International Journal of Research and Review
www.ijrrjournal.com E-ISSN: 2349-9788; P-ISSN: 2454-2237

Review Article

Overview of the Cardiovascular Risk in Rheumatoid Arthritis

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic inflammatory joint disorder that impacts nearly 1% of the general population and ranks among the top 15% of illnesses that cause significant disabilities worldwide. RA shares atherosclerosis with certain pathological characteristics, genetic predisposition and risk factors. Patients with rheumatoid arthritis (RA) have been shown to have increased cardiovascular morbidity and mortality, including the danger of sudden cardiac death (SCD). Inflammation plays a key role in both illnesses of pathophysiology. Abnormalities in autonomic markers such as variation in heart rate and parameters of ventricular repolarization, such as QTc interval and QT dispersion, were correlated with sudden death in RA patients. Based on latest clinical research, this paper will review briefly the cardiovascular complications of rheumatoid arthritis.

Keywords: Rheumatoid arthritis, Cardiovascular risks, Rheumatoid arthritis, Extra articular complications.

INTRODUCTION

Rheumatoid arthritis (RA) is a common systemic inflammatory disease characterized by the presence of destructive polyarthritis with predisposition to affect the small joints of the hands and feet (although the disease process can affect virtually any synovial joint). [1] RA is connected with particular class II molecules of human leukocyte antigen (HLA); antigen-activated CD4-T cells lead to this disease by initiation of the cascade of cellular and soluble inflammatory mediators. [2] The incidence of RA in India varies from 0.5% to 2% among the general population, mostly affecting females in the fourth to fifth centuries of life who are twice as vulnerable as males. [3]

There is no accurate RA definition or pathognomonic test. Therefore, the diagnosis of RA is based on a composite of clinical and laboratory observations. In terms of severity and advancement, RA is highly heterogeneous. [2] Permanent remission may happen but is uncommon once substantial joint harm occurs. While RA is predominantly an articular disease, it is essential to remember that the disease is associated with a number of "additional articular manifestations" (EAMs), such as eye, lung, skin, and nervous system participation. Indeed, almost 50% of RA patients acquire some kind of RAEAMs. [4]

Although RA itself results in considerably decreased survival among those impacted, mortality rates in those with EAMs are further increased. [5] Therefore, proper diagnosis and adequate management of EAM plays a vital role in this situation. This short review will provide an overview and appropriate management of the various RA EAMs to minimize the added mortality due to the EAMs. [3]

Mortality/morbidity from cardiovascular disease in RA

Rheumatoid arthritis patients suffer from excess mortality from cardiovascular disease. [6] CVD is the major cause of death even in the general population; however, RA is correlated with almost twofold enhanced danger of developing CVD, a risk similar to that of diabetes mellitus. [7,8] RA patients are twice as probable to experience a silent myocardial infarction as opposed to non-RA patients. [8]

Traditional cardiovascular risk factors

1. Hypertension (HTN)

Hypertension (HTN) is a well-established cardiovascular disease risk factor with prevalence in the general population of 29 percent. Multiple variables, including inflammation, physical inactivity, and drugs, can affect blood pressure in RA patients. Increased arterial rigidity and decreased blood vessel elasticity are observed in RA patients. Animal model studies indicate a link between continuing inflammation and hypertension. [10]

2. Insulin resistance/metabolic syndrome

In the general population, metabolic syndrome has been described as having three of five elements, including obesity, elevated triglycerides, low-density lipoproteins (HDL), high systolic and diastolic blood pressure, and elevated fasting glucose. Metabolic syndrome raises the general population's risk of CVD by 2 fold. [10] Da Cunha et al. discovered a greater amount of RA patients with metabolic syndrome in a research undertaken in Brazil relative to healthy non-RA controls (39% vs 19%). The writers also observed enhanced waist circumference incidence, hypertension, and enhanced fasting glucose relative to checks in patients with RA. [11]

3. Body weight/obesity

Body mass index (BMI), obtained from an people mass and height (kg / m2), is a frequently used metric in both RA and non-RA individuals for body composition. Obese people (> 30 kg / m2) have a mortality that is two to three times greater than ordinary people. Obesity is correlated separately with CVD burden as well as other risk factors such as hypertension, dyslipidemia, resistance to insulin, etc. [8] It also involves endothelial dysfunction and atherosclerosis advancement. In patients with RA, obesity leads to cardiovascular morbidity in the same way as the general population. Adipose tissue is a source of inflammatory factors including interleukin-6, tumor necrosis factor-alpha, and CRP which induce a state of low-grade inflammation that contributes to CVD risk. [12]

