Review Article

# Rheumatoid Arthritis and Cardiovascular Risk

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**ABSTRACT**

Rheumatoid arthritis is an autoimmune disorder which mainly affects the joints. It is widely accepted that rheumatoid arthritis carries with it the risk of damage not only to the joints but also to the heart and lungs among other organs. The underlying immune mechanisms, inflammatory changes and traditional risk factors are responsible as the pathogenic mechanisms underlying cardiovascular changes in rheumatoid arthritis. In this review, we aim at highlighting the various types of cardiovascular manifestations in rheumatoid arthritis, various screening and assessments tools available in evaluating cardiovascular changes pertaining to rheumatoid arthritis and emphasise the need for patient education and involvement in the prevention, management of these complications.

**Keywords:** Rheumatoid arthritis, cardiovasculardisease, immune system, atherosclerosis, screening.

## INTRODUCTION

Rheumatoid Arthritis is a chronic inflammatory disease associated with premature mortality, severe morbidity and functional impairment leading to considerable financial burden for both patients and society.[1] It is well recognized that patients with rheumatoid arthritis (RA) have an increased mortality rate compared to the general population, due mainly to an excess risk of cardiovascular disease (CVD).[2-4] This is reflected in both the European League Against Rheumatism (EULAR) and British Society for Rheumatology guidelines, which recommend regular CVD screening and aggressive risk factor management in patients with RA.[5, 6]

### Cardiovascular risk in Rheumatoid arthritis

Traditional risk factors such as hypertension, smoking, dyslipidemia, insulin resistance and metabolic syndrome, sedentary lifestyle and obesity contribute to the endothelial dysfunction in RA but cannot fully explain the higher magnitude of CV disease in RA. Other RA-specific , such as immune dysregulation, genetic risk factors, anti-rheumatic drug cardio toxicity, extra-articular RA, and predominantly the chronic high-grade inflammatory state of the disease have been linked to the development of premature atherosclerosis (Fig 1).[7]

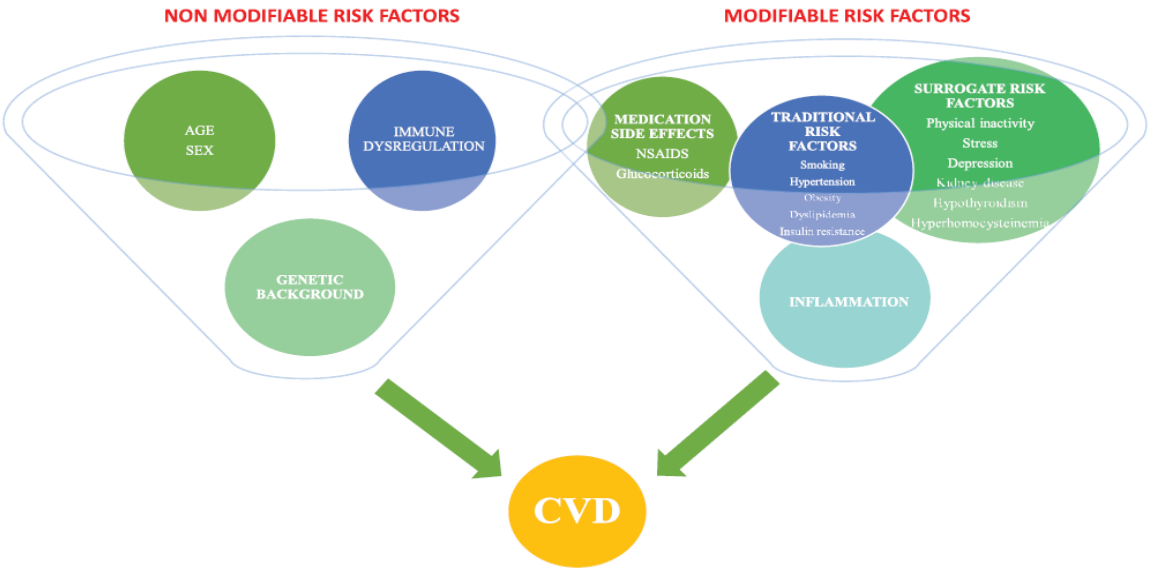



**Figure 1:** Risk Factors in CVD in RA

**Cardiovascular Manifestations and their pathophysiology**

Rheumatoid Arthritis affects the heart by numerous mechanisms. In this review we have attempted to present a few of these manifestations.

