Published in final edited form as:

Nat Rev Cardiol. 2015 March ; 12(3): 168–176. doi:10.1038/nrcardio.2014.206.

Cardiorheumatology: cardiac involvement in systemic rheumatic disease

Megha Prasad, Joerg Hermann, Sherine E. Gabriel, Cornelia M. Weyand, Sharon Mulvagh, Rekha Mankad, Jae K. Oh, Eric L. Matteson, and Amir Lerman

Division of Cardiovascular Disease, Department of Internal Medicine (M.P., J.H., S.M., R.M., J.K.O., A.L.), and Division of Rheumatology and Department of Health Sciences Research (S.E.G., E.L.M.), Mayo Clinic College of Medicine, 200 First Street SW, Rochester, MN 55905, USA. Division of Rheumatology, Stanford University, 300 Pasteur Drive, A100 MC5309, Stanford, CA 94305, USA (C.M.W.).

Abstract

Autoimmune rheumatic diseases can affect the cardiac vasculature, valves, myocardium, pericardium, and conduction system, leading to a plethora of cardiovascular manifestations that can remain clinically silent or lead to substantial cardiovascular morbidity and mortality. Although the high risk of cardiovascular pathology in patients with autoimmune inflammatory rheumatological diseases is not owing to atherosclerosis alone, this particular condition contributes substantially to cardiovascular morbidity and mortality—the degree of coronary atherosclerosis observed in patients with rheumatic diseases can be as accelerated, diffuse, and extensive as in patients with diabetes mellitus. The high risk of atherosclerosis is not solely attributable to traditional cardiovascular risk factors: dysfunctional immune responses, a hallmark of patients with rheumatic disorders, are thought to cause chronic tissue-destructive inflammation. Prompt recognition of cardiovascular abnormalities is needed for timely and appropriate management, and aggressive control of traditional risk factors remains imperative in patients with rheumatic diseases. Moreover, therapies directed towards inflammatory process are crucial to reduce cardiovascular disease morbidity and mortality. In this Review, we examine the multiple cardiovascular manifestations in patients with rheumatological disorders, their underlying pathophysiology, and available management strategies, with particular emphasis on the vascular aspects of the emerging field of ‘cardiorheumatology’.

Introduction

Autoimmune rheumatic diseases, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), spondyloarthropathies, and vasculitides, are inflammatory disorders that can involve multiple organs. Cardiovascular manifestations of rheumatological diseases have become increasingly recognized, and, in some patients, might even constitute the initial

Correspondence to: A.L. lerman.amir@mayo.edu.

Author contributions

M.P., J.H., S.E.G., C.M.W., S.M., R.M., J.K.O., and E.L.M. researched data for the article and made substantial contributions to the content; M.P. wrote the manuscript; M.P. and A.L. reviewed and edited the manuscript before submission.

presentation of a rheumatological disorder. The spectrum of cardiovascular manifestations associated with rheumatic diseases (Figure 1) is considerably broad, given that rheumatological disorders can directly affect the myocardium, cardiac valves, the pericardium, the conduction system, and the vasculature.¹ Whereas the cardiovascular manifestations of autoimmune disease can be mild and clinically silent, they can also increase morbidity and mortality substantially, and thus warrant early diagnosis and treatment.

Patients with systemic autoimmune conditions often develop atherosclerosis, contributing to a higher mortality than in the general population; however, the mechanisms at work during the development of this complication remain incompletely understood, and the processes that cause accelerated atherosclerosis are largely unknown. Atherosclerosis has been labelled as an inflammatory disease that manifests primarily in the arterial intima. Chronic inflammation can result in blood mononuclear cell recruitment, upregulation of adhesion molecules, release of proinflammatory cytokines, and production of matrix-degrading enzymes—all factors that can perpetuate inflammatory rheumatological conditions and promote formation of atherosclerotic vascular plaques.^{2–4} Immune and endothelial dysfunction also has an important part in accelerated atherosclerosis; however, the pathophysiological link between endothelial dysregulation and atherosclerosis has not been demonstrated. Accelerated atherosclerosis is common in patients with rheumatic conditions owing to the presence of underlying autoimmune and inflammatory mechanisms, which promote accelerated vascular plaque formation.⁴

In this Review, we explore each of the vascular, valvular, myocardial, pericardial, and electrical manifestations of rheumatic diseases individually (Figure 1). We also highlight the need to raise awareness to the interface between cardiology and rheumatology—the field of ‘cardiorheumatology’—and explore strategies to improve the cardiovascular care of patients with rheumatic diseases.