4. Smoking

Smoking RA patients have aggressive illness and worse clinical results. Despite the related risks, a meta-analysis determined that the incidence of smoking in patients with RA was greater than in controls. In the general population, cigarette smoking is associated with CVD. [13]

5. Lipids

The atherogenic lipid profile is usually regarded to be total cholesterol (TC), low density lipoprotein cholesterol (LDL-C) and low density lipoprotein cholesterol (HDL-C). Dyslipidaemia is often correlated with increased cardiovascular disease in patients with RA. [12] Gabriel SE performed a retrospective study of 1078 patients showing that lipid modifications (greater TC, reduced HDL-C, greater triglycerides) may occur even before RA begins. High concentrations of lipoprotein were also recorded in patients with RA, which is structurally comparable to LDL-C and is atherogenic in nature. [14]

6. Physical inactivity and cardiopulmonary fitness

According to the INTERHEART case-control research, physical inactivity is correlated with a greater danger of myocardial infarction in the general population. [13] Data from 33 big potential cohorts showed a 35% comparative risk decrease connected with being physically active in CVD-related death. Unfortunately, several trials show that RA patients are often inactive. This is due in part to pain and

tiredness, absence of motivation, and absence of patient knowledge of physical inactivity's adverse effect. [15]

RA related factors

1. Inflammation

Atherosclerosis in the blood vessels is no longer considered to be a straightforward method of lipid accumulation. There is proof that in the growth of rapid atherosclerosis, systemic inflammation plays a pathogenic function. [8] A research discovered that inflammation measured by high inflammatory markers was associated with enhanced danger of CVD even in healthy males. The formation of atherosclerotic plaque starts with endothelial dysfunction which results in the release of pro-inflammatory cytokines and adhesion molecules. [9] Due to enhanced endothelial permeability, inflammatory cells then join the blood vessel wall along with LDL molecules. The macrophages oxidize and absorb LDL, which subsequently become foam cells. This is accompanied by smooth proliferation of cells and neovascularization that eventually causes blood vessel and plaque formation to thicken. [16]

2. Anti-rheumatic agents and CV risk in RA

Non-steroidal anti-rheumatic drugs (NSAIDs) and cyclooxygenase-2 inhibitors (COXIBs): Non-steroidal anti-rheumatic medicines (NSAIDs) and cyclooxygenase-2 inhibitors (COXIBs) have decreased the therapeutic function in RA, but these medications are still widely used. According to meta-analysis, high doses of most NSAIDs are correlated with enhanced danger of MACE (Major Adverse Cardiovascular Events), while naproxen should not be associated with excessive CV events, likely due to its impacts on antiplatelets. There are doubts; however, that naproxen could have less harmful effects on the CV scheme than other NSAIDs and COXIBs. [17]

The most deleterious effects of NSAIDs on the CV system are suggested to be mediated by their hypertensive effect. [18] It was also found that the use of all NSAIDs increases the occurrence of atrial fibrillation. [19] However, it should be noted that some of the deleterious CV effects of NSAIDs and COXIBs could potentially be counteracted by their anti-inflammatory effects. In fact, the use of NSAIDs in RA was not correlated in some research with higher frequency of MACE and increased mortality from all causes. All in all, NSAIDs and COXIBs ' role and impacts on CV mortality are controversial. [20]

Glucocorticosteroids: Glucocorticosteroids (GLUCOR) are frequently used in RA treatment. Even the most conservative assessment shows that, in relation to conventional treatment, GLUCOR can significantly decrease the rate of erosion development in RA. [21] Readers interested in GLUCOR's anti-heumatic characteristics in RA should read particular papers. GLUCOR has a complicated connection with atherosclerosis. [22] By causing insulin resistance, raising body weight, and worsening / inducing hypertension and dyslipidaemia, GLUCOR can encourage CV disease. [23]

On the other side, the use of GLUCOR in RA patients with pre-existing CAD was associated with a decreased danger of heart death. [24] In addition, the combined use of GLUCOR with other anti-rheumatic drugs in RA patients with constant disease activity should decrease the risk of CV. Finally, an inadequate use of GLUCOR in RA appears to boost the danger of CV. All in all, GLUCOR's impact on CV mortality is controversial. [25]

