic literature search was not performed), we will discuss epidemiology and recent insights into the pathophysiology of atherosclerosis in RA. In addition, we will emphasize on early detection of atherosclerosis in RA and we will discuss therapeutic strategies to prevent CVD in RA. It is hoped that this will enable clinicians to intervene at early stages, thereby preventing progression to overt CVD in these patients.

## Epidemiology

Several epidemiological studies have shown that CVD is increased in RA. Wolfe *et al.* [3] found in a Canadian population in 1994 that RA patients died 17 years earlier from cardiovascular and cerebrovascular diseases than the control population (general Canadian population). In the nurses health study, 114 342 nurses participated, of which 527 women had RA. Of these 527 women, 17 had a myocardial infarction and seven had a stroke during the 18-year follow up. These numbers gave an adjusted relative risk of myocardial infarction of 2.0 and 1.48 for stroke. Women with RA who had a disease duration of at least 10 years had a relative risk for myocardial infarction of 3.10 [4]. In a recent study in the Netherlands involving 294 RA patients with an average disease duration of 7 years and high disease activity (DAS-28 score of 3.8), the risk

of developing CVD in RA was even higher than in diabetes mellitus type 2 (OR 2.70, 95%CI 1.24–5.86 in RA vs. 2.01, 95% CI 0.90–4.51 in diabetes, numbers corrected for traditional risk factors) [5]. Disease duration of RA seems to be associated with this increased risk. In a cross-sectional study in the US on 70 patients with early RA and 71 with longstanding RA vs. 86 controls, Chung *et al.* found an OR of 3.42 for having severe coronary artery calcification in longstanding RA. In early RA, no increased incidence of coronary artery calcification was found [6]. Similar results were found by others. Before onset of RA, no increased incidence of ischaemic heart disease (IHD) was found in 8454 patients with RA [7]. However, in newly diagnosed RA patients, an increase in cardiovascular risk was observed by counting cardiovascular events during a 10-year follow-up. During this follow-up of 10 years, CVD developed especially in those with additional traditional cardiovascular risk factors (16.8% vs. 60.4% when additional cardiovascular risk factors were present in the age group of 60–69 years) [8].

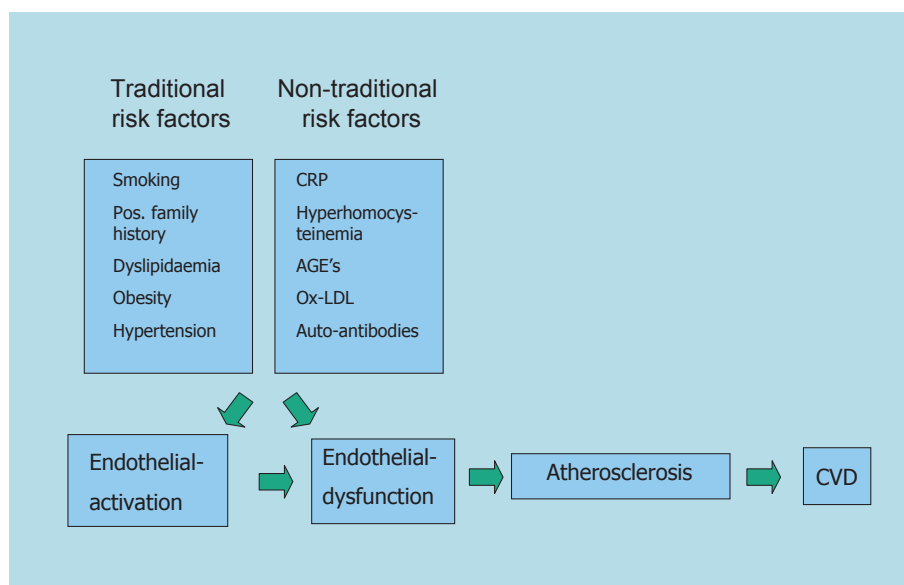
In summary, it is likely to assume that increased risk for CVD as present in RA patients is related to presence and duration of the rheumatic disease and that risk is further increased by the concomitant presence of traditional cardiovascular risk factors.

## Pathophysiology

The so-called traditional risk factors like smoking, dyslipidaemia, hypertension, obesity and a positive family history for CVD, are well established factors known to contribute to the

development of atherosclerosis [9,10]. Of these, smoking and dyslipidaemia are more present in early and active RA [11]. However, also other non-traditional risk factors seem to be involved. Non-traditional risk factors are, for example, elevated C-reactive protein (CRP), oxidized LDL and advanced glycation endproducts (AGEs) – all products of an inflammatory process.

