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Cardiovascular risk and inflammatory rheumatic diseases

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Introduction

Patients with chronic inflammatory rheumatic conditions such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), spondyloarthritis (psoriatic arthritis and ankylosing spondylitis) and juvenile idiopathic arthritis (JIA) are at increased risk of developing premature cardiovascular disease (CVD). The pathogenesis of CVD in these conditions is multi-factorial and is thought to result from an interaction of inflammation, metabolic factors, therapy and disease-related factors. This review provides an overview of the current understanding of CVD risk factors in patients with inflammatory rheumatic diseases. Better understanding of the association between these conditions and cardiovascular morbidities can help in early assessment and management of risk factors; in turn, this may help to improve long-term outcomes in patients with inflammatory rheumatic disease.

Epidemiology of cardiovascular diseases in rheumatic conditions

It is now well established that there is an increased prevalence of CVD in several chronic inflammatory rheumatic conditions. In SLE, CVD has been confirmed as a major cause of mortality and morbidity.[1] Several studies have indicated that the overall prevalence of clinical CVD ranged from 6–10%. Patients with SLE have a 5–6 times increased risk of developing CVD compared to the general population and the risk is particularly marked in young patients. Patients with SLE also have an increased prevalence of sub-clinical atherosclerosis, with up to 40% of SLE patients having evidence of a carotid plaque, nuclear imaging abnormalities or increased coronary calcification.[1]

There are fewer published studies of the epidemiology of CVD in other multisystem autoimmune rheumatic diseases, such as systemic sclerosis (SSc) and Sjögren's syndrome. One study has, however, shown increased carotid intima-media thickness (cIMT) in patients with SSc,[2] although this finding has not been convincingly replicated by other studies.

In rheumatoid arthritis (RA), there is also clear evidence of increases in both clinical and subclinical CVD. A recent meta-analysis showed a 1.5-fold increased risk of death from CVD in RA populations when compared to the general population.[3] Again, as in SLE, the relative risk of CVD is higher in younger patients.[4] Increased cardiovascular mortality in RA patients may be attributed to a combination of factors, including a higher burden of atherosclerosis, more clinically silent events or an increased rate of fatality following myocardial infarction (MI).[4]

With regards to psoriatic arthritis (PsA), current studies have produced conflicting results, but emerging evidence suggests an increased risk of overall mortality in patients with PsA compared to the general population.[5] In addition, CVD morbidity, including hypertension and CVD events, was also increased in PsA patients.[6] Similarly, in patients with ankylosing spondylitis (AS), there are conflicting data regarding mortality. As reviewed by Peters *et al,* some studies reported no difference in mortality between patients with AS and the general population.[7] Others have reported an increased risk of death with a standardised mortality ratio (SMR) ranging from 1.5 to 1.9.[7] Cardiovascular morbidity in AS mainly involves conduction defects and aortic insufficiency, but there is some evidence of an increased prevalence of ischemic heart disease in those with AS.[7]

Box 1. Proposed CVD risk management in SLE.

- Ideal blood pressure: <130 mmHg systolic and <80 mmHg diastolic
- Ideal LDL levels: <2.6 mmol/l
- Statin therapy (LDL >3.4 mmol/l at initial screening or >2.6 mmol/l after lifestyle modification)
- Ideal BMI <25 kg/m^2
- Smoking cessation
- Minimise steroid dose (withdraw if possible)
- Use of anti-malarials
- Strict control of inflammation

BMI = body mass index; LDL = low density lipoprotein; SLE = systemic lupus erythematosus.

The study of CVD in patients with JIA is challenging. This is due to the heterogeneous nature of the disease with distinct clinical forms having differing prognoses and degrees of inflammation. The majority of studies in JIA are within childhood whereas clinical CVD manifestations appear during adulthood.

Risk factors for cardiovascular disease in rheumatic diseases

Systemic lupus erythematosus

Patients with SLE have an increased prevalence of certain classic CVD risk factors including:

- hypertension and diabetes compared with healthy controls[1]
- dyslipidemia with higher triglycerides and lower high-density lipoprotein (HDL) than unaffected controls[1]
- metabolic syndrome which may develop in part due to active disease, especially active nephritis, and also as a consequence of corticosteroid use.[8]

Lupus-related factors, including pre-existing damage in other organ systems, may also contribute to CVD risk.[1] Over time, chronic inflammatory disease will increase CVD risk and this is reflected by the association of increased C-reactive protein (CRP) and/or low C3 complement with both clinical and subclinical atherosclerosis seen in some SLE patients.[1]

With regards to therapy, high-dose and long-term corticosteroid usage also increase

CVD risk; this may, in part, result from exacerbation of classic risk factors including hypertension, diabetes mellitus and dyslipidaemia.[1] By contrast, the use of anti-malarials seems to mitigate cardiovascular risk factors, having both lipid- and glucose-lowering effects, and might be especially beneficial when the patient is taking steroids.[1]

Rheumatoid arthritis

Meta-analysis demonstrates increased prevalence of smoking, diabetes and reduced HDL-cholesterol level in RA.[9] Indeed cigarette smoking is an important risk factor for developing RA, in particular seropositive disease which has a poorer overall prognosis. Interestingly, some of the traditional risk factors do not act as expected when predicting future CVD morbidity and mortality in RA. Of particular note is the observation that lower total cholesterol is associated with increased risk of CVD in RA.[10] This is probably due to the contribution of chronic inflammation to a 'cachectic' effect on RA patients, as well as chronic inflammation affecting lipid subsets to induce a more pro-atherogenic profile.

