Cardiovascular disease in rheumatoid arthritis

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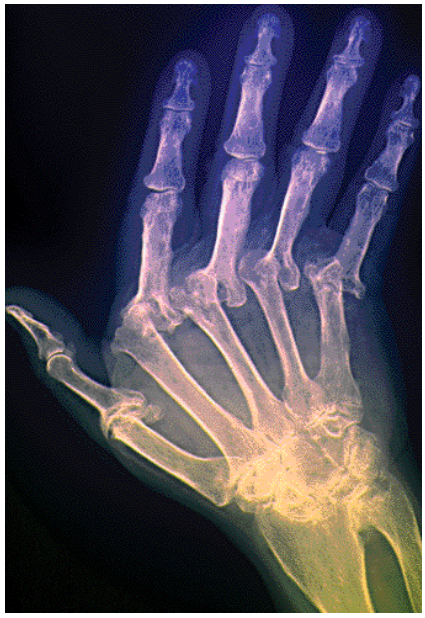
Rheumatoid arthritis is a systemic illness with numerous extra-articular manifestations affecting the heart, vessels, lungs, skin and eyes. In addition to significant disability from pain and joint damage, patients with rheumatoid arthritis have a significantly reduced life expectancy, with cardiovascular disease being a major cause of premature death.



PHOTOLIBRARY

Rheumatoid arthritis affects about 1% of the population. It is commonly regarded as a chronic inflammatory condition of the joints, with pain, swelling and erosion its typical manifestations. It is, however, a systemic illness with numerous extra-articular manifestations affecting the heart, vessels, lungs, skin and eyes. In addition to significant disability from pain and joint damage, patients with rheumatoid arthritis have a significantly reduced life expectancy of between 3 and 18 years. Most studies have identified cardiovascular disease (CVD) as the major cause of premature death in people with rheumatoid arthritis.

One of the largest studies to examine the risk of CVD in people with rheumatoid arthritis was the Nurses' Health Study that followed 114,000 women for 20 years. This study found that the 527 women who developed rheumatoid arthritis were twice as likely to have a myocardial infarction as those without rheumatoid arthritis. Women with rheumatoid arthritis for more than 10 years had a threefold increased risk of having a myocardial infarction.[1] Numerous other studies have reported similar levels of risk for patients with rheumatoid arthritis.

Patients with rheumatoid arthritis are also at an increased risk of cardiovascular morbidity. Congestive heart failure is twice as common in patients with rheumatoid arthritis than in those without. There is evidence that ischaemia alone is not the only cause of congestive heart failure in patients with rheumatoid arthritis. Numerous studies have documented the presence of subclinical pericarditis, myocarditis, valve disease, cardiomyopathy and diastolic dysfunction in patients with rheumatoid arthritis.

Despite the increased risk, CVD is under recognised in patients with rheumatoid arthritis. This may be because a high number of patients with CVD have atypical pain, mask their pain with analgesics, or the patient or healthcare professional assume that the pain is simply a flare of arthritis. Other common pitfalls are that there is often no preceding history of angina to help diagnose a cardiac cause of chest pain in patients with rheumatoid arthritis, and that traditional risk factors for CVD may be absent.

Causes of CVD in rheumatoid arthritis

The mechanisms leading to the increased risk of CVD in patients with rheumatoid arthritis are not yet clear. There are many possible contributors being studied in patients with rheumatoid arthritis. These include traditional risk factors for CVD, medication side effects, risk factors specific to rheumatoid arthritis and the possible role of chronic inflammation.

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Summary points

- Rheumatoid arthritis is an independent risk factor for cardiovascular disease.
- Cardiac events may be atypical or silent in patients with rheumatoid arthritis.
- Effective control of rheumatoid arthritis with disease-modifying drugs may reduce the risk of cardiovascular disease.
- Modifiable risk factors for cardiovascular disease should be assessed and treated in patients with rheumatoid arthritis.
- In patients with rheumatoid arthritis, there is no evidence to guide targets for blood pressure and lipid levels. These should therefore be defined as for the general population without rheumatoid arthritis. Interventions to help patients stop smoking (if applicable) should also be offered.

Traditional risk factors

Traditional cardiac risk factors alone cannot account for the increased burden of CVD in patients with rheumatoid arthritis. A number of studies have found no increase in traditional risk factors in patients with rheumatoid arthritis. Studies that have shown increases in traditional risk factors in patients with rheumatoid arthritis have generally found that adjusting for these factors does not account for much of the increased risk. Hypertension is one such factor identified in some studies of patients with rheumatoid arthritis. The likely causes of increased blood pressure in patients with rheumatoid arthritis include side effects of medication, such as corticosteroids, NSAIDs and leflunomide, and possibly inflammation itself.

