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Review article

Inflammatory arthritis as a novel risk factor for cardiovascular disease

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ABSTRACT

Cardiovascular disease (CVD) comorbidity is a significant issue for the inflammatory arthritides (IA). There is a wealth of mortality studies showing increased cardiovascular mortality in rheumatoid arthritis (RA) and the evidence suggests that the same is likely to be true of psoriatic arthritis (PsA) and ankylosing spondylitis (AS). CVD co-morbidity is due to ischaemic pathologies driven by accelerated atherosclerosis and relates to the increased prevalence and clustering of classical risk factors, which may also be affected by treatments for IA, and their interplay with novel risk factors, namely systemic inflammation.

Currently we are unable to quantify the contribution that classical and novel risk factors make to an individuals' CVD risk and specific algorithms need to be developed and validated in RA, PsA and AS to facilitate clinical management. Furthermore, large clinical trials are required to assess the effect of lifestyle modifications, primary prevention strategies and effective immunosuppression on hard CVD endpoints. However, in the meantime, a pragmatic approach should be adopted towards CVD risk management. Consensus opinion has generated guidelines for the management of CVD risk in IA and we discuss the importance of assessing each individual for CVD risk and establishing a system for routine risk factor identification alongside a commitment to treat identified risk factors to specific targets.

1. Introduction

Inflammatory arthritides are well characterised multi-system conditions. The cardinal symptoms of joint pain, swelling and stiffness (which may cause joint damage and deformity) are frequently accompanied by significant constitutional symptoms such as fatigue, weight loss and pyrexia. Extra-articular manifestations are well taught at medical school: rheumatoid lung (pulmonary effusions, fibrosis or nodules), or apical fibrosis in ankylosing spondylitis (AS); iritis in the sero-negative arthropathies or (epi)scleritis in rheumatoid arthritis; pericarditis or conduction defects in rheumatoid arthritis (RA) or aortic regurgitation in AS; renal amyloidosis due to long-standing inflammation [1]. However, with improved control of systemic inflammation due to use of biologic therapies, the trend over recent years has been to see fewer presentations of such extra-articular manifestations; instead co-morbidities such as cardiovascular disease (CVD), infection, malignancy, osteoporosis and gastro-intestinal ulceration require increasing attention [2].

This review focuses specifically on CVD co-morbidity in inflammatory arthritis, (specifically RA, psoriatic arthritis (PsA) and AS), given its frequency and impact which we hope to illustrate to you in this review. Specifically, CVD co-morbidity in inflammatory arthritis is due to ischaemic pathologies driven by accelerated atherosclerosis and we discuss why inflammatory arthritis is a risk factor for CVD in terms of its effect on classical and novel risk factors. We consider how current research in this area should be translated into clinical practice and identify where further research is required.

2. Cardiovascular mortality and morbidity in inflammatory arthritis

2.1. Rheumatoid arthritis

Numerous mortality studies have examined CVD mortality in people with RA [3]. Whilst some studies have not detected an increase in CVD deaths [4–7], other studies have observed that CVD was responsible for the excess deaths seen in RA [8–10]. However, a recent meta-analysis of observational studies in RA cohorts with clearly defined CVD outcomes has been published; this identified twenty four studies published between 1970 and 2005, representing 111,758 patients with 22,927 cardiovascular events [11]. A weighted-pooled summary estimate of standardised mortality ratio was 1.5 (95% confidence interval 1.39–1.61) indicating a 50% increased risk of death in patients with RA compared to the general population [11]. This increased mortality reflects both increased CVD morbidity and increased case fatality. The prevalence of CVD morbidity is increased two-fold in RA compared to the general population [12]; more recently the magnitude of this increased risk has been shown to be comparable to the risk associated with type 2 diabetes mellitus [13–15]. Increased case fatality in people with RA has been observed [12,16]. Douglas et al. found that RA patients were more likely to experience

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recurrent cardiac events or death after an index cardiac event [17]; similarly, Goodson et al. concluded that CVD in RA likely had a higher case fatality when excess CVD mortality was observed despite unchanged standardised admission rates in the Stockport inception cohort of 1010 patients recruited in the 1980s and 1990s [18].

2.2. Psoriatic arthritis

Cohort and population-based studies have examined CVD mortality in PsA. Some studies have not observed an increased mortality [19,20], although the study from Minnesota only involved 66 patients with PsA [19]. In contrast, other studies have found an increased standardised mortality ratio, for example, Ali et al. observed 680 patients receiving care for PsA between 1978 and 2004 and calculated an overall standardised mortality ratio of 1.36 of which a quarter of the deaths were due to CVD [21] and Ahlehoff et al. calculated a rate ratio for cardiovascular death of 1.84 in 607 people with PsA [22]. A recent systematic review of 28 studies of cardiovascular co-morbidity in PsA concluded that data consistently shows an increased CVD mortality in PsA [23]. Again, this increased mortality reflects increased morbidity; an increased prevalence of ischaemic heart disease [24,25], peripheral vascular disease [24], congestive heart failure [24] and cerebrovascular disease [24] has been observed. Furthermore, this increased prevalence of CVD morbidity has been shown to be similar to that in RA [26] and severe psoriasis [22].

