The continuum of inflammation – cardiovascular risk – rheumatic disease activity: where can we step in?

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Abstract

Chronic inflammatory rheumatic conditions like rheumatoid arthritis, spondyloarthritis, or systemic lupus erythematosus have been linked to a higher cardiovascular disease risk when compared to the general population. Apart from chronic inflammation, which plays a central role, this increased risk is a consequence of traditional risk factors, disease-related factors, or prescribed antirheumatic drugs. Medications like non-steroidal anti-inflammatory drugs or corticosteroids should be used with caution in rheumatic patients with established heart disease because of the additional risk they might bring. Patients with cardiovascular disease should be regularly monitored, having a screening performed every five years. Assessment tools include the SCORE system, which should be multiplied by 1.5 in patients with rheumatoid arthritis. Management of this patient population should include lifestyle changing and pharmacological treatments according to available guidelines, but clinicians should also focus on achieving tight control of the rheumatic disease since lower or no disease activity has been shown to decrease patients’ cardiovascular disease risk.

Keywords: inflammation, rheumatoid arthritis, hypertension, cardiovascular risk, systemic lupus erythematosus, atherosclerosis, spondyloarthritis.

Introduction

Cardiovascular disease is the leading cause of death worldwide [1]. Chronic inflammatory rheumatic conditions have already been linked to a higher prevalence of cardiovascular events than the general population due to an intricate combination of...
disease-related factors, traditional cardiovascular risk factors, and prescribed medication [2].

The traditional cardiovascular risk factors consist of modifiable and non-modifiable risk factors, such as age, gender, and family history. Nevertheless, systemic inflammation plays a vital role in the relationship between rheumatic disorders and cardiovascular disease (CVD) [3]. CVD includes ischemic heart disease, cerebrovascular and peripheral vascular disease and major adverse cardiac events (MACE), referring to acute myocardial infarction (MI) or stroke [4].

Despite the increasing frequency, cardiovascular comorbidities are often overlooked and poorly treated, adding to the morbidity/mortality of patients with rheumatic diseases [5]. Among the latter, rheumatoid arthritis (RA), spondyloarthritis (SpA), and systemic lupus erythematosus (SLE) have an underlying inflammatory status that is involved in promoting atherosclerosis, thus participating in CVD [6].

Since inflammatory joint disorders have brought along a significantly increased risk of CVD, screening and prevention strategies have been discussed by experts, as well as patient targeted management [7].

Systemic inflammation and hypertension

Inflammatory markers like high-sensitive C-reactive protein (hs-CRP) have been associated with an increased risk of developing hypertension (HT) and displaying higher values in hypertensive patients. Moreover, low-grade inflammation proved by higher hsCRP but also by interleukin (IL)-6 and IL-1 leads to atherosclerotic disease and further makes patients prone to CV events [8].

CRP is able to activate the complement system and favor proinflammatory cytokine-like tumor necrosis factor (TNF)-alpha, IL-1,6 release and expression of adhesion molecules that will emphasize the inflammatory process [9].

Atherosclerosis is now acknowledged as having complex pathophysiology centered on chronic inflammation that can be found in atherosclerotic plaques as cell infiltrates [10].

The mechanism behind it is partially explained through endothelial dysfunction and oxidative stress. Inflammation is responsible for reducing nitric oxide leading to vasoconstriction, platelet activation, and thrombosis. CRP can influence the renin-angiotensin system through its receptor and increase blood pressure values [11].

However, if present, hypertension can start the inflammatory process in the vessel wall, leading to the production of acute-phase reactants in the liver. High CRP levels induce a low nitric oxide/endothelin ratio, leading to vasoconstriction [12].

Obesity, sedentarism as part of the metabolic syndrome, and antirheumatic drugs can trigger HT in RA [13].

Rheumatic disease activity and cardiovascular risk

Rheumatoid arthritis (RA) is a chronic inflammatory condition causing polyarticular pain and deformity, affecting up to 1% of the population worldwide. Like other inflammatory rheumatic diseases, it can be responsible for other organ involvement, either through the chronic inflammatory status or previous therapies [14]. Systemic inflammation that occurs in RA is also responsible for the development of atherosclerosis, putting RA patients at risk for cardiovascular disease with up to 48% estimated higher rate. Up to half of the RA deaths are due to CV events that can occur early in young seropositive patients [15].