Vascular manifestations

Mechanisms of accelerated atherosclerosis

The mechanisms that contribute to accelerated atherosclerosis are not well defined, but chronic inflammation has been suggested as a contributing factor to the development of atherosclerotic disease—whereas differences exist between individual rheumatological conditions, chronic inflammation is a common denominator (Figure 2).^{2–6} Notably, systemic autoimmune diseases are associated with a substantial increase in the prevalence of atherosclerosis.⁷

Proinflammatory pathways

The release of proinflammatory cytokines, such as tumour necrosis factor (TNF)- α and interleukin (IL)-6, leads to endothelial dysfunction and activation, primarily via the nuclear factor κ -B (NF κ -B) pathway;⁸ activation of this pathway entails enhanced expression of chemoattractants (such as C-C motif chemokine 2 [also known as monocyte-chemotactic protein-1, or MCP-1]), adhesion molecules (such as vascular cell adhesion protein 1, or VCAM-1), and proinflammatory cytokines, which all promote leukocyte infiltration,

proliferation, and activation in the subendothelial space.^{4,9,10} Notably, this process can be potentiated by immune dysregulation in patients with rheumatological disease. For instance, titres of autoantibodies to oxidized low-density lipoprotein (oxLDL) were higher in a group of patients with autoimmune rheumatic disease than in healthy individuals.¹¹

Toll-like receptor (TLR) signalling is thought to regulate antibody formation in rheumatological diseases. TLRs are present in atherosclerotic lesions, further suggesting an association between autoimmunity and atherosclerosis.^{4,12} TNF- α is also associated with increased dyslipidaemia, insulin resistance, prothrombotic state, and activation of the inflammatory cascade, with the consequent upregulation of IL-1, IL-6, prostaglandins, and matrix metalloproteinases, all of which potentially promote an inflammatory milieu and accelerate atherosclerosis.^{4,8,13,14}

Adhesion molecules and cellular infiltrates

A proinflammatory state is associated with enhanced expression of adhesion molecules and release of proinflammatory cytokines by the endothelium. In fact, VCAM-1 is associated with cardiovascular disorders in several autoimmune rheumatological diseases, including RA, SLE, and large-vessel vasculitides.^{4,10} Adhesion molecules can be expressed on the endothelial and smooth muscle cell surfaces, and promote atherosclerosis by recruiting leukocytes into the subendothelial space.⁴

Migration of leukocytes and monocytes into the endothelial cell layer is an important step in the acceleration of atherosclerosis.⁵ MCP-1, expressed by endothelial and smooth muscle cells, can be upregulated by TNF- α and further promote atherosclerosis.⁹ Additionally, MCP-1 correlates with coronary calcification in patients with SLE, and increased levels of this chemoattractant have been associated with increased risk of coronary artery disease even among healthy individuals.^{4,8}

Leukocytes

T-cell activation can also be involved in the immune dysregulation that leads to acceleration of atherosclerosis. Patients with unstable atherosclerotic plaque and RA have an increased percentage of activated cells expressing the IL-2 receptor subunit α (CD25).¹⁵ Activated T cells are thought to be present in atherosclerotic plaques, and unstable plaques contain an increased percentage of activated T cells expressing CD25 when compared with stable plaques.¹⁵ Other studies have shown increased levels of an unusual subset of T cells (CD4+CD280+) often associated with extra-articular RA in patients with unstable angina.^{15–17} TLRs are also thought to modulate antibody formation in both SLE and RA, and have been detected in atherosclerotic lesions, further suggesting an association between autoimmunity and atherosclerosis. Importantly, TLR signalling can induce TNF- α and IL-6, by mediating macrophage activation in patients with RA, and activating dendritic cells and interferon (IFN)- α release in patients with SLE. Prolonged TLR activation can induce chronic inflammation through recruitment of cytokines and result in accelerated atherosclerosis.^{4,12}

Several similarities between the underlying pathophysiology of RA and atherosclerosis have been identified, including macrophage activation, T-cell activation, elevation in C-reactive protein (CRP) level, and upregulation of adhesion molecules (Figure 2).

