Cardiovascular involvement in Rheumatoid Arthritis

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INTRODUCTION

Rheumatoid arthritis (RA) along with SLE and other autoimmune inflammatory arthritides are associated with increased cardiovascular morbidity and mortality predominantly due to accelerated and premature atherosclerosis. Thus both men and women with RA are twice as likely to suffer from myocardial infarction as compared to general population. The overall life expectancy in RA is significantly reduced, with standardized mortality rates ranging from 1.28 to 3.0.

Cardiovascular events occur approximately a decade earlier in RA like that in diabetes mellitus. Moreover, like DM, there is an independent association of RA and preclinical and overt CV disease and most of the time it is silent with unfavourable outcome. Another very important recent finding is the increased prevalence of heart failure with preserved ejection fraction and lack of typical symptom of heart failure in RA patients compared to non RA patients. In this study Davis et al found an increased incidence of diastolic dysfunction and a 1.9 fold increased mortality.

In some way there is a close similarity between RA and DM. Both RA and DM are independent risk factors for preclinical as well as overt CV disease. Like diabetes, RA patients are less likely to report symptoms of angina, have increased incidence of unrecognized myocardial infarction and sudden death. There is also increased prevalence of heart failure with preserved ejection fraction due to left ventricular diastolic dysfunction related to disease duration as seen in DM.

Thus the various cardiovascular involvements in RA are -

1. Preclinical CV disease - which includes endothelial dysfunction and structural cardiovascular remodelling.
2. Overt C. V. - which includes heart failure and cardiovascular death.
3. Other morbid events like Pericarditis, myocarditis, valvular regurgitation especially of aortic and mitral valve, embolic events, rheumatoid nodule and atrioventricular block.

In this review, I will focus mainly on the increased prevalence of premature and subclinical atherosclerosis in RA and the potential role of disease modifying drugs and novel targeted biologic therapies in preventing CV disease.

Epidemiological evidence

Deaths due to CAD have been reported in several RA mortality study series.

Standard mortality ratios (SMRs) for patients with RA dying from CV diseases ranges from 1.13 to 5.25. The most striking finding of increased mortality in RA due to CAD have been in young women aged 15-49 years, where SMRs were as high as 3.64. Solomon et al, in a prospectively cohort study, conducted among 114342 women participating in the Nurses Health Study who were free of CV disease and RA at baseline in 1976. At the end of the 10 years follow up an incident diagnosis of RA in 527 women were made and there were 2296 myocardial infarction and 1326 strokes. The age adjusted risk of MI was two fold higher for patients with RA than those without relative risk.

In another recently published population based cohort study,
patients with RA had a significantly higher risk of CVD than non-RA patient. More than half of the newly diagnosed RA aged 50-59 years and all those older than 60 years had a more than 10% increased risk of CVD within 10 years of the onset of RA.

Meta-analysis of observational studies showed that CV disease mortality is increased by about 50% in patients who have RA compared to the general population.

In the QUEST-RA study which analysed the prevalence of CV disease in 4363 patients with RA (78% female) and its association with traditional CV risk factors, clinical features of RA and the use of DMARDs in a multinational cross-sectional cohort of non-selected patients of RA. There was an association between any CV event and age and male gender and between extra-articular disease and myocardial infarction. Prolonged use of methotrexate, leflunomide, salsalazine, glucocorticoids and biological agents was associated with a reduction of the risk of CV mortality.

**Risk factors for premature atherosclerosis**

RA is associated with both traditional and non-traditional CV risk factors.

Various studies have confirmed that markers of systemic inflammation confer a statistically significant additional risk for CV death among patients with RA, even after controlling traditional risk factors like smoking, hypertension, obesity and lipid abnormalities. Various non-traditional risk factors are:

1. Genetic determinants - HLA DRB1 shared epitope allele.
2. Elevated highly sensitive CRP
3. RF positivity and erosive disease
4. Extra-articular disease

**Immunological / Molecular markers**

- TNF-alpha, IL-1 and IL-6 are all linked to severity of subclinical atherosclerosis.
- Adhesion molecules - intracellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1) and endothelial leukocyte adhesion molecule - are all higher in active RA patients. VCAM-1 levels were associated with carotid atherosclerosis.

6. Cellular markers

- CD4+ and CD28 null lymphocytes - clonal expansion of these sub-set of T-lymphocytes have been reported in the blood and atherosclerotic plaque of patients with unstable angina as well as in patients with RA.
- Toll-like receptor antagonists 2 and 4 which are involved in innate immunity have been suggested to mediate inflammation related premature atherosclerosis.
- Endothelial progenitor cells (EPCs) - in the bone marrow are the most important cells in endothelial repair after vascular injury. Decreased levels of circulating EPCs as well as impaired function of EPCs has been noted.

