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Cardiovascular Co-Morbidity and role of exercise in Rheumatoid Arthritis: A Review

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Abstract:

Patients with rheumatoid arthritis have an increased risk of cardiovascular disease (CVD). Cardiovascular event rates are markedly increased in rheumatoid arthritis (RA). Data from population- and clinic-based epidemiologic studies of rheumatoid arthritis patients suggest that individuals with rheumatoid arthritis are at risk for developing clinically evident congestive heart failure (CHF). The vasculature plays a crucial role in inflammation, angiogenesis, and atherosclerosis associated with the pathogenesis of inflammatory rheumatic diseases. There is overwhelming evidence that, in the general population and several at risk subpopulations, exercise provides significant physical and psychosocial benefits, and facilitates management and improvements of outcome in Rheumatic disease. There is increased recognition of the need for structured preventive strategies to reduce the risk of CVD in patients with RA. In this review, the research agenda for understanding and preventing CVD co-morbidity in patients with rheumatoid arthritis is discussed.

Key-words: Rheumatoid arthritis, Cardiovascular Disease, Inflammation, Exercise

Introduction:

Cardiovascular disease is an increasingly recognized contributor to excess morbidity and mortality in rheumatoid arthritis (RA) [1-3]. The most probable cause of cardiac death in rheumatoid arthritis, as in the general population, is atherosclerotic coronary artery disease leading to ischaemic heart disease [4]. Rheumatoid arthritis, which is characterized by inflammatory polyarthritis with progressive joint damage, occurs in about 0.5%-1% of adult population in most countries [5]. Several studies have shown a higher incidence or prevalence of ischaemic cardiac pathologies such as myocardial infarction, congestive heart failure, and coronary deaths in patients with rheumatoid arthritis than in the general population [3,6-7].

Traditional cardiovascular risk factors do not adequately account for the extent of

cardiovascular disease in RA [3,8]. Although hypertension and age are potential additional contributors to cardiovascular events in this disease [6], markers of current and cumulative inflammation (white cell counts and radiographic joint damage, respectively) are associated with ultrasonographically determined subclinical atherosclerosis [9] – a predictor of cardiovascular events [10].

The use of methotrexate is associated with a significantly lower risk for cardiovascular (CV) events in RA patients compared with patients who had never used disease-modifying antirheumatic drugs (DMARDs) [11]. Suissa and colleagues [12] found a negative association between the rate of myocardial infarction and the current use of any DMARD in a case control study. A study from Sweden [13] suggested that the risk for developing first CV events in RA was lower in patients who

were treated with tumour necrosis factor-alpha (TNF- α) blockers. In this review we examine the evidence of risk for CVD in patients with rheumatoid arthritis and the suggested underlying mechanism and discuss the role of exercise for the prevention and management of CVD in such patients.

Epidemiology of Cardiovascular disease in patients with rheumatoid arthritis

Fewer statistics on incidence and prevalence rates for Congestive heart failure (CHF) in patients with RA are available and are derived from a handful of population-based^[7,14] and clinic-based RA cohorts^[15]. Gabriel *et al.*^[7] estimated the incidence of CHF among all RA patients in Olmsted County, Minnesota, from data abstracted from medical records. Between 1955 and 1985, 78 cases of incident CHF were identified among 450 prevalent cases of RA compared to 54 cases among the same number of non-RA community controls matched for age, sex, and baseline comorbidity, yielding a relative risk of 1.60 (95% CI 1.12-2.27). In contrast, the risk of incident CHF in patients with osteoarthritis (OA), a non-inflammatory arthritis, was not increased compared to non-OA community controls^[7].

In a follow-up retrospective review of the same cohort extended to 1995, now using the Framingham diagnostic criteria for CHF, Nicola *et al.*^[14] confirmed an increased risk of incident CHF in both rheumatoid factor (RF) negative and positive RA patients compared to non-RA controls adjusted for age, sex, and CV risk factors. Incident CHF risk remained elevated after further adjustment for comorbid ischemic heart disease, although the risk relationship was no longer statistically significant for RF negative patients in this model^[14].

In a combined cohort of RA patients from community-based practices and drug safety monitoring studies ($n = 9093$), Wolfe *et al.*^[2] estimated an adjusted lifetime relative risk of CHF in patients with RA is more as compared with OA

controls. The adjusted lifetime prevalence of CHF in the RA population was 0.7 % greater as compared to OA controls. Data were collected via patient survey of self reported, physician-diagnosed CHF, and confirmed by review of a random sample of medical records in 50% of patients reporting CVD events. In a subsequent analysis^[15], in which the drug safety cohort represented a third ($n = 4,307$) of the total sample ($n = 13,171$), Wolfe *et al.* reported an adjusted frequency of CHF of 3.9% (95% CI 3.4-4.3%) in RA patients compared to 2.3% (95% CI 1.6-3.3%) in controls with knee or hip OA. Factors associated with prevalent and incident of CHF were those typically associated with CHF in the non-RA population (e.g., age, male gender, hypertension, coronary artery disease, diabetes, and smoking) while RA-related measures (patient-reported disability, pain, and RA global severity) were also associated with prevalent and incident of CHF.