Apart from atherosclerosis, patients with RA can suffer from myocardial infarction (MI) with a 68% higher risk, stroke with a risk estimated at 41% greater than in the general population, or heart failure [16].

RA doubles the risk of MI that can go silent, but recovery is more difficult in this population because of further ischemic complications and higher mortality rates than in patients without RA. Patients who suffer from hypertension or type 2 diabetes have a considerably higher risk of MI, as is the case of patients with high cholesterol levels, obese patients, or smokers. Thus, correcting traditional CV risk factors is still essential for lowering the global burden [17].

Previously published studies suggest that RA patients are at risk of developing atrial fibrillation and even stroke, either ischaemic or hemorrhagic, with a higher recurrence risk (up to 40%), because of the underlying inflammatory process [18].

Higher rates of heart failure have also been noted in RA patients when compared to the general population, most likely associated with rheumatic disease activity. Seropositive RA forms, characterized by the presence of rheumatoid factor (RF), have a more increased risk of heart failure, leading to a more unfavorable outcome [19].

Regarding disease-specific CV risk factors, RA is characterized by inflammation of the synovial membrane that in turn, stimulates the release of proinflammatory cytokines like TNF-alpha, IL-1, IL-6, and activation of the complement. This process is responsible for atherosclerosis, endothelial damage and increased arterial stiffness or high circulating lipids, leading to CVD [16].

A study published in 2017 aimed to assess whether an optimal control of RA disease activity over a
three-year period might influence the progression of atherosclerosis. Results showed that effective control of inflammation leads to a slower progression of atherosclerosis evaluated through arterial stiffness, presence of plaques in the carotid or femoral arteries, and common carotid artery hypertrophy, making it similar to patients without RA [20].

Knowing that an adequately controlled RA might lead to a decrease in CVD risk and CV-related morbidity/mortality, struggles are being made to respect treat-to-target strategies in order to achieve tight control of the disease.

Spondyloarthritis (SpA) refers to a group of inflammatory diseases with overlapping clinical and imaging features and similar pathogenic mechanisms but varying clinical outcomes or treatment responses [21]. Genetic and environmental triggers seem to be responsible for SpA occurrence. SpA has spinal involvement and mono- or oligoarthritis of the peripheral joints, enthesitis, but it may also exhibit mucocutaneous, ocular, and/or digestive symptoms [22].

CVD seems to be the leading cause of death in SpA patients, ranging from 30 to 50%. The increased mortality rate is due to the presence of multiple risk factors in SpA patients compared to the general population, and has a higher risk for cardio and cerebrovascular events.

Prediction factors of death were shown to be the male gender, older age, lower level of education, and traditional risk factors like diabetes or kidney disease [23].

The prevalence of ischaemic heart disease in SpA is around 2.7%, depending on the geographic region. The CV risk in SpA is caused by a combination of traditional CV risk factors, systemic inflammation, and treatments, mainly non-steroidal anti-inflammatory drugs (NSAIDs), which are still the first-line treatment [5].

Stroke can occur in up to 1.3% of SpA patients, and registry data suggest a higher risk of ankylosing spondylitis (AS) and PsA versus the general population. Nonetheless, the risk of deep vein thrombosis or pulmonary embolism seems to be increased in SpA cohorts because of the ongoing inflammatory status with hyperproduction of cytokines like TNF-alpha, IL-16, and CRP that favor a procoagulant state [24].

Hypertension is the most frequent CV risk factor in SpA and PsA patients. The mechanisms are multiple, like disease activity, increased inflammation, decreased mobility and a sedentary lifestyle [25].

Smoking is the second most frequent risk factor, and it has been linked to increased acute phase reactants, higher disease activity, and structural progression of the disease [26].

Dyslipidemia has a higher prevalence in patients with SpA and PsA, the latter finding an explanation in the fact that psoriasis is connected to metabolic disorders. Study results are not uniform since some have reported a decreased high-density lipoproteins (HDL) value, while others found increased total cholesterol and low-density lipoproteins (LDL) cholesterol [27].

Type 2 diabetes mellitus (DM) is twice more prevalent in SpA, with rates increasing in the past years. The use of corticosteroids might contribute to the development of DM [28].

Studies have shown a relationship between a higher body mass index (BMI) and a greater risk for CVD, and obesity is more frequent in peripheral SpA and in up to a third of patients with PsA [25].