7. Increased procoagulant activity-

- Antiphospholipid antibodies
- Plasminogen activator Inhibitor-1 (PAI-1)
- Hyperhomocysteinaemia

8. Lipid abnormalities

Rheumatoid arthritis is associated with pro-atherogenic lipid profiles. There is increased synthesis of LDL, and serum lipoprotein (a) is found to be significantly increased, high-density lipoprotein decreased and HDL function abnormal as it is unable to protect oxidation of LDL.

**Pathogenesis of Premature CV disease.**

There are striking similarities between inflammatory and immunological responses in atherosclerosis and RA. The endothelial dysfunction is the earliest stage of atherosclerosis and is an expression of systemic phenomenon. Chronic inflammation can promote endothelial cell activation and vascular dysfunction leading to atheroma formation.

Activated inflammatory cells, mostly macrophages and mast cells release enzymes involved in collagen degradation. There is upregulation of adhesion molecules such as E-selectin, intracellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and endothelial leukocyte adhesion molecule. The adhesion molecules bind and recruit monocytes/macrophages and T-lymphocytes, which migrate into the subendothelium where along with oxidized LDL, they form the fatty streak. In the absence of down regulation of this inflammatory process, the fatty streak develops into a fibrous plaque which can rupture and lead to an ischaemic event.

**Endothelial dysfunction and sub-clinical atherosclerosis**

Endothelial dysfunction, which is being recognized as a promoter of CAD progression and a trigger of CV events like plaque rupture has been recently described in patients with RA with high disease activity without evidence of clinical atherosclerosis i.e. angina.

**Direct and indirect evidence of Atherosclerosis**

**Direct evidence:** Warrington et al, at the Mayo clinic
analysed the angiogram data of 79 patients with RA and new onset CAD. They also measured the pro-inflammatory CD 4+ and CD28 null T cells by flow cytometry. They observed that patients with RA were more likely to have multivessel coronary involvement at first coronary angiogram compared to control (p=0.002). CD4+ and CD null T cell population were significantly higher in patients with CAD and RA than in controls with stable angina (p=0.001) and reached levels found in acute coronary syndrome.

Chung et al, observed that the prevalence and severity of coronary calcification is more in long standing RA and is related to inflammatory markers and smoking.

**Indirect evidence:** There are two non invasive methods of detecting subclinical atherosclerosis and endothelial dysfunction- CIMT and FMV.

**Flow mediated vasodilation (FMV)**

This is an accurate and reproducible method for evaluating endothelial function.

Altered function of arterial endothelium can be detected ultrasonographically by determining arterial vasodilatation after post occlusion reactive hyperaemia (FMV).

Vaudo et al demonstrated that young to middle aged patients with RA and low disease activity, free from cardiovascular risk factors and overt CV disease, have an altered endothelial reactivity which indicates a higher susceptibility to the development of atherosclerotic disease.

Wong M et al measured the small artery elasticity (SAE), large artery elasticity (LAE) and Systemic Vascular Resistance (SVR) in 43 patients of RA. Fifteen with CAD and 36 without CAD and compared with 38, age and sex matched controls. LAE was significantly lower and SVR was significantly higher in RA patients than in controls. They also observed that SAE and LAE values were inversely correlated with markers of inflammation viz HsCRP, serum amyloid A and VCAM1. The authors concluded that arterial elasticity inversely associated with markers of inflammation.

**Carotid Intima Media Thickness (CIMT)**

Measurement of the CIMT and of carotid plaque non-invasively by B-mode ultrasound using a high resolutions 7.5MHz transducer is an important tool for diagnosis early sub-clinical atherosclerosis. The CIMT is strongly correlated with the presence of coronary artery disease.

The CIMT assesses the atherosclerotic burdens and provides information that is independent and incremental to that provided by standard risk factors. It is a feasible, reliable, valid and cost effective method for both population studies and clinical trials of atherosclerosis progression and regression, subsequent to DMARDs and statin therapy.

**Our Experience**

*Carotid Ultrasound:*

We did a small study on 30 seropositive RA patients and compared with age, sex matched had they control. Common carotid IMT were assessed with US doppler using a high resolution 7.5MHz linear transducer common carotid IMT was significantly higher in patients with RA. Carotid atherosclerosis was present in 13.33% of RA patients and was statistically significant carotid atherosclerosis was present in 50% of smokers in RA group and showed significant correlation with carotid IMT levels. Even though both groups had similar lipid parameter distribution, CIMT was significantly higher in RA patients compared to the control group (0.626 ± 0.124 Vs 0.455 ± 0.5, p<0.0001). Among 30 RA patients, 4 (13.3%) patients had carotid artery plaque on US which was statistically significant (p<0.0001). RA patients with carotid artery plaque had higher mean ESR and CRP values.

