Cardiovascular risk factors in inflammatory arthritis

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Purpose of review

To assess factors that promote atherogenesis and cardiovascular disease (CVD) in rheumatoid arthritis (RA). Also, to determine how control of inflammation with conventional and biological antirheumatic drugs affects cardiovascular risk.

Recent findings

An excess risk of CVD occurs early in the RA disease course and indeed may predate disease onset. Inflammation is a key driver of CVD risk as it adversely affects body composition, glucose handling and lipid function, especially the atheroprotective role of high-density lipoprotein. Therapies for RA, especially hydroxychloroquine and methotrexate (MTX) have positive effects on cardiovascular risk factors such as glycaemic control and reverse cholesterol transport. MTX and antitumour necrosis factor- α drugs also appear to have beneficial effect on CVD event risk, although the data on MTX appears more consistently to favour such a benefit.

Summary

Future work needs to understand which aspects of the inflammatory state contribute most to CVD risk and whether specific anti-inflammatory agents, either alone or in combination, afford maximal CVD protection in RA.

Keywords

atherosclerosis, inflammation, rheumatoid arthritis, tumour necrosis factor

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Introduction

A growing body of evidence supports the role of low-grade inflammation in atherogenesis and cardiovascular events in the general population. Within rheumatology, a number of inflammatory rheumatic conditions have been associated with excess mortality and morbidity from atherosclerotic cardiovascular disease (CVD). These conditions act as a model for how inflammation may contribute to atherogenesis. In this review, we will present an overview of recent advances in our understanding of the risk factors for CVD in inflammatory arthritis, with the focus on rheumatoid arthritis (RA), and how anti-inflammatory therapies influence this risk.

The excess risk of cardiovascular disease in rheumatoid arthritis

The excess risk of cardiovascular disease in rheumatoid arthritis is now well established. Meune *et al.* [1[•]] reviewed 17 studies that included data from more than 120 000 patients. The overall standardized mortality ratios (SMRs) for both fatal myocardial infarction (MI) and stroke were increased in RA [MI 1.77 (95% confidence interval, CI 1.65–1.89) and stroke 1.46 (95% CI 1.31–1.63), respectively] [1[•]]. This accords with an earlier meta-analysis of 24 studies demonstrating an increased

risk of CVD mortality in RA [metaSMR 1.5 (95% CI 1.39–1.61)] [2]. There is also evidence that this relative excess risk has not reduced significantly over the past few decades. Two cohorts of RA patients from the same region of Sweden were followed up from 1978 and 1995, respectively. In both cohorts, the standardized morbidity ratio (SMoR) for cardiovascular events was increased and there was no major reduction between the two eras studied (1975 cohort SMoR 158%; 95% CI 111–225 and 1995 cohort SMoR 168%; 95% CI 118–232, respectively) [3].

When does this excess risk of cardiovascular disease in rheumatoid arthritis begin?

An important question is how early this increased risk is observed. This is linked to the question of whether there is a shared susceptibility for both RA and CVD. Holmqvist *et al.* [4] assessed the risk of ischaemic heart disease (IHD), MI or angina pectoris prior to the onset of RA in two Swedish inception cohort studies. In both of these cohorts, the odds ratios for CVD were not increased in RA patients before the onset of arthritis [4]. This contrasts to a previous study, in which, at the time of diagnosis, patients with RA already had an increased prevalence of previous MI and subclinical IHD noted on a screening electrocardiogram [5].

A subsequent study of 7469 patients with early RA from the Swedish National Register found that the relative risk (RR) of MI was increased over the first 5 years of disease [RR 1.6 (95% CI 1.4–1.9)] [6[•]]. Similarly, Franklin *et al.* [7[•]] noted in the Norfolk Arthritis Register (NOAR), a primary care-based inflammatory polyarthritis cohort, that during a median follow-up of 7 years, hospitalization for CVD was increased in inflammatory polyarthritis patients [RR 2.0 (95% CI 1.5–2.5)] [7[•]]. Similarly, with subclinical disease, Södergren *et al.* [8] found in a cohort of 79 early RA patients that carotid intima-medial thickness (IMT) and brachial artery flow-mediated dilatation (FMD) did not differ at baseline compared to controls. However, in 27 patients who had further follow-up at 18 months, IMT appeared to increase at a higher rate in RA patients [8].