Chronic inflammation, as present in RA, is considered an important contributing factor in all stages of the formation of the atherosclerotic plaques. Three important stages are recognized in the development of these plaques (Fig. 1). In the first stage, endothelial cell activation occurs which is reflected by upregulation of adhesion molecules such as vascular cellular adhesion molecule (VCAM). Several cytokines and acute phase proteins like TNF- $\alpha$ , IL-6, IL-1 $\beta$  and CRP can directly induce endothelial cell activation. For example, VCAM is expressed directly under influence of TNF- $\alpha$  [12]. TNF- $\alpha$  is known to enhance translocation of NF- $\kappa$ B from the cytoplasm to the nucleus, finally leading to formation of VCAM. VCAM expression then results in adhesion of circulating monocytes and T-lymphocytes to endothelial cells where, under influence of chemotactic factors, they might migrate to the intima and media. NF- $\kappa$ B activity is under tight regulation of endothelial nitric oxide (eNOS). The eNOS produces nitric oxide which is known to have the potency of inactivating NF- $\kappa$ B through the process of S-nitrosylation [13]. Indeed, eNOS inhibition, for example, through increased levels of asymmetric dimethylarginine (ADMA), a strong inhibitor of eNOS, is associated with a decrease in coronary flow reserve [14]. Next to a direct effect on



**Figure 1** Proposed scheme of development of cardiovascular disease.

endothelial cells, the above-mentioned cytokines like TNF- $\alpha$ , IL-1 $\beta$  and IL-6 might have an indirect effect on the vascular endothelium. For example, TNF- $\alpha$  stimulates formation of superoxide molecules by endothelial cells and monocytes. These superoxide molecules induce formation of oxidized LDL, which plays an important role in atherogenesis [15]. Also, TNF- $\alpha$  in particular may cause insulin resistance through inhibition of insulin-mediated uptake of glucose in tissues. Increased insulin resistance is regarded as part of the metabolic syndrome and as such related to increased cardiovascular morbidity and mortality. Increased insulin levels in themselves seem not to be related to increased cardiovascular risk [16].

In activated endothelium, AGEs can be formed in the presence of oxidative stress. These AGEs can be a ligand for the receptor of AGE (RAGE). RAGE is expressed on the cell surface of neutrophils, macrophages, T-cells and synovial fibroblasts [17] and a soluble form of RAGE can be identified in serum (sRAGE). After ligation, RAGE activates p21ras and mitogen-activated protein kinase, which results in translocation of NF- $\kappa$ B to the nucleus. Under the influence of NF- $\kappa$ B, pro-inflammatory genes are activated [18]. This process of AGE-RAGE interaction can have a positive feedback loop and thus maintain endothelial inflammation [19].

In the second stage in the development of atherosclerosis, endothelial cell activation proceeds into endothelial cell dysfunction, associated with ADMA, released by endothelial cells [20]. This stage is characterized by influx of mononuclear cells and their production of cytokines. Lipoproteins such as oxidized LDL are absorbed by monocytes and macrophages to form foam cells. Also, in this stage, smooth muscle cells migrate from the tunica media to the intima where they can proliferate and produce extracellular macromolecules like fibrillar collagen leading to 'stiffness' of the arteries, known as endothelial dysfunction [21].

Finally, in the third stage, the atherosclerotic plaque matures. Apoptosis of cells in the plaque leads to formation of extracellular lipids and cellular debris. The macrophages in the plaque secrete proteinases that break down the extracellular matrix. The fibrous cap of the plaques thus weakens and can rupture. In this phase of rupture, secondary thrombosis on the plaque may occur [21]. Cytokines like TNF- $\alpha$  may enhance this process by increasing production of plasminogen-activator inhibitor-1 and fibrinogen and thus create a thrombogenic state [22].

## Methods to detect (preclinical) atherosclerosis in RA

### Endothelial activation

As stated, endothelial cell activation is characterized by upregulation of adhesion molecules. In its soluble form, these mole-

cules like solubleVCAM (sVCAM), von Willebrand Factor (vWF), soluble intercellular adhesion molecule (sICAM) and soluble E-selectin (sEsel) can be measured in sera, reflecting endothelial cell activation. In RA, in a study from the UK on 66 RA patients with a median disease duration of 10.7 years, levels of sVCAM, vWF and sICAM were shown to be elevated compared with 48 controls. sVCAM correlated with TNF- $\alpha$  levels. After 1 week of intensive treatment in a subgroup of 29 RA patients, levels of sVCAM and sEsel decreased significantly [23]. In another study, 46 RA patients with an average disease duration of 12 years had significantly increased levels of sVCAM and sEsel compared with healthy controls ( $P = 0.029$  and  $P < 0.001$  respectively). Levels of sVCAM in this study correlated with intima media thickness (IMT) ( $r = 0.37$ ,  $P = 0.012$ ) [24]. These studies indicate that endothelial cell activation is present in RA.