Disease modifying antirheumatic drugs: Disease-modifying antirheumatic drugs (DMARDs) include antimalarials, sulphasalazine, d-penicillamine, oral and parenteral gold, azathioprine, cyclosporine, leflunomide, and methotrexate (MTX). [26] DMARDs may reduce the risk of CV either by directly influencing the atherosclerotic process or by indirectly eliminating inflammation or by affecting some risk factors for CV. There is no proof, however, that MACE in RA is reduced by antimalarials, sulphasalazine, d-

penicillamine, gold, azathioprine and cyclosporine. Parenteral gold can have a negative effect on renal function and should therefore boost MACE in RA. [27]

Biologic agents: The introduction of tumor necrosis factor-α (TNFα) antagonists revolutionized the management of RA and catalyzed the growth of other biological agents (BAs). [28] According to present suggestions, TNFα-antagonists should be regarded a first-line therapy in RA. [29] The new TNFα-antagonist remicade may stop RA from advancing but about 20 percent of patients do not react to other TNFα-antagonists. [30]

Note that TNFα-antagonists available can induce / aggravate congestive heart failure. Nevertheless, accessible TNFα antagonists appear to decrease aortic stiffness and enhance endothelial dysfunction and decrease CV morbidity, particularly in respondents. [31,32] The impacts of available and newer (Abatacept, Rituximab and Tocilizumab) BAs on MACE and CV death stay to be determined. However, the impacts of BAs on the arterial system differ, not all agents enhance stiffness and the beneficial impact may also be transient. [33] Not surprisingly, some trials in RA-patients did not detect a favorable impact of TNFα antagonists on MACE. [34]

Mechanisms of RA Pertinent to Cardiovascular Disease

Emerging proof indicates that in both RA and heart disease, T lymphocytes play a vital pathogenic role. By encouraging the selection and survival of autoreactive CD4 + T cells, the significant risk gene for RA, HLA-DRB1, predisposes to disease. [35] HLA-DRB1 alleles are also correlated with increased risk of MI and various kinds of heart disease that are not associated with RA. Perhaps the most convincing proof that T cells are pathogenic in RA is the demonstrated effectiveness of antagonizing T-cell co-stimulation. Likewise, percutaneous stents that elute drug-inhibiting T-cells (e.g., sirolimus) discourage in-stent restenosis and repeat CAD re-vascularization. [36]

CD4 + T cells typically lose expression of the co-stimulatory molecule, CD28, in people with either RA or heart disease, which usually offers the' second signal' needed for T-cell activation. It is thought that so-called' CD28null' T cells have been reprogrammed, leading to premature senescence. [37] Expansion of these senescent T cells among people with RA is associated with extra-articular inflammatory manifestations, including vasculitis and lung disease, as well as CAD. [38] CD28null T cells are recognized in atherosclerotic plaque in the environment of heart disease, where they are thought to add to the inflammatory process by generating cytokines and killing smooth muscle cells in the lung. Interestingly, the above-mentioned RA-risk gene HLA-DRB1 also predisposes CD28null T cells in RA and CAD to expand. [39]

Premature T cell senescence in RA appears to be caused by the hematopoietic system's basic defects. CD34 + hematopoietic progenitor cells, a sign of senescence, have accelerated telomere erosion. Naive T cells in people with RA are also prematurely old owing to inadequate activity of fundamental DNA repair enzymes, with enhanced fragility and harm to their DNA. Similarly, shortened telomeres. [40] The onset of both RA and heart disease coincides with the loss in the fifth century of thymic emigration of naive T cells, indicating that T-cell senescence may undermine the pathogenesis of these two age-related circumstances. Senescent T cell rejuvenation could potentially be an effective strategy for cardiovascular disease prevention and treatment in the foreseeable future, using new drugs to restore genomic repair and integrity. [41]

Cardiovascular risks of RA

Accelerated CAD, cardiac congestion and inflammation.

While there is a higher occurrence of ischaemic heart disease (IHD) in RA, several authors have shown that this enhanced incidence cannot be explained by

traditional risk variables alone, [42] as this has led to increased interest in the role of inflammation as a novel risk factor for atherosclerosis. [43,44] Indeed, small rises in C-reactive protein (CRP) were associated in the general population. [45] Sudden cardiac death and rheumatoid arthritis Studies have also proposed distinct patterns of CAD in RA with chronic inflammation leading to early endothelial dysfunction [46,47] and a greater incidence of unstable plaques ascribed to inflammatory cytokines. [48] Indeed, tumor necrosis factor alpha (TNF-α) has been involved in all phases of atherosclerosis, including endothelial dysfunction, plaque dysfunction. [49] Systemic inflammation was also associated with dyslipidemia, impaired glucose metabolism, platelet activation and reduced clotting factors. [50,51] However, despite proof connecting inflammation to accelerated atherosclerosis and IHD, Maradit-Kremers et al [52] showed that the double danger of SCDs in the RA population persisted after modifications to the history of hospitalized or unruly patients. This suggests that increasing IHD rates alone cannot explain the enhanced danger of SCD in RA. [53]