Another approach is to consider whether patients with relevant autoantibodies without existing rheumatic diseases are at increased risk of developing CVD. In a previous population study, men with a history of CVD were more likely to be rheumatoid factor-positive [9]. More recently, an Icelandic cohort of 11 872 individuals, who were part of a community-based cardiovascular study, also had rheumatoid factor testing on an entry blood sample [10]. Within this cohort, 140 were rheumatoid factor-positive and being rheumatoid factor-positive was associated with increased all-cause and cardiovascular mortality, independent of classic risk factors, erythrocyte sedimentation rate (ESR) and the presence of joint symptoms. The adjusted hazard ratio for all-cause mortality in rheumatoid factor-positive individuals was 1.57 (95% CI 1.15–2.14) [10]. Similarly, Liang *et al.* [11] identified patients from a community-based sample who had undergone testing for rheumatoid factor, antinuclear antibodies (ANAs) or cyclic citrullinated peptide (CCP) antibodies. Rheumatoid factor and ANA were both associated with increased CVD risk after adjustment for potential confounders, including a diagnosed rheumatic disease. The hazard ratio point estimates for CVD related to rheumatoid factor or ANA positivity were 1.24 (95% CI 1.01–1.51) and 1.26 (95% CI 1.09–1.46), respectively [11]. For anti-CCP antibodies (which are more specific for RA), there was also an increased risk of future CVD [hazard ratio 3.1 (95% CI 0.8–12.3)] [11]. Owing to the smaller numbers and the shorter follow-up period, this did not reach significance but suggests it may be an even stronger risk factor in asymptomatic individuals.

Therefore, in symptomatic individuals with inflammatory polyarthritis and RA, subclinical and clinical CVD risk increases early in the disease course and CVD prevention needs to be considered from the outset in these patients. The risk of CVD prior to the onset of disease and/or in patients with associated antibodies also seems to be increased. Further work is needed to confirm this. If

Key points

- The excess CVD risk in RA occurs early and may indeed precede RA onset.
- The inflammatory disease process in RA adversely affects body composition, glucose handling and the atheroprotective role of high-density lipoprotein.
- Hydroxychloroquine and methotrexate (MTX) appear to have beneficial effects on CVD risk factors.
- Cohort studies have found that MTX and anti-tumour necrosis factor drugs are associated with a reduced risk of CVD events.

confirmed, this will open up new opportunities to screen and perhaps prevent CVD onset in this population.

Chronic inflammation and altered metabolic risk factors

Patients with a chronic disabling condition such as RA may be expected to have lower physical activity with associated weight gain. This relationship may not be as straightforward as it appears as inflammation is a catabolic state that itself may lead to weight loss rather than weight gain. A catabolic state may also affect the relative proportion of fat and muscle in a given individual, thus altering these relationships. Some investigators have noted that in RA patients, physical activity in RA is comparable to the general population [12] and although low physical activity was not associated with increased BMI, it was associated with low HDL, ApoA1 and increased insulin resistance [12]. Several other studies also suggest that BMI is not significantly increased in RA populations [13[•],14^{••}]; however, metabolic syndrome (MetS) is more common in RA patients both in early and established disease [13[•],15[•]]. This is driven by an increased waist circumference, higher blood pressure (BP) and dyslipidaemia [13[•],15[•]]. In addition, even where clinical measures of waist circumference are comparable to healthy controls, visceral fat distribution differs in RA patients [14^{••}]. In a study of 131 RA patients and 121 healthy controls, men with RA had more visceral fat area (VFA) on abdominal computed tomography (CT) and women with RA had a higher subcutaneous fat area (SFA) demonstrated [14^{••}]. VFA was associated with a positive rheumatoid factor and higher cumulative steroid exposure as well as a higher C-reactive protein (CRP), suggesting that inflammation contributes to this phenotype in RA [14^{••}]. In other studies, the MetS was also associated with a higher clinical inflammatory disease burden [15[•]] and higher levels of disability [13[•],15[•]].

Inflammation alters lipid measurements and potentially affects the interpretation of their impact on CVD risk by conventional risk scoring systems. Myasoedova *et al.*