### Endothelial dysfunction

Endothelial dysfunction can be measured by Pulse Wave Velocity (PWV), Pulse Wave Analysis (PWA), Flow Mediated Dilatation (FMD) or Glyceryl-trinitrate mediated dilatation (GMD). In PWV, the speed of the pulse wave from the brachial artery to the radial artery is measured. The increased speed of the arterial pulse wave is indicative of arterial 'stiffness' and, as such, for endothelial dysfunction. In PWA, the pulse wave is visualized through tonometry of the radial artery. In stiff arteries, there is an augmentation of the pulse wave in the systolic part of the pulse wave. The increment of this augmentation is indicative of the 'stiffness' of the artery and, as such, for endothelial dysfunction. In FMD, the diameter of the brachial artery is measured in basal state and after a period of ischaemia when there is a reactive hyperaemic state. The percentage difference between the diameter measured after reactive hyperaemia and the basal diameter is taken as FMD. Also, endothelial dysfunction can be measured by administering vasodilating drugs like acetylcholine and glyceryl-trinitrate. A decrease in dilatation after administering the drug is then indicative of endothelial dysfunction.

Endothelial dysfunction as measured by PWV was proven to be associated with excess cardiovascular and cerebrovascular morbidity and mortality in several prospective longitudinal studies in hypertensive patients [25–27]. Several studies have demonstrated presence of endothelial dysfunction in RA [28–30], but association with excess cardiovascular morbidity and mortality has not been proven yet in longitudinal studies.

Wong *et al.* showed in a cross-sectional study in 53 RA patients, with a median disease duration of 7 years (15 RA patients had known coronary artery disease) and 53 controls matched for age, gender and CAD-status, that endothelial dysfunction as measured by PWA was significantly

increased in RA ( $P = 0.001$ ). There was no significant difference in endothelial dysfunction between the RA patients with or without CAD. Endothelial dysfunction was inversely correlated with CRP ( $r = -0.340$ ,  $P < 0.001$ ), indicating that chronic inflammation is associated with reduced arterial elasticity [28].

In a longitudinal study on 20 patients with early RA, endothelial dysfunction was measured by FMD and GMD and compared with 20 healthy controls. Both FMD and GMD were significantly reduced in early RA and inversely correlated with IMT [29]. In a somewhat larger study, in 80 RA patients (disease duration not mentioned in the article), also increased arterial stiffness was found. The arterial stiffness was independently correlated to age at diagnosis, serum cholesterol, disease duration and CRP [30].

The above-mentioned studies indicate that endothelial dysfunction is present in RA and seems related to disease activity. The role of this endothelial dysfunction as a predictor of future CVD and possible monitor of successful reduction of cardiovascular risk is yet to be investigated.

### Intima media thickness

Intima media thickness can be measured and reported in many different ways. IMT can be reported as the maximum IMT of the carotid bulb or the common carotid artery, or as the mean of measurements of IMT on both sides. In the general population, IMT is regarded a prognostic risk factor of developing CVD in the future [31,32]. IMT as a surrogate marker for atherosclerosis is used in several studies to investigate premature atherosclerosis in longstanding and early RA. In a prospective study on 47 RA patients with longstanding disease and with no previous cardio-vascular events and no traditional cardiovascular risk factors, IMT was measured in the right common carotid artery at the start of the study and patients were followed up for 5 years. Eight patients experienced a cardiovascular event. Of these patients, 75% had an IMT  $> 0.91$  mm, whereas only 10% experienced such an event in the group with no cardiovascular event ( $P < 0.001$ ). All patients who experienced a cardiovascular event had IMT plaque formation (defined as a distinct protrusion  $> 1.5$  mm into the vessel lumen). Moreover, RA patients who had an IMT below  $0.77$  mm at the beginning of the study had no cardiovascular events at all [33]. In a study on early RA patients ( $n = 40$ ) without traditional cardiovascular risk factors, Georgiadis *et al.* [34] found an increased IMT before start of treatment. After 1 year, IMT had decreased significantly and also the lipid profile had improved. Altogether, these studies suggest that IMT might be used as a marker for prediction of cardiovascular events in RA patients and, as such, be a surrogate marker to start intervention aiming at reduction in the cardio-

vascular risk profile of the patient. Studies concerning endothelial dysfunction and IMT in RA are listed in Table 1.