**FMV**

Another study to evaluate the influence of chronic inflammatory state on endothelial function in patients with RA was undertaken on 50 young to middle aged patients with RA (age 18 to 55years) with DAS ≤ 3.2 and without overt CV disease. This was compared with 50 age sex matched control. FMV was assessed on the brachial artery in supine position. The brachial artery was scanned longitudinally just above the anticubital crease using a 10MHz transducer probe. FMV was expressed as the relative increase in brachial artery diameter during hyperaemia and defined as 100 (post hyperaemia diameter - basal diameter / basal diameter). It is expressed as percentage value. We observed that FMV of the brachial artery was significantly lower in patients with RA (4.03 ± 1.9) compared to control (8.7 ± 1.57) which was statistically significant (p<0.0001). No significant difference in brachial artery FMV was seen between patients with and without serum rheumatoid factor, bone erosion, peri articular osteopenia and deformity. Baseline FMV showed an inverse correlation with CRP.

**Early detection of CV disease in RA**

Early detection of CV disease in RA is important and
advantageous for the prevention of long term morbidity and mortality. This can be effectively done by identifying subclinical atherosclerosis by the use of biomarkers of vascular health already described and endothelial dysfunction as measured by surrogate methods like FMV and carotid CIMT.

Management of CV risk in RA and role of DMARDs

There is no treatment strategy with proven prognostic significance and predictive accuracy for targeted control of cardiovascular risk in RA as evidenced by higher CRP levels - more than 3mg/L in 66% and more than 10mg/L in 10-14%, in RA patients on remission or mildly active disease suggestive that well controlled RA may still be accompanied by increased CV risk.

There are numerous evidence based studies highlighting the cardioprotective effects of DMARDs particularly methotraxate and biologics. Choi et al, have demonstrated that methotrexate-treated patients had a 70% reduction in CV mortality compared with those who did not receive DMARD. The role of corticosteroids is controversial. Though there are reports of increased incidence of carotid plaque and arterial stiffness with prolonged use of steroids, Davies et al found no association between corticosteroid exposure and CV events in RA patients followed for a median period of 15 years. In fact low dose steroids may confer some beneficial effect on lipid profile and inflammatory mechanism.

The new ongoing cardiovascular inflammation reduction trial (CIRT) proposes to test the effect of a very low dose methotrexate therapy versus placebo in the secondary prevention of cardiovascular events in the general population. This will test the inflammatory hypothesis of atherothrombosis. If successful, the results of this trial would increase the understanding of the impact of inflammation in atherothrombosis and offer novel approaches for the targeted cardioprotective treatment in RA.

EULAR - recommendations

Based on the extensive data on CV disease in RA, European League Against Rheumatism (EULAR) multidisciplinary expert committee has given recommendations for CV risk management in RA, Psoriatic arthritis and ankylosing spondylitis. The ten recommendations are

1. RA should be regarded as a condition associated with higher risk for CV disease. This may apply also to AS and PSA. The increased risk appears to be due to both an increased prevalence of traditional risk factors and the inflammatory burden.
2. Adequate control of disease activity is necessary to lower the CV risk.
3. CV risk assessment is recommended in all RA patients as well as PSA and AS.
4. Risk score models should be adapted for RA patients by introducing a 1.5 multiplication factor - when disease duration is more than 10 years, RF or anti CCP positivity and presence of certain extra-articular manifestations.
5. TC/HDL cholesterol ratio should be used when the SCORE model is used.
6. Intervention should be carried out according to national guidelines.
7. Statins, ACEI / AT II blockers are preferred to treat HTN.
8. The role of COXIBs and most NSAIDS regarding CV risk is not well established and needs further investigation. Need to be cautious while prescribing COXIBs in patients with documented CV disease or presence of CV risk factors.
9. Corticosteroids - use the lowest dose possible.
10. Recommended smoking cessation.

CONCLUSION

Evidence continue to accumulate indicating that patients with RA present an increased risk of CV mortality and morbidity. The factors involved in the pathogenesis of increased CV disease are complex and multi-factorial involving complex inflammatory mechanism leading to accelerated and premature atherosclerosis. Apart from traditional risk factors, there are some risk factors like clonal expansion of CD 4+ T cells, interleukins, adhesion molecules, atherogenic lipids and abnormal vasculogenesis (neo-angiogenesis) which come into play in the atherogenesis. Similar to diabetes, premature development of CV disease is silent with unfavourable outcome. Apart from accelerated atherosclerosis there is also diastolic dysfunction leading to heart failure with preserved ejection fraction.

There is now a growing body of opinion regarding early detection and prevention of CV disease. Apart from early use of DMARDs, statins' lipid lowering and vasculotropic effect should be fully utilized. Role of anti TNF therapies and other biologics in CAD prevention in RA has been validated but needs further well controlled studies.
As CRP has a strong correlation with disease activity in RA, monitoring the patients’ CRP level is necessary to assess the level of inflammatory burden as well as CV risk.

Cardiovascular risk assessment yearly in all patients of RA is mandatory and the recently published EULAR guidelines for CV risk management in RA, Psoriatic arthritis and Ankylosing spondilitis will go a long way.

REFERENCES


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