Atherosclerosis in rheumatic disease

Rheumatoid arthritis

Patients with RA have an increased risk of developing cardiovascular disease, in particular coronary artery disease.^{7,18–25} The main cause of cardiovascular deaths in patients with RA is ischaemic heart disease^{26,27}—several studies have shown a more than twofold increase in the frequency of myocardial infarction (MI) in patients with RA when compared with age-matched individuals.^{25,28,29}

Patients with RA were also shown to have higher case fatality after an acute MI than patients without RA.²⁹ Scoring systems such as the Framingham Risk Score do not adequately capture this increased risk in patients with RA.³⁰ Therefore, RA might have an important effect on the development of premature atherosclerosis, even in the absence of traditional risk factors.^{22,31,32}

As a result of chronic inflammation, patients with RA also have dyslipidaemia, including a decreased HDL-cholesterol level, and an increased small LDL-cholesterol level.^{26,27} Intriguingly, the coronary vasculature is affected by accelerated atherosclerosis.^{18–23} An increase in the cumulative incidence of silent MI and sudden cardiac death is observed in patients with RA compared with individuals without RA (Figure 3).³³ Moreover, when compared with healthy individuals, patients with RA and patients with type 2 diabetes mellitus have a similar risk of developing cardiovascular events, suggesting that RA, similarly to diabetes, is an important risk factor for cardiovascular disease (Figure 4).³⁴

Patients with RA have higher case fatality after an acute MI than the general population.²⁹ Given the increased risk of premature atherosclerosis, aggressive control of traditional risk factors is particularly important in these patients.¹⁸ Additional, noninvasive assessments might be considered, but widespread screening of patients with RA with carotid ultrasonography and calcium scoring is not currently mandated owing to limited supporting data on the efficacy of these tools in patients with RA.¹⁸ Nevertheless, these approaches are used in focused subspecialty clinics to define and assess the effect of autoimmune disorders on increased cardiovascular risk.

Cardiovascular disease is also a leading cause of morbidity and mortality among patients with SLE.^{7,35} Death second ary to cardiac causes has been described as the major cause of ‘late’ death in patients with SLE, who are at increased risk for premature atherosclerosis and coronary artery disease.¹⁸ This observation is thought to be independent of traditional risk factors, because SLE itself has been shown to be a substantial risk factor for the development of atherosclerosis.^{36,37} Older age at diagnosis, longer duration of both immunosuppressive therapy and disease, and elevated homocysteine levels have all been associated with subclinical atherosclerosis in patients with SLE.^{18,38–43}

In addition to the role of inflammation in accelerating atherosclerosis (as occurs in other autoimmune rheumatic diseases), patients with SLE have antinuclear antibodies which might have a pathophysiological role—indeed, antinuclear antibodies have been associated with increased risk of cardiovascular disease and mortality in patients with SLE,^{4,44} possibly explaining why cardiovascular disease is a leading cause of morbidity and late mortality in these patients.^{35,45}

Systemic sclerosis

In addition to RA and SLE, patients with systemic sclerosis (SSc) might also have an increased risk of atherosclerosis secondary to changes in the vascular wall. The underlying mechanisms for atherosclerosis in patients with SSc involve endothelial injury and reduced oxygen transport to tissues.²⁷ Patients with SSc have diffuse involvement of the entire microcirculation and macrocirculation, and undergo oxidation which promotes inflammation of the vessel wall, injury to the endothelium, and subsequent release of cytokines. This inflammatory cascade leads to upregulation of inflammatory markers such as CRP and homocysteine, further contributing to an increase in the risk of atherosclerosis.^{43,46,47}

SSc is also associated with increased stiffness of the vasculature: a study of patients with both limited and diffuse disease showed increased carotid artery stiffness when compared with control individuals.⁴⁸ Statins can help to manage microvascular and macrovascular involvement of SSc.²⁷ Additional invasive or noninvasive testing to assess endothelial function might be useful to estimate the cardiovascular risk in these patients.