### Advanced glycation end products (AGEs) and receptor for AGE (RAGE)

As described, AGEs are the result of non-enzymatic glycation and oxidation of lipids and proteins under the influence of a hyperglycaemic state or oxidative stress. AGEs can be quantified in peripheral blood and urine and their accumulation in the skin can be quantified using an autofluorescence reader [35]. AGEs in the skin are strongly predictive of the development of future cardiovascular and microvascular events in diabetes [36,37] possibly because AGEs in themselves can propagate inflammation by ligation of their receptor, RAGE. This interaction is supposed to be blocked by the soluble form of RAGE. sRAGE might act as a decoy for AGEs and, as such, have a protective effect on the development of atherosclerotic disease. Indeed, in 180 non-diabetic patients with suspected coronary artery disease, high levels of sRAGE were associated with a lower incidence of major adverse cardiovascular events; 23 events (26%) occurred in the lower sRAGE group (defined as sRAGE level  $\leq 809$  pg  $\text{ml}^{-1}$ ) vs. 11 events (12%) in the higher sRAGE group (defined as sRAGE levels  $> 809$  pg  $\text{ml}^{-1}$ ) ( $P = 0.032$ ) [38]. In RA, elevated levels of AGEs in urine were observed. By effective treatment of RA with infliximab, excretion of AGEs in the urine diminished [39]. In other autoimmune diseases like systemic lupus erythematosus (SLE), de Leeuw *et al.* found that AGEs are increased compared with healthy controls ( $n = 55$ ) and are associated with an increase in IMT ( $r = 0.35$ ,  $P = 0.01$ ) [40].

### Effect of therapy

Recently, EULAR recommendations for management of CVD risk were published [41]. In brief, CVD risk assessment should be performed annually and after disease modifying anti-rheumatic drugs (DMARD) therapy has been changed. In particular, patients with a disease duration of more than 10 years, rheumatoid factor or anti-CCP positive patients, or patients with certain extra-articular manifestations, are considered to have an increased CV risk. In those with an increased CV risk, according to national guidelines, statins, ACE-inhibitors and A-II-antagonists are preferred treatment options. The prescription of COXIBs and most NSAIDs should be avoided wherever possible, smoking cessation is encouraged, and adequate control of disease activity is needed. The assumption that (ongoing) disease activity in RA patients is a risk factor for the development of atherosclerosis resulted in several studies evaluating the relationship between therapeutic intervention to reduce RA disease activity and its effect on either endothelial activation, dysfunction and/or atherosclero-

sis. Changes in endothelial activation in response to intra-articular injection of methylprednisone into inflamed joints, together with initiation or intensification of DMARD therapy, were studied in a Caucasian population in South-Africa. Significant reductions in sVCAM, sICAM and IL-6 levels were found after 2 weeks of treatment in 21 RA patients with a mean disease duration of 6 years. Moreover, reduction in sVCAM and sICAM was correlated with a decrease in IL-6 ( $P < 0.0001$  and  $P = 0.005$  respectively), suggesting that lowering IL-6 might attenuate atherogenesis in RA [42]. A large prospective study with an average follow-up of 6 years on 1240 RA patients revealed a Hazard ratio for cardiovascular deaths of 0.3 (0.2–0.7) for methotrexate vs. no methotrexate after adjustment for confounding by indication. For all-cause mortality, the Hazard ratio for the methotrexate group vs. no methotrexate was 0.6 (0.2–1.2) [43]. In a study of 26 RA patients starting infliximab therapy, a significant improvement of arterial stiffness was seen during the study period of 54 weeks, without improvement of IMT [44]. Hurliman *et al.* also studied the effect of infliximab on FMD in 11 RA patients. After a treatment period of 12 weeks, a significant improvement in FMD was

seen along with a significant improvement in disease activity (DAS-28 decreased from 5.6 to 3.5 and ESR from 34 mm to 19 mm) [45]. Another study in five female RA patients treated with rituximab, 1000 mg on day 1 and day 15, showed a significant improvement of FMD of 81% at week 16. Also, HDL cholesterol concentration improved significantly in this study with a relatively short follow-up. Only a slight improvement in IMT was found [46]. The effect of prednisone on top of DMARD therapy in early RA was studied by Hafstrom *et al.* Thirty-four RA patients were treated with 7.5 mg prednisone on top of DMARD therapy and were compared with 33 RA patients on DMARD therapy alone. After 2 years, no significant differences were found in CRP or disease activity (DAS-28) [47]. In accordance, no change in endothelial dysfunction or IMT was found.