The treatments prescribed in patients with SpA can influence the onset or outcome of CVD. NSAIDs inhibit the cyclooxygenase (COX) that converts the arachidonic acid in prostaglandins, mediating inflammation and pain. Inhibiting COX-1 favors anti-aggregation and vasodilation, while the inhibition of COX-2 stimulates a pro-thrombotic and vasoconstriction state. However, it is thought that the vascular risk of NSAIDs is similar when inhibiting either isoform – COX-2 inhibitors versus non-selective NSAIDs [29].

NSAID treatment can lower inflammation, thus reducing the CV risk through better disease control. While rofecoxib was removed from use because of increased CV events, diclofenac was also associated with MI in SpA patients. Naproxen seems to have a lower CV risk. Patient individual features and medical history should guide the prescription of the most appropriate NSAID to avoid adverse events [30].

The COMOSPA registry data proved there is a difference between recommendations for CV risk avoidance and their use in clinical practice since only half of the patients were monitored for CVD. If scores like the Framingham Risk Score or SCORE confirm a high risk of CVD events, lipid-lowering treatment and lifestyle changes are recommended, and an assessment should be done every five years. These actions are essential together with the control of disease activity since the frequency of flares contributes to the CVD risk [31].

Systemic lupus erythematosus (SLE) is a chronic inflammatory disease with multisystemic involvement, characterized by transient loss of self-tolerance and the emergence of immune abnormalities with autoantibody formation and destructive cell and tissue consequences [32].

Hypertension is a major risk factor for the progression of heart, kidney, and vascular disease. Studies indicate a high prevalence of hypertension in patients with SLE, reaching 74% in some cohorts. The mechanism of its production is incompletely explained, but the literature mentions the role of the immune system and chronic inflammation [33].

There is a 50-times higher risk of cardiovascular events like myocardial infarction and angina in the lupus population than in the general population.
Risk factors involved in inducing “accelerated atherosclerosis” and ischemic heart disease in patients with SLE are both traditional and disease-specific factors like complement activators, double-stranded DNA antibodies, and lack of use of hydroxychloroquine treatment or systemic inflammation [33].

Higher CV risk was found in SLE patients with older age at disease onset, longer duration of the condition, long-term corticosteroid use, high cholesterol levels, and a menopausal state.

Controlling blood pressure in patients with SLE is essential to avoid and reduce organ damage and improve the long-term prognosis. First-line antihypertensive drugs are inhibitors of the renin-angiotensin system, and if not sufficiently controlled, other classes of antihypertensives may be added, like diuretics or calcium blockers [34].

Apart from the presence of traditional CV risk factors, like hypertension, hypercholesterolemia, obesity, and smoking present in SLE patients, the use of NSAIDs and corticosteroids, there are also disease-specific contributors to increased CVD risk. Disease-induced damage, measured by the SLICC Damage Index, is linked independently to the CIMT and arterial stiffness. SLE patients with renal involvement have shown a higher carotid plaque formation frequency than non-nephritis patients [35].

Moreover, besides favoring a prothrombotic state, antiphospholipid autoantibodies are involved in endothelial damage. Endothelial injury is also due to oxidized LDL, which has higher levels in SLE patients, making patients more prone to fast installation and progression of atherosclerosis [36].

**Antirheumatic drugs and cardiovascular risk**

Considering that rheumatic disease activity and underlying inflammation lead to a higher CVD risk, efforts have been made to identify the role of antirheumatic drugs in CV events.

Non-steroidal anti-inflammatory drugs (NSAIDs) remain widely utilized in rheumatic illnesses, with multiple indications.

A meta-analysis that included 50 studies on multiple NSAIDs showed a 5-mmHg increase in systolic blood pressure, and another review showed a significant increase in mean blood pressure after four weeks of treatment with ibuprofen and indomethacin versus placebo [37].

Selective COX-2 inhibitors are responsible for increasing systolic blood pressure, thus being associated with significant cardiovascular risk.

Patients in need of NSAID use should be evaluated for CVD risks, and prescription should be done with caution in those with established heart disease or multiple risk factors [38].

