
Comparison of cardiovascular risk in ankylosing spondylitis and rheumatoid arthritis

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ABSTRACT

Cardiovascular co-morbidity is now a recognised complication of chronic inflammation and an elevated acute phase response predisposes to hypertension, stroke and myocardial infarction. Dyslipidaemia is a feature of inflammatory joint diseases and is closely related to elevated CRP and IL-6 levels. Rheumatoid arthritis (RA) has an increased standardised mortality ratio largely attributable to cardiovascular risk. An increased although lesser, cardiovascular morbidity has also been observed in ankylosing spondylitis (AS) which has a similar abnormal lipid profile to that seen in RA. There is some evidence that therapeutic agents such as anti-tumour necrosis factor- α (TNF- α) drugs that down-regulate the acute phase response, also have an effect in reducing cardiovascular complications in RA and AS.

Introduction

In the last ten years there has been much scientific interest in the concept of chronic inflammation being a “driver” for accelerated atherogenesis in auto-immune diseases (1). It is now established that a persistent low-grade acute phase response characterised by elevation of C-reactive protein (CRP) and interleukin-6 (IL-6) increases the cardiovascular risk in rheumatic diseases and is associated with a dyslipidaemia (2). Rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) confer an enhanced risk of cardiovascular complications such as hypertension, myocardial infarction and stroke thus contributing to an increased mortality in these diseases (3). It has recently become apparent that ankylosing spondylitis (AS) is also associated with an increased cardiovascular risk and the evidence for this will be reviewed and a comparison made with RA. Cardiovascular risk in the context of AS and RA will be confined to

generalised vascular disease and will not include other familiar cardiological associations such as valvular disease, conduction defects and cardiomyopathy.

Cardiovascular risk in AS

Epidemiology

There have been few extensive epidemiological studies of AS that specifically address morbidity and mortality. Lehtinen studied 398 AS patients with a follow-up time of 25 years and noted that the overall mortality rate was 1.5 times greater than expected and that there was an increased incidence of cardiovascular complications in the cohort studied (4). Another study of cardiovascular outcomes using an integrated outcomes database found that cardiovascular morbidities and usage of beta-blockers and calcium channel blockers etc. were higher in RA, PsA compared with controls (5). A more recent review of the literature by Zochling quotes standard mortality rates (SMR) varying from 1.3 to 1.51 excluding patients who had previous radiotherapy treatment where the mortality rate is much higher as a result of radiation induced malignancies (6).

Dyslipidaemia, inflammation and metabolic syndrome

The reason for the increased cardiovascular complications in AS was hinted at in a much earlier study which demonstrated that the lipid profiles of AS and SLE patients were similar to RA patients in that there was a low total triglyceride level attributed to low LDL concentrations but HDL levels were similar to controls whereas the RA patients had low HDL levels in contrast to the AS and SLE patients (7). The authors concluded that there may be specific alterations in lipid profile in various rheumatic diseases.

The increased risk of cardiovascular complications in RA and the mechanisms underlying this observation led to

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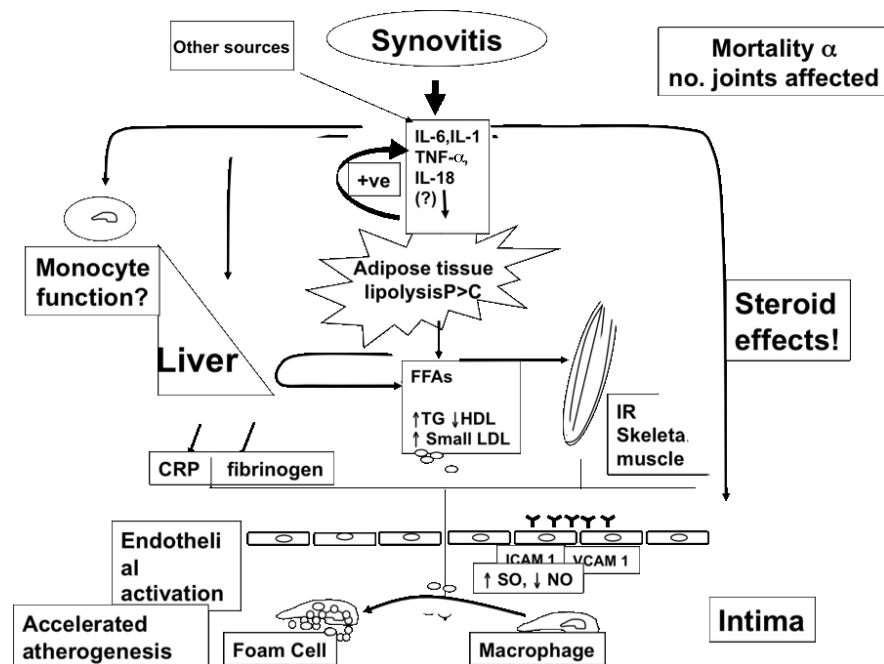


Fig. 1. In AS, primary site of inflammation are the enthesis and synovial tissue, from which cytokines can be released into systemic circulation. These circulating cytokines alter function of distant tissues, including adipose, skeletal muscle, liver, and vascular endothelium, to generate a spectrum of pro-atherogenic changes that include insulin resistance, characteristic dyslipidemia, prooxidative effects, and endothelial dysfunction and damage. !ve indicates positive; P>C, peripheral greater than central; TG, triglyceride; vWF, von Willebrand factor; and tPA, tissue plasminogen activator. (after Sattar *et al.* *Circulation* 2003;108:2957-2963)

