ABSTRACT – Rheumatoid arthritis (RA) is a multi-system disease with high rates of morbidity and mortality. In recent years, there has been increasing focus on the growing rates of cardiovascular disease (CVD) in RA, over and above expected levels allowing for ‘traditional’ risk factors. In this paper the impact of CVD in RA, the relative contributions of traditional risk factors and novel risk factors (including homocysteine, oxidised low-density lipoprotein, high-sensitivity C-reactive protein and leptin), and the need to address cardiovascular risk in the fight against premature death from coronary artery and stroke disease in RA are discussed.

KEY WORDS: C-reactive protein, cardiovascular disease, coronary artery disease, homocysteine, hyperlipidaemia, hypertension, rheumatoid arthritis

Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disorder that affects at least 1% of women and 0.44% of men in the UK.1 Severe RA carries a five-year survival rate similar to three vessel coronary artery disease (CAD) or stage four Hodgkin’s disease.2 Although the increased mortality has been linked with disease severity, disability and the presence of extra-articular disease, accelerated atherosclerosis leading to CAD remains the main reason for the increased death rate.3 Traditional risk factors are heavily implicated, but there is also increasing awareness that the chronic inflammation and endothelial damage associated with rheumatoid disease itself has a role to play, and this may enhance the undesirable effects of traditional factors (Fig 1).4

Cardiovascular disease in rheumatoid arthritis

Patients who suffer from RA have a greater incidence of diastolic hypertension, angina and stroke, and have an increased risk of sub-clinical vascular disease as shown by a higher prevalence of carotid disease, peripheral arterial disease and electrographic abnormalities.5,6 Deaths from cardiovascular disease (CVD) occur earlier than in the general population, and it has been suggested that the increased risk of ischaemic heart disease (IHD) in RA precedes the onset of clinical rheumatoid disease.7

Traditional risk factors for atherosclerosis, such as smoking, hypercholesterolaemia, hypertension, diabetes and a sedentary lifestyle may be common or indeed more common in RA than in the population as a whole, but do not account for all of the increase in circulatory disease. There is now a large body of evidence8 that the chronic inflammatory state can enhance the deleterious effects of some traditional risk factors, such as the association between systemic inflammation and arterial wall stiffness in hypertension,9 or the proatherogenic lipid profile (high LDL and lipoprotein(a), low HDL) seen with increasing rheumatoid disease activity,10 as well as introducing some new ones. The burden of addressing IHD in RA is therefore divided between rigorous control of traditional risk factors, and effective disease control through immunosuppression.

How does systemic rheumatoid disease accelerate cardiovascular damage?

Rheumatoid arthritis is an independent risk factor for accelerated atherosclerosis, and although many connections between systemic inflammation and endothelial damage have been suggested, some areas are identified as potentially of major influence.

Oxidised LDL

Oxidised LDL (oxLDL) and antibodies to oxidised LDL are both now established as significant risk factors for CVD in RA,11 and levels of oxLDL are higher in patients with active disease. OxLDL is found in abundance in atherosclerotic lesions, and prolongs the inflammatory reaction by interfering with apoptotic cell clearance.12 Oxidised LDL is also produced in the inflamed rheumatoid joint, where it prolongs the inflammatory response in a similar way.13

C-reactive protein

C-reactive protein (CRP) is thought to be a link between local and systemic inflammatory processes.
It is raised in patients with unstable angina, involved in the initiation and progression of atherosclerotic lesions, and independently predicts the risk of future myocardial infarction (MI), stroke and death. Higher levels of CRP are associated with CVD in non-RA patients, and treatment of CVS disease with statins or angiotensin-converting enzyme (ACE) inhibitors has been demonstrated to lower CRP levels. Attention has specifically focused on high-sensitivity CRP (hsCRP) or CRP values less than 5 mg/l. Raised hsCRP is found in hypertension, smoking and diabetes mellitus, as well as CAD, and CRP is also found deposited in atherosclerotic lesions.

In RA, CRP at baseline predicts cardiovascular mortality, and rather than being simply a marker of systemic inflammation, the molecule acts directly in a pro-inflammatory manner at a range of sites. For example, CRP activates vascular endothelial cells to express adhesion molecules in a dose-dependent manner, and CRP also activates monocyte chemotactic protein-1 (MCP-1), which can be inhibited by statins and fenofibrates.