[16^{••}] proposed a 'lipid paradox' in RA. They noted in a prospective study of RA patients that cardiovascular mortality was associated with lower total cholesterol (TC) and low-density lipoprotein (LDL) and is also predicted by an elevated ESR [16^{••}]. There is also an inverse relationship between CRP and both TC and HDL [17[•],18[•]]. Toms *et al.* [17[•]] noted a positive association between the ESR (but not CRP) and the TC:HDL ratio and Peters *et al.* [18[•]] found a positive relationship between this ratio and CRP. In this latter study, the TC:HDL ratio also predicted future cardiovascular events [18[•]]. Therefore; the TC:HDL ratio may be a better summary of future cardiovascular risk in RA patients and a more reliable assessment of lipid status in this population. In addition to altered levels of individual lipid subfractions, the atheroprotective function of lipids is also affected by the inflammatory state in RA. Pro-inflammatory HDL (piHDL) has gained a lot of attention in recent years both in systemic lupus erythematosus (SLE) and RA [19]. piHDL is increased in RA patients and clinically it is associated with disease activity, erosive disease, smoking, diabetes mellitus and older age [19]. In addition, there is a significant correlation between piHDL and the 28 joint Disease Activity Score (DAS28), a measure of clinical disease activity ($r=0.54$) [20]. With regard to HDL itself, piHDL in RA was associated with alterations in the HDL molecule, including increased haemoglobin, and myeloperoxidase as well as reduced lecithin-cholesterol acyltransferase (LCAT) activity [20]. Proinflammatory HDL may, therefore, be atherogenic in RA. In addition, increased oxidative stress associated with RA can also further negate the usual atheroprotective effect of HDL [21[•]]. Rho *et al.* [21[•]] found higher urinary 8-isoprostane (8-IP) levels in RA compared to healthy controls. In this study, there was a significant interaction between 8-IP and HDL such that with increased 8-IP, HDL was no longer protective against coronary calcification.

Conventional disease modifying antirheumatic drugs and cardiovascular risk in rheumatoid arthritis

If inflammation is a key driver of CVD risk in RA, then therapy to reduce disease activity and preferably to achieve remission should help attenuate CVD risk. In addition, certain drugs may have additional benefits (and some harm) with regard to cardiovascular safety in RA. Provan *et al.* [22[•]] found that patients with active RA had significantly increased brachial and central systolic pressure compared to RA patients in remission and healthy controls [22[•]]. In contrast, patients in remission did not differ from controls on most of the vascular function measures assessed but did have reduced aortic pulse wave velocity (PWV) when compared to healthy controls.

Similarly, Cansu *et al.* [23] examined 27 patients prior to and 3 months after starting conventional disease modifying antirheumatic drugs (DMARDs). In this population, both HDL and adiponectin increased 3 months following a change of treatment. Hydroxychloroquine (OHCQ) shows significant evidence of potential benefit in RA patients and it reduces the risk of future diabetes development in RA patients [24]; it is also associated with lower fasting glucose in both RA and SLE patients [25[•]]. OHCQ is associated with a more favourable lipid profile, including reduced LDL, triglycerides and increased HDL [26[•]]. Methotrexate (MTX), a mainstay of most modern therapeutic regimes in RA, also appears to have beneficial effects on CVD risk. A recent systematic review identified studies that showed a consistent favourable overall trend for MTX with regard to a range of cardiovascular outcomes, including mortality, all-cause cardiovascular morbidity and rates of MI [27^{••}]. In addition to an anti-inflammatory effect, MTX treatment may promote reverse cholesterol transport [28] by upregulation of the ABC1 transporter and Hy27. There is a reduced prevalence of MetS in MTX-treated RA patients, which may in part be due to improvements in the inflammation-related dyslipidaemia that can contribute to MetS criteria [14^{••},29].

Biologics and cardiovascular risk in rheumatoid arthritis

In the past decade, targeted therapies for RA have resulted in a step-change in our ability to control disease and improve clinical outcomes for patients. Antitumour necrosis factor (anti-TNF) agents have been the first wave of such agents and are used widely in RA management. A number of studies have examined their effects in attenuating cardiovascular risk with inconsistency noted in the studies to date [30^{••},31^{••}]. Indeed, Westlake *et al.* [27^{••},30^{••}] noted that the cardioprotective effects of MTX seemed to be more consistent across studies than those of anti-TNF drugs. Barnabe *et al.* [31^{••}] also found in their review that cohort studies tended to show reduced risk across a range of clinical end-points; for example, the adjusted RR for all cardiovascular events after anti-TNF therapy in the cohort studies was 0.46 (95% CI 0.28–0.77). In a meta-analysis of trials to date, however, the pooled RR for all cardiovascular events was 0.85 (95% CI 0.28–2.59) [31^{••}]. The point estimate for the cohort studies may of course reflect heterogeneity of studies as well as probable publication bias. The small absolute number of events in all trials to date may also affect power to detect a true difference mediated by this drug class. Nevertheless, the point estimate from the trials is still much less favourable than that seen in cohort studies. Lunt *et al.* [32] reported mortality data from the British Society for Rheumatology Biologics Register (BSRBR). In this study, cardiovascular mortality was