2.3. Ankylosing spondylitis

There is less information about mortality rates in AS, but standardised mortality ratios are increased with circulatory diseases, the most frequent cause of death accounting for 40% [27,28]. Prevalence ratios for ischaemic heart disease, peripheral vascular disease, congestive heart failure and cerebrovascular disease are increased [24] although a meta-analysis of 3279 patients with AS compared to 82,745 control patients gave a risk ratio for myocardial infarction of 1.88, but the 95% confidence intervals spanned 1 (0.83–4.28) [29].

3. Why is inflammatory arthritis a risk factor for CVD?

The risk of CVD in inflammatory arthritis is increased due to accelerated atherosclerosis which results from the interplay between classical and novel cardiovascular risk factors, all of which may be affected by treatments, other co-morbidities or an underlying genetic predisposition (Fig. 1).

3.1. Importance of classical risk factors for CVD

Smoking, hypertension, insulin resistance, physical inactivity, dyslipidaemia and obesity are highly prevalent and tend to cluster in people with RA [30] and may frequently be undertreated in this population [31,32]. These risk factors may be exacerbated by RA itself, for example, joint pain or structural damage may contribute to physical inactivity and increased obesity. Whilst obesity is widely appreciated as an undesirable body composition for CVD risk, rheumatoid cachexia should similarly be considered. Here, pro-inflammatory cytokines mediate the involuntary loss of skeletal lean muscle which is progressively replaced by fat [33]. Thus a person with RA with an apparent normal or low weight may in fact have a high percentage of body fat; it has therefore been proposed that body mass index thresholds defining overweight and obesity should be amended to 23 and 28 respectively in RA [34].

Treatments for inflammatory arthritis may specifically affect these classical risk factors (Table 1). Non-steroidal anti-inflammatory drugs and cyclo-oxygenase II inhibitors may induce or aggravate hypertension [35]. Disease-modifying drugs, used to treat RA, PsA or a peripheral arthritis associated with AS, such as leflunomide and ciclosporin may also contribute to hypertension [35] whereas hydroxychloroquine may be beneficial by producing a less atherogenic profile due to increasing high density lipoprotein levels [36]. Methotrexate may increase homocysteine levels (and hyperhomocysteinaemia has been shown to be an independent risk factor for atherosclerotic disease) but this needs to be balanced against its effectiveness in reducing systemic inflammation [30]. Corticosteroids are often used in inflammatory arthritis to rapidly treat active disease, both early in the disease course, and during a flare or as bridging therapy between disease-modifying drugs; occasionally corticosteroids are used long-term at a low dose if disease-modifying drugs are contraindicated [37]. For many years it has been assumed that corticosteroids associate with a more atherogenic lipid profile. However, over more recent years, conflicting data has been produced from several prospective studies, indicating that corticosteroids may actually improve the lipid profile by increasing high density lipoprotein and lowering the total cholesterol to high density lipoprotein ratio. In RA, the most widely reported changes include an increase in both total cholesterol and high density lipoprotein levels. However, high density lipoprotein appears to increase at a proportionately higher rate compared with total cholesterol, thus generating a more favourable atherogenic index. Much of the witnessed normalisation of total cholesterol and high density lipoprotein levels with steroid use in RA has been attributed to the suppression of disease activity through their

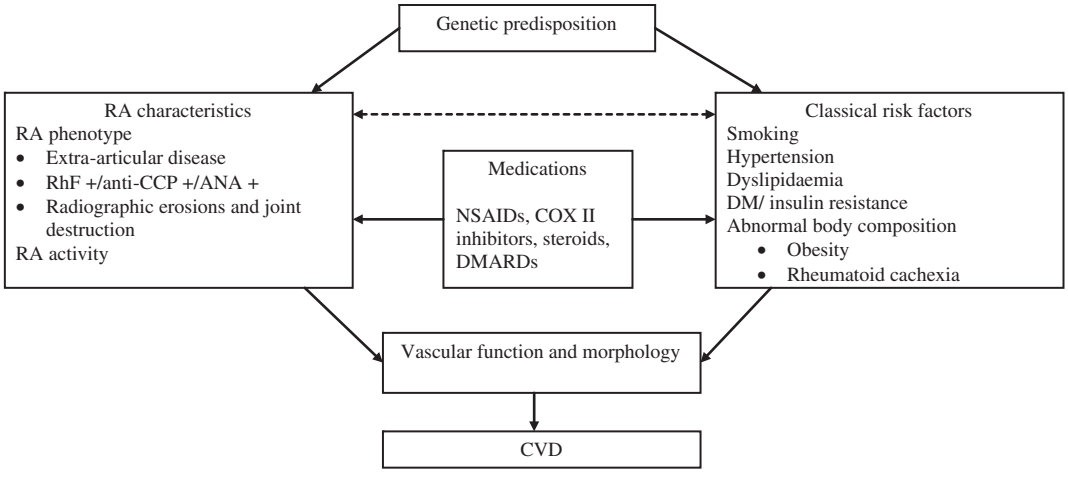

Fig. 1. Pathways leading to CVD in RA showing the role of traditional and classical risk factors. RhF = rheumatoid factor; anti-CCP = anti-cyclic citrullinated peptide antibodies; NSAIDs = non steroidal anti-inflammatory drugs; COX II inhibitors = cyclo-oxygenase II inhibitors; DMARDs = disease modifying anti-rheumatic drugs; DM = diabetes mellitus.