Abnormal ventricular repolarization, autonomic dysfunction and inflammation

Recent study has specialized on inflammation as an independent predictor of cardiovascular mortality and sudden death. [54] Indicators of abnormal ventricular repolarization such as QTc prolongation, QT interval dispersion and autonomic dysfunction are included in the SCD etiopathogenesis. The QT interval is the moment from the start of ventricular depolarization (the start of the Q wave) to the completion of repolarization (the end of the T wave). The corrected QT interval (QTc) estimates QT at a uniform heart rate of 60 bpm, whereas QT interval dispersion (QTd) is a metric of ventricular repolarization dispersion (maximum QT interval- minimum QT interval). Both QTc prolongation and enhanced QTd are considered risk factors for SCD in the general population, and information are linked to both QTc prolongation and SCD. [55]

Atherosclerosis

RA-related excess mortality is mainly due to cardiovascular illness, especially ischemic heart disease. Recent observational studies indicate that the increased risk is not mainly associated with traditional risk variables for atherosclerosis or corticosteroid and disease-modifying treatment. The existence of RA per se may be of main significance given the significance of chronic inflammation in atherogenesis. A case-control research of preclinical atherosclerosis, in which RA patients had a 3-fold rise (44% versus 15%) in carotid atherosclerosis, given unambiguous proof of the autonomy of atherosclerosis from traditional risk variables and a direct relationship to the existence of RA. [56]

Pericardial Disease

In RA patients, fibrinous pericarditis may be identified but is usually not clinically relevant. In RA patients ' echocardiographic studies, pericardial effusions can also be seen. Although clinically silent in general, there may be constrictive pericarditis. Case-control studies based on echocardiography have shown similar or enhanced rates of pericardial effusion. [57]

Rapid atherosclerosis is associated with the enhanced inflammatory state of RA, with systemic inflammation exacerbating adverse modifications in both known and novel cardiovascular (CV) risk factors. [58] In addition, the use of certain anti-inflammatory drugs is also correlated with enhanced risk of CV. Traditional and/or biological DMARD treatment-to-target methods can be highly effective in obtaining tight control of disease activity and rapidly decreasing inflammation. Lipid profiles can then be tracked and handled in accordance with domestic guidelines with lipid-lowering drugs, if necessary. [59]

Ten recommendations for CV risk management in RA [60]

1. RA should be considered a condition associated with increased danger of CV disease. The enhanced risk seems to be due both to the enhanced incidence of traditional risk variables and the burden of inflammation.
2. To reduce the risk of CV, adequate control of disease activity is required.
3. CV risk assessment is suggested for all RA patients using domestic guidelines. When anti-rheumatic therapy has been altered, risk assessments should be repeated.
4. Models of risk rating should be adjusted by implementing a 1.5 multiplication factor for RA patients. This multiplication factor should be used when the RA patient meets two of three requirements: (i) duration of illness >10 years, (ii) positivity of RF or anti-CCP, and (iii) presence of certain extra-articular manifestations. TCh/HDL cholesterol ratio should be used when the SCORE model is used.
5. Intervention in accordance with domestic rules should be carried out.
6. The preferred therapy choices are statins, ACE inhibitors and/or AT-II blockers.
7. In CV danger, the function of coxibs and most NSAIDs is not well founded, and further inquiry is needed. We should therefore be very careful to prescribe them, particularly in patients with a documented CV disease or in the presence of risk variables for CV.
8. Use the smallest possible dose of corticosteroids.
9. Recommend cessation of smoking.

CONCLUSION

RA is a chronic condition of inflammation associated with important cardiovascular mortality and morbidity. In rheumatoid arthritis, the cardiovascular burden is considerably increased. In addition to controlling RA disease activity, it is essential to manage traditional CVD risk factors. A multidisciplinary strategy should be attempted in which primary care professionals, rheumatologists and cardiologists can work together to enhance cardiovascular results and decrease death among RA patients.

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How to cite this article: Vidhya PV, Cindy J, Sambathkumar R. Overview of the cardiovascular risk in rheumatoid arthritis. International Journal of Research and Review. 2019; 6(11):399-407.

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