Risk factors for cardiovascular events in patients with rheumatoid arthritis:

Traditional risk factors for vascular disease such as, smoking, hypertension, diabetes and hyperlipidemia are important for the increased risk of CVD in subjects with RA^[16]. However, traditional risk factors alone do not fully explain the excess CVD risk in RA. Other non-traditional factors are hypothesized to play a role, in particular the burden of inflammation as indicated by the C-reactive protein (CRP) and/or erythrocyte sedimentation rate (ESR)^[17, 18]. In a community-based cohort of patients with inflammatory polyarthritis, Goodson, *et al* also noted that excess CVD mortality was confined to patients who were rheumatoid factor positive^[19]. These markers of inflammation and inflammatory burden confer additional risk of CVD death in those with RA after adjusting for traditional CVD risk factors and comorbidities^[20].

Severity of disease has consistently been associated with an increased risk of CVD events in

RA. Patient with severe extra articular RA manifestations are at an increased risk of developing coronary artery disease ^[21] as well as peripheral vascular disease ^[22]; and severe extra articular RA is a predictor of both overall mortality ^[23] and cardiovascular mortality ^[20], indicating that systemic inflammation is a major determinants of vascular comorbidity in RA. In contrast with the general population, a low body mass index (BMI), rather than obesity, has been associated with increased CVD in patients with RA ^[24, 25].

Role of exercise in Rheumatoid arthritis and Cardiovascular disease:

Exercise is one of the most important behavioral interventions that can have a major beneficial impact on the likelihood to develop, suffer symptomatically or die from CVD. Any physical activity is better than no, or little, physical activity. There is overwhelming evidence that, in the general population and several at risk subpopulations, exercise provides significant physical and psychosocial benefits, and facilitates management and improvements of outcome in Rheumatic disease. It helps maintain a healthy life-style, reduce CVD risk factors including obesity ^[26], dyslipidaemia ^[27, 28], hypertension ^[29], diabetes mellitus ^[30] and possibly even inflammation ^[31]; it is also effective for preventing acute coronary syndromes ^[32-34]. Moreover, exercise helps the management of established CVD: both aerobic exercise ^[35, 36] and resistance training ^[37] improve myocardial contractility and quality of life in patients with chronic heart failure and produce significant functional benefits in people with intermittent claudication ^[38]. More importantly, cardiac exercise rehabilitation programmes are an important part in the management of patients after an acute coronary syndrome (ACS) ^[39] and lead to significantly improved quality of life and reduced mortality rates ^[40, 41].

The overall physiological adaptations that occur as a result of exercise ^[42] provide protection against CVD mortality, even in the presence of well-established CVD risk factors ^[43, 44]. CVD mortality is lower in highly fit than in moderately fit individuals ^[45], while physical inactivity is an independent risk factor for the development of CVD ^[46, 47]. Even though cardiorespiratory fitness may have a familial component ^[48], it can be increased significantly by exercise training, regardless of age, gender, race and initial fitness levels ^[49]. The required activity levels can be accrued through formal training programmes or leisure-time physical activities ^[50]. Moreover, supervised exercise programmes are more effective compared with non-supervised exercise ^[51, 52], most likely due to greater adherence.

Great controversy still exists about the optimum amount of exercise for eliciting the greatest cardiovascular benefit. Different exercise intensity ^[53] and duration ^[54], as well as various combinations of them ^[55], may have different impacts on the magnitude of cardiorespiratory fitness improvement. Most authors agree that there is a dose–response relation between the amount of exercise, all-cause and cardiovascular mortality ^[53, 54]. The greatest potential for reduced mortality is in sedentary individuals (such as many RA patients), in whom even slight increases in daily physical activity are beneficial ^[56,57]; for more active individuals, higher levels of intensity should be pursued ^[56]. Depending primarily on the starting levels of physical activity, cardiovascular fitness has been reported to increase by 8–51% following an exercise intervention ^[54, 56].

Moderate-intensity exercise of long duration appears to elicit the most benefit on CVD risk and mortality ^[53, 55-57]. Current guidelines by the American College of Sports Medicine (ACSM) suggest that an individual should engage in exercise at least three times a week, at an intensity of 60–80% of maximum oxygen uptake (VO₂max), for at least 20–30 min, in order to

experience significant improvements in cardiorespiratory fitness and optimum cardiovascular benefits^[58]. In terms of caloric expenditure, this can be translated to 1000–2000 kcal/week^[59]. These calories can be expended in either continuous exercise or accumulated from several short bouts of exercise during a day^[59, 60]. Aerobic exercise is the most appropriate, but this can be supplemented by low-to-moderate intensity resistance training^[60]. The exercise regimen should be reconsidered regularly, usually every 4–6 weeks, based on the principles of exercise periodization^[61] so that participants continue to improve their performance.

Summary

There is strong evidence that persons with rheumatoid arthritis are at high risk for developing cardiovascular disease. Several studies have shown a higher incidence or prevalence of ischaemic cardiac pathologies such as myocardial infarction, congestive heart failure, and coronary deaths in patients with rheumatoid arthritis than in the general population. Severity of disease has consistently been associated with an increased risk of CVD events in RA. CVD mortality was more confined to patients who were rheumatoid factor positive. Role of exercise in the management and prevention of CVD in RA patients is very important yet neglected area of RA patients treatment programmes. As this review shows, there is accumulating evidence that in patients with RA, exercise therapy is effective in improving the prognostic risk factor profile. There is little has been investigated and published on the role of exercise as a means to control risk and manage CVD in individuals with RA. More research is required to identify the optimal regimens, timing and environment for exercise, as well as educational and behavioural intervention that will facilitate long term adherence to an active life style and/or structured exercise.

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