Coronary heart disease risk

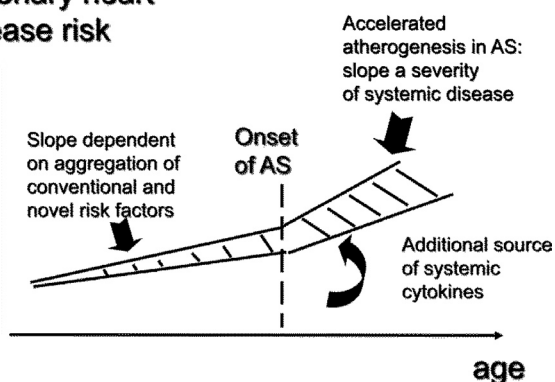


Fig. 2. Before onset of AS, classic risk factors predict risk of event. However, after onset of disease, severity of systemic inflammation secondary to AS joint disease is critical in acceleration of atherogenesis, and thus risk factors influenced by systemic inflammation will predict risk of future events.

a number of studies investigating a possible link between chronic inflammation and a vasculopathy in AS. In contrast with RA, AS patients with clinically active disease may have a normal ESR or CRP. However the ability to measure CRP using more sensitive ELISA techniques (hs-CRP) has demonstrated that even small elevations of CRP are associated with increased cardiovascular risk even in apparently normal individuals (8). Divecha and co-workers studied a small number of AS patients and measured hs-CRP and pro-inflammatory cytokines such as IL-6 and

correlated these with lipid profiles (9). They found that CRP and IL-6 levels were elevated in the AS patients compared with controls and that there was an inverse correlation between IL-6 and LDL levels. There was also an increase in pulse pressure in the AS group. The lower cholesterol and LDL levels showed a similar trend to that seen in RA patients and they observed that that receptor-independent uptake of LDL particles enhances plaque formation and atherogenesis. A similar study confirmed the findings of low LDL levels and total cholesterol in AS and also

noted that the changes observed were greater in patients with active disease when compared with a small group of patients whose disease was well controlled on etanercept (10).

Elevated plasma homocysteine levels are also recognized as a risk factor for cardiovascular disease (11) and two studies have shown increased homocysteine levels in AS (12, 13).

Vasculopathy

The consequences of an "atherogenic" lipid profile in AS has been explored by studying carotid artery intima /media thickness (IMT) by ultrasound (US) and by assessing small vessel vascular responses. A small study reported that carotid artery intimal thickness was not abnormal in AS but flow related dilatation of the brachial artery was impaired in the AS patients (13). However, the patient population was too small to achieve robust statistical significance. A subsequent study, however, did demonstrate an increased IMT in AS patients but found no difference between AS patients treated with anti-TNF agents compared those who were not on this therapy although the patient number was again small (14). A more recent publication from the Dutch group has shown impaired small vessel responses in AS that improve with anti-tumour necrosis factor- α (TNF- α) therapy with a correspondent normalization of the lipid profile thus suggesting that the down-regulation of inflammation improves cardiovascular risk and complications (15). Large vessel disease in AS has been studied by Hollan *et al.* by examining the timing of first myocardial infarction (MI) in patients who were undergoing their first coronary artery bypass graft (CABG) and they have demonstrated that the time from first MI to CABG was shorter in the AS group when compared to controls (16). The same authors also noted a chronic mononuclear inflammatory cell infiltrate in biopsies of the aorta and internal mammary artery in patients with inflammatory joint diseases including AS (17).

Novel approaches to therapy

In RA anti-TNF therapy and early treatment with DMARDS reduces cardiovascular risk and events and has

shown that physiological changes in arterial vessel wall elasticity improve with this therapy (18, 19, 20). Similar effects have yet to be demonstrated in AS patients.

It is now clear that the use of statin drugs reduces cardiovascular events in individuals who are at risk with a high cholesterol and an abnormal HDL/LDL ratio (21). McCarey and colleagues performed a clinical trial of atorvastatin in RA patients and demonstrated that the statin drug had an anti-inflammatory effect as well as producing significant reductions in total cholesterol, LDL cholesterol, triglyceride, and VLDL-cholesterol concentrations in the statin treated group (22). The authors concluded that atorvastatin could modulate lipid moieties – particularly oxidised LDL – that in turn regulate local inflammation. It would be interesting to see if similar effects could be demonstrated in the AS population.

Conclusion

It is clear that AS confers an increased cardiovascular risk and that that risk is enhanced in patients with active disease. The mechanisms involved are illustrated in Figure 1 where chronic inflammation dysregulates lipid metabolism and also has indirect effects on immune regulation at the vascular endothelium. The chronic inflammation found in AS accelerates the risk of atherogenesis (Fig. 2) and as a result potentiates cardiovascular events such as myocardial infarction and stroke. A comparison with the cardiovascular risk seen in RA is one of degree of effect rather than a difference in kind and this probably reflects the lower acute phase response seen in AS patients compared with RA. Therapy with biologic agents such as anti-TNF drugs show promise in reducing inflammation and cardiovascular risk in AS patients.

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