Smoking has been identified as being more prevalent among patients with rheumatoid arthritis. It is recognised as a risk factor for developing the disorder and is also associated with more severe rheumatoid arthritis. Smoking should therefore be strongly discouraged in people with rheumatoid arthritis.

Obesity is a well-recognised risk factor for CVD. Interestingly, in patients with rheumatoid arthritis, there is an association between low body mass index (BMI) and cardiovascular mortality. A low BMI (<20 kg/m^2) due to rheumatoid cachexia is a sign of severe rheumatoid arthritis. So the association with CVD may be caused by the biological effects of inflammation and active rheumatoid arthritis, or possibly caused by other results of severe rheumatoid arthritis such as inactivity.

Medication effects

Medications used to treat rheumatoid arthritis may have variable effects on cardiovascular risk. NSAIDs and COX-2 inhibitors are associated with an increased risk of CVD and are known to increase blood pressure. Corticosteroid treatment can lead to hypertension, dyslipidaemia and insulin resistance, but may conversely improve these risk factors by reducing inflammation.

Retrospective studies examining methotrexate use and CVD in rheumatoid arthritis have suggested that patients who respond to methotrexate have a dramatically reduced risk of CVD compared with those with persistently active rheumatoid arthritis. Whether or not this improvement is a direct effect of methotrexate use or simply the result of improved control of inflammation is unproven.

Tumour necrosis factor inhibitors are contraindicated in patients with severe heart failure. There is evidence that they may be safely used in patients with mild to moderate heart failure, and that they may be beneficial for some risk factors such as high density lipoprotein cholesterol levels and carotid intima media thickness. There is conflicting evidence regarding improvement in aortic stiffness with tumour necrosis factor inhibition. The long-term effects of tumour necrosis factor inhibition on risk of CVD are currently being investigated in large open registry studies.

Novel risk factors and inflammation

Inflammation is involved in CVD from the earliest stage of endothelial dysfunction, through to rupture of a vulnerable plaque. Elevated levels of high-sensitivity C-reactive protein correlate with the risk of CVD in studies of healthy populations, even when levels are at the high end of the normal range. Levels of high-sensitivity C-reactive protein are often elevated in patients with active rheumatoid arthritis. Whether C-reactive protein itself plays a role in CVD or is simply a marker of inflammation remains controversial.

Systemic inflammation in rheumatoid arthritis has been associated with a number of possible pro-atherogenic changes including endothelial dysfunction, increased aortic stiffness, dyslipidaemia, insulin resistance, increased oxidation and a prothrombotic state. Some of these changes have been found to correlate with rheumatoid arthritis disease activity and may even normalise with adequate control of inflammation. These parameters are increasingly being used in studies of CVD in rheumatoid arthritis because the time and number of patients needed to show differences in actual rates of CVD events would be very high.

It is not yet clear if the increased risk of CVD in rheumatoid arthritis is due simply to the presence of more atheromatous plaques or to greater vulnerability of the plaque. A recent postmortem study has compared findings in the arteries of patients with rheumatoid arthritis with those of patients without rheumatoid

arthritis. Although it was a small study with several limitations, the intriguing findings were that plaques from patients with rheumatoid arthritis had less atheroma, but appeared more vulnerable to rupture and more inflamed.[2] Although far from conclusive, this provides some evidence for the role of inflammation in rheumatoid arthritis associated with CVD.

Recommendations

Rheumatoid arthritis should be considered an independent risk factor for CVD. There is little direct evidence to guide specific targets for lipid levels and blood pressure in people with rheumatoid arthritis (unlike in patients with diabetes for example). The best approach currently is to have a high degree of suspicion for CVD in patients with rheumatoid arthritis. Screening for cardiac risk factors should be a high priority, with targets for blood pressure and lipid levels defined as for the general population without rheumatoid arthritis. Interventions to help patients stop smoking (if applicable) should also be offered. Low-dose aspirin prophylaxis is not advisable if rheumatoid arthritis is the only risk factor for CVD in the individual.

Effective control of rheumatoid arthritis with disease-modifying drugs may also reduce the risk of CVD. Effective suppression of inflammation in rheumatoid arthritis will also lead to better joint function and less disability, which has obvious benefits beyond the possible cardiovascular effects. This can be achieved for most patients by close consultation between the patient, GP and rheumatologist. Summary points of this article are listed in the box on page 56. MT

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Further reading

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COMPETING INTERESTS: None.