not significantly different in anti-TNF-treated patients compared to DMARD-treated controls [weighted hazard ratio 0.73 (0.44–1.23)]. Similarly, in a study of 20811 patients with RA recruited across the USA from the Veterans Administration system, exposure to anti-TNF drugs did not significantly reduce the risk of the composite CVD end-point, but in a subsequent analysis, it appeared to reduce stroke risk [RR=0.83 (95% CI 0.7–0.98)] [33[•]]. In contrast, in the Consortium of Rheumatology Researchers of North America (CORRONA) study, that includes 10 156 patients treated for RA, anti-TNF therapy was associated with a reduced risk of the composite CVD end-point [RR=0.39 (95% CI 0.19–0.82)] after adjustment for classic risk factors, disease duration and steroid use [34[•]]. Interestingly, in this cohort, there was no effect of MTX on CVD risk.

With regard to potential mechanisms of benefit, anti-TNF drugs may improve peripheral insulin sensitivity [35] and also has been found to improve BP [36^{••}]. In a secondary analysis of the BeST trial, which examined four different treatment strategies for RA therapy one arm of which was initial use of infliximab; achieving a DAS28 less than 2.4 (low disease activity) was associated with reduced BP. The use of infliximab also added further improvements in BP over that from achieving remission [36^{••}]. Also in a mixed population of patients taking anti-TNF drugs for RA, psoriatic arthritis or ankylosing spondylitis, anti-TNF therapy reduced aortic PWV independent of the magnitude of change in disease activity and inflammatory markers [37].

Preventive practices: time for a more concerted approach?

What is clear, therefore, is that patients with RA have an excess risk of cardiovascular events that is not fully explained by classic CVD risk factors. As such, the usual risk equations will not truly reflect the risk for an individual with RA as there is an overall 1.5–1.7-fold excess risk of CVD [1[•],2]. The updated QRISK2 models include RA to reflect this excess risk [38]. Recent guidance from The European League Against Rheumatism (EULAR) has addressed cardiovascular risk stratification in RA and starts with a recommendation to assess risk on an annual basis against local guidelines. Smoking cessation is a central theme and in addition, proactive suppression of disease activity is also recommended [39]. To address the excess risk associated with RA, they recommend that the risk calculation be multiplied by 1.5-fold if two of the following three factors are present: positive rheumatoid factor, positive anti-CCP antibody or disease duration more than 10 years [39]. Such recommendations and guidance is likely to improve screening and consideration of cardiovascular risk in RA populations. To date, there is

a poor understanding of this risk and poor delivery of cardiovascular risk screening to this population. In a recent RA patient sample from Medicare in the USA, only 45% of RA patients had lipid screening over the period of follow-up including 26% of patients who saw only a rheumatologist and 44–48% of patients who had some primary care input into their follow-up [40[•]]. In the UK, a recent survey of general practitioners (GPs) found that only 32% were aware that RA was an independent risk factor for CVD. Within this group of GPs, only 15% undertook primary screening in RA patients and only a small proportion of those who actively screened patients (18%) adjusted for the presence of RA [41[•]]. This lack of screening also is reflected in the high number of patients with RA who are eligible for statin therapy but fail to receive this [42]. These studies confirm the evidence gap and a range of issues need to be addressed, including better patient and primary care education as well as agreed guidance on thresholds for interventions and the best interventions for this population.

Conclusion

RA is associated with an excess risk of CVD and this excess risk begins early in the disease course and may indeed precede the actual onset of clinical disease. This is evidenced by the fact that RA-associated antibodies may in themselves be risk factors for CVD. Chronic inflammation plays a central role in atherogenesis and this is mediated by a number of pathways, including altered lipid function, insulin resistance and increased fat:muscle mass ratio. Altered HDL structure and function also contributes to atherogenesis in chronic inflammatory states.

Therapies for RA suppress inflammation and would be hypothesized to have atheroprotective effects by this pathway. Indeed, there is good evidence to support a role for MTX in reducing overall CVD morbidity and mortality. In addition, OHCQ has beneficial effects on inflammation, lipid profiles and glycaemia. Anti-TNF drugs are more targeted therapies and have been shown to improve aortic stiffness as well as clinical CVD risk, although the studies are less consistent than those for MTX on the actual degree of protection they confer. Despite this accumulated experience and recognition of CVD risk within rheumatology, there is poor delivery of preventive screening and use of statin therapy in high-risk groups within the RA population. There is an urgent need to better define which aspects of the inflammatory state contribute most to CVD risk and whether specific anti-inflammatory agents either alone or in combination afford maximal CVD protection in RA. In addition, we also need to better understand how to deliver the most effective preventive strategies to all our RA patients.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 309–310).

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