Antiphospholipid syndrome

Patients with antiphospholipid syndrome (APS), a disorder characterized by a prothrombotic state with a high propensity for recurrent arterial and venous thrombosis, and by the presence of antiphospholipid antibodies, also have an increased risk of atherosclerosis.⁴⁹

Atherosclerosis in patients with APS is thought to result from direct proinflammatory and prothrombotic activity of antiphospholipid antibodies on endothelial cells, as well as other inflammatory mechanisms that can result in autoantibody-mediated thrombosis.^{45,50–52} A high prevalence of antibodies to β 2-glycoprotein I (also known as apolipoprotein H) in patients with APS has also been observed; the measurement of such mediators might be helpful in predicting the risk of venous and arterial thrombosis.⁵³ Additionally, antiphospholipid antibodies might be able to crossreact with oxLDL in patients with SLE.

Whereas patients with APS do not have an increased likelihood of developing cardiovascular risk factors, the pathogenesis of accelerated atherosclerosis is probably secondary to nontraditional risk factors, such as antiphospholipid antibodies, which are thought to have an important role in the development of arterial atherosclerosis.^{51,52} As such, patients with APS should be treated with aggressive management of traditional risk factors.⁴⁹

Vasculitis

Systemic vasculitides, such as giant cell arteritis, Takayasu arteritis, polyarteritis nodosa, and anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, are immune-mediated rheumatological diseases characterized by inflammation of the vasculature that results in accelerated atherosclerosis. In patients with vasculitis, the intima of affected blood vessels becomes activated, leading to endothelial cell activation and damage, and an ensuing immune response—factors that can all promote atherosclerosis.⁴ After activation, endothelial cells can expose adhesion molecules and secrete cytokines. This increase in secretion of mediators of inflammation promotes enhanced adhesion between the endothelial cells and monocytes, and serves as a proatherogenic substrate by promoting plaque formation. In addition to inflammatory reactions that can lead to atherosclerosis, vasculitis might also promote increased expression of autoantigens (such as heat shock proteins) on activated endothelial cells. Furthermore, accumulation of oxLDL can promote activation of endothelial cells, monocytes, and macrophages, as well as formation of foam cells. Importantly, patients with vasculitis have generalized endothelial dysfunction characterized by impaired endothelium-dependent vasodilatation.⁵⁴

Valvular manifestations

Valvular manifestations are common among patients with rheumatological conditions, particularly in patients with RA, SLE, APS, or ankylosing spondylitis.^{21,38,55} Several studies have shown that patients with RA and SLE are more likely to have valvular calcifications, which can affect up to 80% of patients; this effect might be mediated by mechanisms similar to those promoting accelerated atherosclerosis.⁵⁶

Rheumatoid arthritis

Patients with RA have an increased incidence of valvular disease when compared with the general population. Valvular disease can be seen by echocardiography or in autopsies in ~30% of patients with RA, but is normally clinically silent.¹ Mitral regurgitation is the most common valvular disorder among patients with RA, affecting up to 80% of patients, but, again, is not necessarily clinically relevant.³⁸ In a study of individuals undergoing transoesophageal echocardiography, mitral regurgitation was reported in 80% of patients with RA compared with 37% of the control population; no differences in the prevalence of aortic or tricuspid regurgitation were observed between the two groups.⁵⁷

Systemic lupus erythematosus

SLE is associated with both endocarditis and the presence of valve nodules, and transoesophageal echocardiography has revealed that >50% of patients with SLE have valvular abnormalities.¹⁸ Valvular nodules are fairly common on autopsy reports of patients with SLE, but are not clinically relevant.¹⁸ Endocarditis is a common complication of SLE, but is often asymptomatic and detected only on autopsy studies.¹⁸ Nonbacterial vegetations, also referred to as Libman–Sacks vegetations, have been reported in up to 60% of patients with SLE in autopsy studies.⁵⁸ These vegetations are generally univalvular, small, and left-sided, and can be seen in up to 15% of mitral valves and 19% of aortic valves.^{18,59,60}

Nonbacterial vegetations are often associated with the presence of antiphospholipid antibodies.