Corticosteroids (CS) still represent a key treatment in many inflammatory joint conditions due to their prompt reduction of inflammation. However, they are known to produce hypertension, dyslipidemia, diabetes, and obesity depending on treatment dose and duration. Patients who receive a higher dose of CS, namely over 7.5 mg of prednisone daily, have a doubled risk of developing heart disease. In an RA cohort treated with CS, the risk of MI increased by 68% [39].

CS treatment should be used on short-term and at a minimum effective dose to avoid installation of adverse events that concur to the increase of CV risk. CS tapering is mandatory whenever possible, and reassessment of CS needs should be done. Patients taking CS treatment should be regularly screened and promptly treated if these occur [38].

Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) such as methotrexate, sulfasalazine, hydroxychloroquine, and leflunomide are beneficial in decreasing rheumatic disease activity and show decreased CVD-related morbidity and mortality.

Methotrexate has been shown to lower CVD-related deaths in patients with RA. Data from meta-analysis identified that rheumatic patients treated with methotrexate had a 21% lower risk of CVD and an 18% lower rate of MI [40].

Leflunomide can induce hypertension in 3.7% of treated patients, or it can aggravate pre-existing hypertension. If newly induced, hypertension appears early in the first 2–4 weeks after starting the treatment. The conduct in the case of these patients is to maintain or reduce the dose of DMARD and add antihypertensive therapy, with frequent monitoring of blood pressure. Despite this unwanted effect, leflunomide can prevent myocardial fibrosis and improve myocardial hypertrophy caused by overload [41].

Hydroxychloroquine, an antimalarial drug, has an anti-inflammatory effect, inhibiting the production of proinflammatory cytokines. Benefits like inhibiting platelet aggregation, reducing total cholesterol levels, and preventing thrombotic events make it broadly utilized in rheumatic diseases. However, physicians should be aware of potential QT interval prolongation or atrioventricular blockage that might rarely occur [42].

Targeted synthetic DMARDs, like JAK-inhibitors, are used as an alternative in the treatment of RA. Studies have linked them to a higher risk of thromboembolic events, especially in patients with risk factors like obesity, smoking, cancer, and previous venous thromboembolism. Moreover, they can increase levels of total cholesterol and LDL-cholesterol, increasing the CV risk [43].

Biologic therapies have drastically changed the outcome of patients with rheumatic diseases. Their effect on inflammation is able to lower the CV risk, as shown in meta-analyses that confirm lowering the
MI, stroke, and MACE overall rates. TNF blockers facilitate cholesterol transport and improve glucose metabolism but should be avoided in patients with heart failure.

Rituximab, a monoclonal antibody targeting CD20, can reduce lipid plaque deposition in patients prone to atherosclerosis, as shown in experimental studies. However, some patients may experience arrhythmia, hyper-, or hypotension during infusion [44].

Managing cardiovascular risk in patients with inflammatory joint disorders

Acknowledging that RA is an independent risk factor for CVD, the European League Against Rheumatism (EULAR) has issued an updated set of principles and recommendations, aiming to lower the CV risk in patients with inflammatory rheumatic conditions [38].

Thus, apart from signaling to clinicians that care for patients with RMDs that RA, SpA, and PsA have a higher risk than the general population, principles state that rheumatologists carry the responsibility for regular CVD risk management. Moreover, frequently used therapies like NSAIDs and corticosteroids are beneficial for lowering inflammation but are known to add to the CV risk, so their use should be guided by the patient’s individual profile and international treatment strategies.

Rheumatic disease activity, namely the frequency and intensity of flares, has been associated with increased CV risk; therefore, physicians’ objective should be to control systemic inflammation using available therapeutic options like csDMARDs or bDMARDs. Methotrexate and TNF blockers have a positive role in modulating arterial stiffness, while anti-IL6 and anti-CD20 agents can influence carotid intima-media thickness (CIMT), decreasing the CVD risk [38].

Evaluation of the CV risk should be performed every five years using the SCORE model, and therapeutic intervention is mandatory in patients at very high risk (SCORE over 10%).

The European Society of Cardiology (ESC) built up the SCORE system that estimates the risk of cardiovascular-related death in the next ten years. The SCORE method estimates the total cardiovascular risk taking into account both the coronary heart disease and the non-coronary component, and includes patient age, gender, systolic blood pressure, total cholesterol level and smoking status. Since SCORE was intended for the general population, EULAR proposed that the value be multiplied by 1.5 in RA patients to eliminate the risk underestimation bias. The QRESEARCH Cardiovascular Risk Algorithm 2 (QRisk) comprises a 1.4 multiplication for RA, leading to an overestimated CVD risk [24].