**Accelerated Atherosclerosis**

Several studies have shown that the presence of RA alone especially cases in which RA factor were positive was a strong determinant of carotid atherosclerosis. Roman et al conducted a case control study of preclinical atherosclerosis in which 98RA patients (as well as SLE cases) and 98 controls were observed. Results showed that RA patients had a 3-fold increase than controls (44% versus 15%) in carotid atherosclerosis prevalence despite a similar risk profile.[8](Fig2) Other studies have proven that coronary calcification and carotid atherosclerosis seen in RA are proportionate to the duration of RA disease.[9,10] In addition, lower levels of circulating endothelial progenitor cells, markers of the capacity for vascular regeneration that are inversely related to cardiovascular risk, are associated with heightened disease activity in RA patients.[11] Evidence that therapy with methotrexate[12,13]reduces risk of cardiovascular disease further supports the hypothesis that chronic inflammation is primarily responsible for accelerated atherosclerosis in RA.

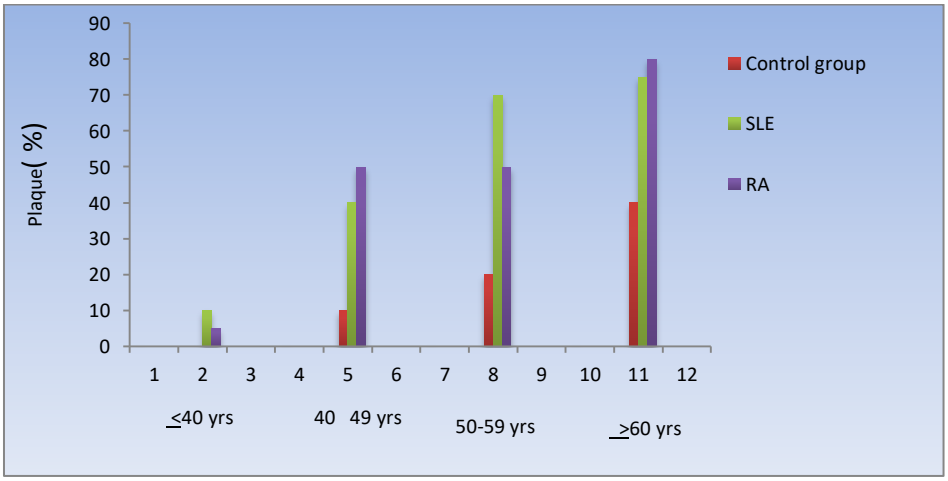



**Figure 2:** Prevalence of carotid atherosclerosis

Autoimmune diseases like RA and SLE are associated with underlying abnormalities in the patients' immune system. Systemic inflammation is accompanied by elevated levels of cytokines, chemokines and coagulation proteins, which causes endothelial activation and damage. Auto-antibodies and immune complexes are hallmarks of autoimmune disease; some of them have the potential to promote atherosclerosis. Expansion of CD4+, CD28, T-cells seen in RA immune mediators pose risk to endothelium, leads to higher carotid internal thickness, contribute to premature or accelerated atherosclerosis by infiltrating the atherosclerotic plaques and promoting vascular injury through inflammatory and tissue-damaging pathways[Fig 3].[14]