There is a reported positive association between inflammation and CVD mortality in RA patients.[11] Similarly in this group, elevated levels of CRP and erythrocyte sedimentation rate (ESR) are associated with increased all-cause and CVD mortality. Interestingly, seropositivity for rheumatoid factor (RF) and/or anti-cyclic citrullinated protein antibodies (ACPA) and the shared epitope are also associated with increased risk of CVD.[12] In relation to drug therapy, several reports, including a systematic review, have noted a reduction in CVD morbidity and mortality among methotrexate-treated patients.[13] The use of biological agents such as tumour necrosis factor (TNF)-inhibitors is also associated with improved disease activity and reduced inflammatory burden. The effect of biological agents on individual events and on CVD mortality is still the subject of intense study, and larger studies are needed to completely resolve this question. However, a meta-analysis of studies published to date suggests that use of anti-TNF drugs might reduce the risk of future CVD when compared to standard disease-modifying anti-rheumatic drug (DMARD) therapy.[14]

Spondyloarthritis

Less is known about risk factors for CVD in patients with psoriatic arthritis (PsA). There is an increased prevalence of obesity, hypertension and diabetes mellitus in patients with PsA when compared to healthy controls.[15] The inflammatory process may also increase the risk of CVD in PsA; one report found that levels of CRP and ESR were associated with increased carotid intima medial thickness and endothelial dysfunction.[16]

As is the case for PsA, no conclusive studies have been published on CVD risk factors in AS. In addition to classic risk factors, inflammation and genetic predisposition may contribute to increased CVD risk.

There is also some evidence of increased hypertension, dyslipidemia and physical inactivity in patients with JIA compared to healthy individuals.[17]

Key points

Regular assessment of cardiovascular disease (CVD) risk factors is strongly recommended

Standard CVD risk assessment tools are not appropriate for estimating CVD risk for patients with systemic lupus erythematosus (SLE) as they significantly underestimate the actual risk

For rheumatoid arthritis (RA) patients, adjusting standard risk formulae to account for RA, or using the QRISK 2 tool, which includes RA in the risk assessment, is recommended

In SLE, a 'target-based' approach to individual CVD risk factors is proposed

'Tight-control' of inflammatory disease activity might also contribute to CVD risk reduction across these conditions

KEY WORDS: Rheumatoid arthritis, systemic lupus erythematosus, inflammation, cardiovascular disease, risk management

Risk management

There are no clinical trials to inform the ideal risk management strategies in populations of patients with inflammatory disease. Approaches to the screening and management of risk factors are therefore based on evidence from observational studies and expert opinion. Indeed, whether the modification of classic risk factors will materially affect CVD outcomes in these conditions remains an unanswered question. In addition, whether CVD screening in these patient groups should be the responsibility of primary care physicians or should be led by the rheumatology team is also open to debate. To date, pragmatic guidelines have been suggested for both RA and SLE. In addition, the NICE Quality Outcomes Framework (QOF) also includes a statement on the assessment of cardiovascular risk in RA patients as one of four key performance indicators for RA in General Practice in England (www.nice.org.uk/nicemedia/live/13840/60229/60229.pdf).

Rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis

The European League Against Rheumatism (EULAR) has developed recommendations focused on CVD risk management in patients with RA and other inflammatory arthropathies (PsA and AS).[18] These recommendations recognise the association between chronic inflammation and atherosclerosis in patients with inflammatory arthritis. Thus, pro-active control of inflammatory disease activity is recommended to reduce CVD risk. Annual assessment of classic CVD risk factors is recommended for all patients, and it is recommended that 10-year CVD risk is calculated in individual countries according to a nationally used prediction model, such as the Systematic Coronary Risk Evaluation (SCORE). Such models should be adjusted to take in to account the excess CVD risk in RA by multiplying the calculated risk by 1.5 if two of the following three criteria apply:

- disease duration >10 years
- positive rheumatoid factor
- positive anti-cyclic citrullinated peptide (anti-CCP) antibodies.

It should also be noted that in the UK, the QRISK2 model for predicting CVD risk already includes the diagnosis of RA and this model can therefore be used as the primary risk calculator without need for additional adjustment.[19] Statins and angiotensin converting enzyme inhibitors are favoured drugs for lipid lowering and control of blood pressure, respectively, because of their proposed pleotropic effects. Cyclo-oxygenase 2 inhibitors and non-steroidal anti-inflammatory drugs should be prescribed cautiously and sparingly, especially in patients who have CVD or CVD risk factors. In addition, therapy adjustment, especially minimizing the use of steroids and the introduction of antimalarials where appropriate, can also help in risk management. Lifestyle changes, especially smoking cessation and weight management, are vital. Large-scale studies are, however, needed to identify the most effective approaches for primary and secondary prevention of CVD in RA.

Similarly, in PsA and AS, the use of the available risk management tools with an appropriate adjustment according to EULAR guidance is advisable until clearer risk models are available. With regards to JIA, no current evidence on risk management is available.

Systemic lupus erythematosus

A proposed approach to CVD risk management[20] recommends annual assessment of individual risk factors and that screening should involve measuring fasting lipid profiles and blood glucose. As the relative risk of CVD in SLE is much higher than in other conditions, an adjustment or multiplier might be prone to significant error. Therefore, in contrast to the approach in RA, a target-based approach to CVD risk factors has been suggested in SLE (Box 1). This approach recognises that SLE is a very high-risk condition and can be viewed as a 'coronary heart disease equivalent'. As such, stringent targets for each risk factor should be set as 'ideal'.

Conclusions

Over recent decades, there has been considerable interest in the long-term outcomes of individuals with chronic inflammatory conditions. An increased prevalence of CVD in this population is now recognised, with the risk being best described in RA and SLE. This increased risk is attributed to an increased prevalence of traditional risk factors, systemic inflammation and genetic predisposition. The assessment and management of risk factors are therefore key elements of the management strategy for these patients.

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