The CVD risk evaluation in RMD patients should include dosing total cholesterol and high-density lipoprotein cholesterol levels, knowing that disease activity status or certain therapies like JAK-inhibitors can increase lipid fractions. Moreover, carotid ultrasound should be used to identify asymptomatic atherosclerosis that imposes statin treatment initiation [38].

Antihypertensive drugs and statins should respect national guidelines, and the same reference values as in the general population should be preserved in rheumatic musculoskeletal diseases (RMD) patients. Lifestyle changes apply to all patients with inflammatory joint disease, including dieting, regular exercise, and smoking cessation. Exercise has previously shown its impact on lowering inflammation and hsCRP values in relation to reducing fat tissue but also on micro- and macrovascular function.

Regarding medication that targets inflammation, NSAID prescriptions should be made with caution since they have been proved to increase the CV risk for both COX2-selective and non-selective NSAIDs. Patients with established CVD should be omitted from the long-term prescription of NSAIDs. CS, which still represent a mainstay bridging therapy in inflammatory joint diseases (IJD), should be used rationally, and duration and dose tapering should be made whenever disease activity allows it. Corticosteroid-related CV risk is dependent on the dose and duration of CS exposure, so the lowest effective dose should be prescribed for the shortest possible duration [38].

Comorbidity screening and prevention strategies in rheumatic diseases

Cardiovascular comorbidities are more frequently associated with rheumatic diseases due to the disease itself or prescribed treatments. Screening and treating these comorbidities is essential since their presence might impact the outcome of the RMDs.

Managing comorbidities should be conducted by a specialist in the field, but rheumatologists can
lead the way in implementing specific recommendations issued by EULAR [46]. Acknowledging and reporting patients’ comorbidities is strongly advised since it can guide the choice of optimal treatment.

In order to correctly collect patient data, EULAR has issued recommendations for reporting, screening, and preventing comorbidities in inflammatory rheumatic diseases that involves the entire medical staff (rheumatologists, nurses) through self-administered questionnaires [46].

Patients should be investigated for cardiovascular risk factors like smoking, body mass index, hypertension, dyslipidemia, renal insufficiency, as well as documentation of a history of myocardial infarction, stroke, heart failure, or peripheral arterial disease. To prevent additional drug risks, patients’ treatments like antihypertensive drugs, antiplatelet or anticoagulants, statins, or diabetes therapies should be listed [46].

Implementation of screening and prevention programs is still problematic in daily practice. Thus, practitioners should encourage patients to adhere to routine screening investigations and self-fill preset forms to expect a better clinical outcome and avoid unfavorable prognosis.

Conclusions

The review article reiterates the link between inflammatory rheumatic diseases and cardiovascular disease. The latter comes as an intertwined between known traditional cardiovascular risk factors, the disease itself, or prescribed medication. However, it seems that the bedrock of changes is the continuous inflammatory state that occurs in certain rheumatic conditions, like rheumatoid arthritis, spondylarthrthesis, or systemic lupus erythematosus. Despite screening and prevention strategies for patients with RMD, the risk for CV events remains higher than in the general population.

Evaluating CVD risk in patients with chronic inflammatory joint disease should be performed regularly since it can guide optimal therapeutic strategy for RMD while avoiding additional side effects and promptly treating conditions that add to the disease burden and increase morbidity and mortality of patients.

Assessing CV risk can be done using the SCORE system, multiplying by 1.5 in RA patients to obtain a more realistic percentage. Treatment of CV risk factors should include lifestyle changes, smoking cessation, and traditional medication like antihypertensives, statins, or diabetes drugs.

Moreover, physicians need to be aware that tight control of the rheumatic disease leads to a decrease in CVD risk and overall death rate. Prescription of NSAIDs or corticosteroids should be done cautiously and individually since they can aggravate CVD. Antirheumatic drugs like DMARDs or BDMARDs seem to benefit CVD risk since they can lower inflammation and disease activity.

International initiatives for prevention, screening, and treating CVD risk factors are of interest to all clinicians, and their efforts should be oriented towards implementing these strategies.

Conflict of Interest

The authors confirm that there are no conflicts of interest.

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