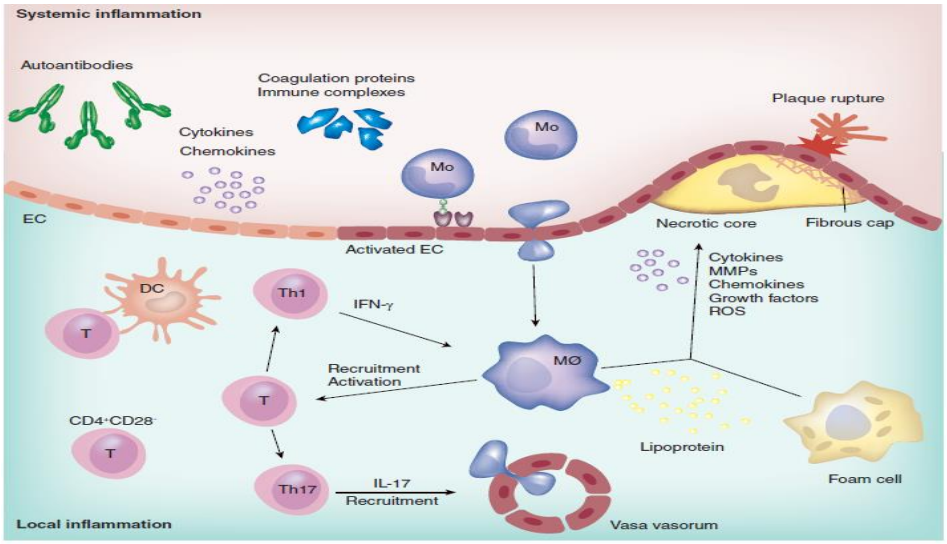



**Figure 3:** Immune Mediators in RA

**Arterial Stiffness**

Arterial stiffness, which can be quantified accurately with the use of noninvasive techniques, is recognized increasingly as an important independent risk factor for adverse cardiovascular outcomes. In view of the development of premature atherosclerosis in RA and of the observation that arterial stiffening is associated with inflammatory markers in the general population, it is not surprising that arterial stiffness is increased in RA, even in the absence of atherosclerosis. Arterial stiffening is related to disease duration, as described for atherosclerosis, and to inflammatory mediators and has been found to be reduced by anti TNF therapy or atorvastatin30.

**Coronary Arthritis**

Coronary arthritis is the inflammation of any or all layers of the walls of the coronary arteries.

At present it is rarely of clinical significance in rheumatoid arthritis. In fact, the occurrence of rheumatoid vasculitis, in general, has markedly declined in the setting of effective anti- inflammatory therapy.

**Myocardial Disease**

RA is associated with an increased risk of congestive heart failure. Data from the Mayo Clinic indicate that heart failure in RA patients primarily affects those who are positive for rheumatoid factor, may occur before the onset of arthritis, and is independent of traditional risk factors for cardiovascular disease. Similar to evidence in atherosclerosis, anti-TNF therapy may protect RA patients from developing heart failure.[15]

**Valvular Disease**

Clinically significant valvular disease attributable to RA appears to be uncommon. In contrast, mitral regurgitation was detected in 80% of RA patients undergoing Trans esophageal echocardiography versus 37% of a control population[16].

**Pericardial Disease**

Pericardial effusions may be seen in echo cardio graphic studies of RA patients. Although usually clinically silent, constrictive pericarditis may develop in such patients.

**Screening for cardiovascular disease in Rheumatoid Arthritis: "An ignored threat"**

Both the EULAR as well as the British Society for Rheumatology guidelines recommend regular CVD screening and aggressive risk factor management in patients with RA.

Studies suggest that the excess CVD risk in RA is comparable to that seen in Type 2 Diabetes Mellitus, with an approximate doubling of the risk of CVD over three years. Although guidelines recommend CVD screening for patients with RA, few studies have addressed whether this is being implemented in routine clinical care or whether this screening should occur.

One such screening study undertaken in 2009 [17] involved screening of five traditional CVD risk factors: blood pressure, lipid levels, smoking status, body weight or body mass index and blood glucose in 401 Rheumatoid Arthritis and 1198 controls. The database records were also checked for morbidity and related prescriptions that indicated a diagnosis of diabetes mellitus, hypertension or hyper lipidaemia. These results do not show any significant risk of cardiovascular disease in RA patients (Table 1).

**Table 1:** Demographics of RA and non- RA patients

| Characteristic | RA(n=401) | Non RA (n=1198) | P value |
|---|---|---|---|
| Female Gender | 265(66.1) | 793 (66.2) | |
| Age groups (years) | | | |
| 27-50 | 97 (24.2) | 291(24.3) | |
| 51-65 | 181 (45.1) | 543 (45.3) | |
| 66-74 | 79 (19.7) | 237 (19.8) | |
| 75+ | 44 (11.0) | 127 (10.6) | |
| Diabetes | 48 (12.0) | 127 (10.6) | 0.447 |
| Hypertension | 209 (52.1 | 547 (45.7) | 0.025 |
| Hyperlipidemia | 134 (33.4) | 398 (33.2) | 0.943 |

**EULAR and recommendations for cardiovascular risk calculation in RA**

Risk factor assessment algorithms, including the SCORE and the Framingham risk equation, are recommended worldwide as part of CVD risk management in the population at large. These equations allow for stratifying subjects into low, intermediate, high and very high risk groups based on cardiovascular risk.[17]

EULAR recommendations suggest the adaptation of traditional cardiovascular risk calculators like SCORE and Framingham and attempt to adjust them in RA. (Table 2) The recommendation is to modify the risk obtained by a factor of 1.5 multiple if two of the three criteria below are fulfilled: (1) RA disease duration >10 years, (2) presence of RF or anti-CCP and (3) presence of severe extra-articular manifestations. In addition, EULAR proposes an annual CV reassessment excluding patients with low CV risk or low disease activity which may be followed up every two or three years.