Limited data are known for the effect of DMARD therapy on AGEs. Apart from the above-mentioned study, another study in Japan evaluated the effect of etanercept on urine pentosidine excretion. Pentosidine is a known advanced glycation end product of N $\epsilon$ -hexanoyl lysine and of 8-hydroxy-deoxy guanosine. A significant decrease in urine pentosidine was found

**Table 1** Overview of studies in RA concerning surrogate markers for early atherosclerosis and effect of intervention where applicable

| Reference              | Type of study   | Number of RA patients | Disease duration       | Surrogate marker for CVD | Results   |
|------------------------|-----------------|-----------------------|------------------------|--------------------------|---|
| Wong [28]              | Cross-sectional | 53                    | 7 years (median)       | PWA                      | Increased arterial stiffness in RA vs. HC. Inverse correlation with CRP and serum amyloid A   |
| Hannawi [29]           | Case-control    | 20                    | 1.8 month (mean)       | FMD and GMD and c-IMT    | Significant increase in arterial stiffness in RA vs. HC. Significant improvement of arterial stiffness after 1 year of treatment, significant correlation with change in ESR and CRP                                    |
| Roman [30]             | Cross-sectional | 80                    | Unknown                | PWA and IMT              | Arterial stiffness significantly increased in RA vs. HC, correlating with disease duration  |
| Gonzalez-Juanatey [33] | Prospective     | 47                    | Approximately 15 years | c-IMT                    | c-IMT in patients who experienced CVD event during follow-up was significantly higher than in RA patients who did not have CVD event. Patients with IMT < 0.77 mm at the start of the study did not have any CVD event. |
| Georgiadis [34]        | Case-control    | 40                    | < 1 year               | c-IMT                    | Significant increase in IMT in RA vs. HC. Significant decrease in IMT after 1 year of treatment. Independent association with change in inflammatory markers.   |

c-IMT, carotid Intima Media Thickness; CRP, C-reactive protein; CVD, cardiovascular disease; ESR, erythrocyte sedimentation rate; FMD, flow mediated dilatation; GMD, glyceryl-trinitrate mediated dilatation; HC, healthy controls; PWA, pulse wave analysis; RA, rheumatoid arthritis.



after a 6-month treatment with etanercept from 8.1 nmol mmol<sup>-1</sup> creat to 6.1 nmol mmol<sup>-1</sup> creat ( $P < 0.01$ ). Urine pentosidine levels significantly correlated with DAS-28 ( $r = 0.395$ ,  $P < 0.05$ ) [48].

The exact mechanisms of DMARD therapy on endothelial function and atherosclerosis are not yet clear, although it seems likely that inflammation in the joint and inflammation in atherosclerosis are interrelated. As a reduction in disease activity in RA patients reduces endothelial activation and endothelial dysfunction, it seems prudent to state that lowering disease activity in RA will also reduce the progression of atherosclerosis.

## Summary

Rheumatoid arthritis and atherosclerosis are both inflammatory disorders that share comparable inflammatory features at the site of inflammation in the synovium and the endothelium. Due to systemic inflammation in RA also inflammation of the endothelium is enhanced, leading to accelerated atherosclerosis. In epidemiological studies, indeed, increased morbidity and mortality due to CVD have been shown. Several methods for predicting a worse outcome for the individual RA patient have been investigated including measurement of endothelial dysfunction by PWA, PWV or FMD. Also, IMT and AGE accumulation in the skin have been investigated as tools for identifying early atherosclerosis. Endothelial dysfunction is present in RA and has been proven to be associated with a poor outcome in other diseases, but not yet in RA. More research is needed to evaluate whether endothelial dysfunction can be used as a tool for identifying development of atherosclerosis at an early stage. Increased IMT has been proven to be a valuable tool for identifying patients at risk for developing CVD, but increased IMT is a phenomenon that occurs later in the course of the disease and may, as such, be of less value for identifying patients at risk early in the disease course. AGEs are known to be of prognostic value for predicting CVD in other diseases like diabetes and hypertension. Increase of AGEs has also been found in RA. Whether AGEs are a useful tool for identifying atherosclerosis at an early stage is yet to be proved. Moreover, intervention studies with several DMARD therapies have shown improvement of cardiovascular risk, suggesting that, together with tight disease control of RA, also the risk for developing CVD decreases.

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