Homocysteine

Elevated levels of homocysteine have been associated with CAD in the general population and reduced levels of various vitamins including folate and B6. Administration of the folate-analogue methotrexate in RA causes elevation of serum homocysteine levels, and it has often been speculated that this relationship with homocysteine might play a role in the increased CVS disease seen in RA. The issue is not entirely straightforward: although supplementation with folate and vitamin B6 has been shown to effectively reduce homocysteine levels in non-rheumatoid patients, the incidence of cardiovascular events may not fall as a consequence. Moreover, while many reports have found homocysteine levels to be higher in RA patients using methotrexate, this finding is not universal, and others have instead linked it to factors such as body mass index. It has also been shown to present in higher concentrations in the joints of RA patients, where it may enhance production of inflammatory cytokines such as IL-1 and thus act as a driver for joint damage; it may accelerate atherosclerosis in a similar manner. In the wider sphere, however, homocysteine is increasingly regarded as an epiphenomenon of CVS disease rather than a causative factor, and it is now clear that long-term methotrexate use has a positive effect on heart disease in rheumatoid arthritis as well.

Physical disability due to rheumatoid arthritis

Another potential cause for an increased rate of IHD is physical deconditioning as a result of disability from RA. Regular exercise is known to have beneficial effects on the cardiovascular system, and exercise capacity is also inversely related to the presence of the metabolic syndrome. Many patients with chronic RA have physical disabilities which prevent them from taking regular exercise. This influences CVD in several ways. If CVD is present, reduced physical activity may not exacerbate symptoms and so delay in the individual’s presentation to clinician. The delay in presentation would also prevent treatment at an earlier stage of CVD. If the individual had no CVD, physical disability would still stop adequate exercise. Poor functional status, especially in the lower limbs, is a powerful predictor of mortality in RA.

Leptin and the adipocytokines

Leptin is an adipokine that functions both as a hormone and a cytokine. It is produced in adipose tissue, and its main role appears to be to reduce food intake and stimulate the sympathetic nervous system, although it is now known to stimulate
inflammatory cytokine production, and have directly deleterious effects on articular cartilage. It is also known to cause endothelial dysfunction, oxidative stress and platelet aggregation and to be elevated in RA; while fasting has been implicated as a means of reducing leptin levels and improving RA disease activity, significant immunosuppression with anti-tumour necrosis factor (TNF) alpha therapy controls RA while leaving leptin levels unaffected. Although much remains unknown about its function, leptin has the potential to play a key role linking obesity, inflammation and cardiovascular damage.

Drug therapy

The initial response to the increased incidence of CVS disease in RA was to implicate RA therapy as one of the main culprits. There is now a gradual realisation that effective immunosuppression may actually be the key to reducing CVS disease in RA, and that the increased use of drugs such as methotrexate, regardless of steroid doses, has reduced CVS morbidity and mortality. Likewise, anti-TNF alpha therapy has been shown to improve lipid profiles and endothelial function, as well as reducing the likelihood of a first MI. TNF alpha is directly implicated in the pathogenesis of atherosclerotic plaques, and lowering TNF alpha levels per se should have a positive effect on the circulation. Statins and ACE inhibitors are among other drugs believed to have anti-inflammatory effects in RA as well as directly positive effects on the cardiovascular system, and several major studies are currently underway to further delineate their role in both aspects of the condition. Finally, hydroxychloroquine, a common adjunct therapy in RA, has been shown to effectively lower cholesterol levels in patients with systemic inflammatory disease such as systemic lupus erythematosus, and is particularly effective in those also taking corticosteroids.

The use of coxibs in RA and non-RA patients has received much attention, following the withdrawal of Vioxx after it was shown to increase the incidence of MI in a trial examining recurrence of colonic polyps. Subsequent work has shown a small but quantifiable risk associated with using many non-steroidal anti-inflammatory drugs (NSAIDs) and coxibs for long periods of time, and a more considered response is now advocated when weighing up the risks and benefits of this class of drugs. In patients with few other risk factors for CVS disease, including those with RA, the benefits will usually still outweigh the potential adverse effects. There is little evidence to suggest that traditional NSAIDs are any safer in terms of CVS risks than coxibs, and indeed in patients who are also taking an aspirin, the gastrointestinal side effect profile points in favour of the newer drug class.

Conclusion

Coronary artery disease is common in RA, and more common than one would expect from traditional risk factors alone. A considerable body of evidence now links accelerated atherosclerosis to inflammatory disease, and suggests that effectively reducing levels of systemic inflammation in RA may reduce endothelial damage. Nevertheless, a bigger task still exists in effectively addressing conventional risk factors in RA patients, a key component of which is raising awareness of the need for aggressive intervention in primary care in this group of patients, as currently exists for diabetics or patients with established CAD. The attractions of the Quality Outcomes Framework system in general practice for this purpose have been highlighted as an area for discussion.

References

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