EULAR has introduced revised recommendations in 2015 based on newer findings on risk factor assessment in RA patients. The integration of carotid ultra sonography in the screening of patients and the multiplication of the risk score by 1.5 irrespective of the presence of the aforementioned three criteria represent new additions. The effectiveness of these new

recommendations remains to be established by future studies.[2]

**Table 2**

Novel tools have been tailored more recently to pinpoint which rheumatoid arthritis patients need stepped up heart disease prevention. Studies done by Mayo Clinic researchers have come up with a tool called ATACC-RA (Transatlantic cardiovascular Risk calculator – RA ) and has been presented at the European League Against Rheumatism and has been found to be much more sensitive than the Framingham or SCORE tools in detection of cardiovascular risk in rheumatoid arthritis patients specifically.[18]

**USE of biomarkers and Imaging Techniques:-**

CVD risk stratification can be further refined by the use of biomarkers and these can be serving as a reflection of the extent of underlying cardiovascular damage. Some of them have been listed in the table (Table 3) given below. [19]

**Table 1.** EULAR recommendations for cardiovascular risk assessment and management [Peters *et al.* 2010].

1. RA is associated with greater risk for CVD
2. The control of the disease activity is imperative for lowering the CVR
3. Cardiovascular risk assessment according to national guidelines, annually or whenever the antirheumatic treatment changes, is necessary for all patients with RA
4. Risk score models should be adapted for RA patients after the multiplication by a factor of 1.5 if two of the three following criteria are fulfilled:
   - Disease duration >10 years
   - RF or ACPA positivity
   - Extra-articular manifestations
5. When the SCORE model is applied the TC/HDL ratio should be used
6. Pharmacological treatments should follow the national guidelines
7. Statins, ACE inhibitors/A-II blockers are the first treatment options
8. The effect of NSAIDs and coxibs on the CVR is not well established. Caution is required when prescribing them, especially for patients with documented CVD or at high CVR
9. The lowest dose possible of corticosteroids is advised
10. Smoking cessation is recommended

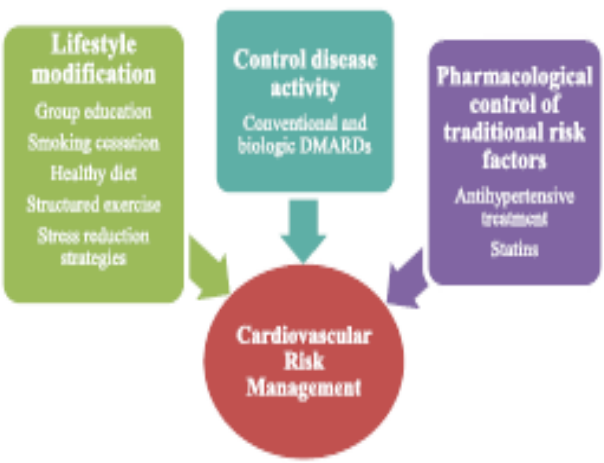
ACE, angiotensin converting enzyme; ACPA, anticitrullinated protein antibody; CVD, cardiovascular disease; CVR, cardiovascular risk; HDL, high density lipoprotein; NSAID, nonsteroidal anti-inflammatory drug; RA, rheumatoid arthritis; RF, rheumatoid factor; TC, total cholesterol.

**Table 3:** Cardiac Biomarkers useful in Rheumatoid Arthritis

| High-sensitivity C reactive protein concentrations | Osteoprotegerin (OPG) | Endothelial Leukocyte Adhesion Molecul;e (ELAM-1) |
|---|---|---|
| Proinflammatory HDL (piHDL), | Angiopoietin- 2 (Angpt-2). | von Willebrand factor, |
| Leptin. Serum uric | MCP1 | tPA |
| Serum uric | sICAM1, sVCAM 1, sE-selectin and) | PAF1 |

**Future Directions**

Rheumatoid arthritis management should adopt measure as in other cardiovascular health threatening diseases like Type II Diabetes Mellitus (Fig 4). Primary prevention therapy like setting targets for blood pressure and cholesterol should also be implemented effectively in RA. A tight control inflammation is necessary for clearance of cardiovascular risk. Newer imaging techniques like cardiac magnetic resonance (CMR) should be integrated into
RA management.




**(Figure 4)**

## CONCLUSION

It is important for patients with rheumatoid arthritis to know that their disease alone carries an added risk of heart disease.[20] The significance of cardiovascular risk should be explained to the patient and the patient should be advised consultation with a preventive cardiologist along with his rheumatologist. The screening , risk estimation and prevention techniques for any cardiovascular event should be carried out early on in therapy rather than having a 'waiting until it happens' approach as is presently the dictum.

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