Although any valve can be affected in patients with SLE, vegetations are most commonly located on the atrial sides of the mitral and aortic valves.¹⁸ Currently, no guidelines exist on when to initiate antibiotic prophylaxis, but administration of prophylactic antibiotics should be considered.³⁸

High levels of anticardiolipin immunoglobulin G (IgG) antibodies were associated with the development of severe valvular regurgitation and a high incidence of thromboembolic events in patients with SLE, dictating the need for valvular surgery. Treatment of Libman–Sacks endocarditis involves aggressive control of SLE and lifelong anticoagulation therapy, owing to the potential risk of thromboembolic events.⁵⁸

Ankylosing spondylitis

Ankylosing spondylitis has also been associated with both aortic disease and aortic regurgitation, and is characterized by severe thickening of the aortic wall owing to scarring and intimal proliferation.^{61,62} Both aortic valve and aortic root thickening have been shown on transoesophageal echocardiographic studies with an incidence of 5–13%.⁶¹ In a study of patients with ankylosing spondylitis undergoing transoesophageal echocardiography, 61% had aortic root thickening and stiffness, and 25% had aortic root dilatation; aortic valve thickening was reported in 41% of patients, and 50% had valvular regurgitation.⁶¹ Valvular disease seemed to be unrelated to progression of ankylosing spondylitis.⁶¹

Myocardial manifestations

Autoimmune rheumatic diseases can also directly affect the myocardium, and present as myocarditis or myocardial dysfunction secondary to a variety of inflammatory and autoimmune mechanisms. Not all myocardial manifestations of rheumatological conditions are clinically relevant, but myocardial involvement can confer considerable morbidity and mortality.^{38,63}

Rheumatoid arthritis

RA predisposes patients to the risk of myocardial disease, although typically not resulting in clinical manifestations.⁶³

Patients with RA have an increased risk of myocardial dysfunction and congestive heart failure independently of traditional risk factors for cardiovascular disease.⁶⁴ The underlying aetiology of heart failure in patients with RA is uncertain, but both left ventricular systolic and diastolic dysfunction has been reported in these patients.^{9,63,65,66}

Furthermore, rheumatoid factor-positive patients were at increased risk of developing congestive heart failure in a population-based study, even after adjusting for ischaemic heart disease and traditional risk factors.⁶⁴ Amyloidosis leading to myocardial dysfunction was also diagnosed frequently in patients with RA in the past, but is now a rare observation.⁶³

Systemic lupus erythematosus

Despite being a common manifestation of some rheumatological conditions, myocarditis is rarely observed in patients with SLE, in whom the prevalence of myocarditis has been reported to be low in both autopsy and clinical studies.¹⁸ Nevertheless, patients with myositis (a possible complication of SLE) might be at increased risk of developing myocarditis. SLE is associated with abnormalities of myocardial function assessed using echocardiography—dysfunctions that can be multifactorial and secondary to ischaemia, hypertension, renal failure, valvular disease, or arterial stiffness.

Arterial thickness can predispose patients with SLE to left ventricular hypertrophy and elevated left ventricular ejection fraction owing to increased end-diastolic and end-systolic dimensions.¹⁸ Cardiomyopathy can be diagnosed by endomyocardial biopsy, which can reveal myocardial fibrosis, mononuclear cell infiltrates, and immune complex deposition.⁵⁶ Patients with SLE are commonly treated with hydroxychloroquine as a component of therapeutic strategies, potentially placing patients at increased risk of cardiomyopathy.

Systemic sclerosis

Myocardial fibrosis is an important cardiac manifestation of SSc.⁶⁷ Fibrosis can cause both coronary vasospasm, triggered by cold or exertion, and left ventricular systolic and diastolic dysfunction.^{67,68} Pulmonary involvement of SSc might result in pulmonary hypertension and associated myocardial changes, whereas renal involvement might cause underlying hypertension and left ventricular hypertrophy. Myocardial abnormalities, including segmental wall motion abnormalities and impaired coronary flow reserve, occur in the absence of coronary artery disease.¹⁸ In patients with SSc, almost half of autopsies reveal contraction band necrosis, reperfusion lesions, and fibrosis in both ventricles, despite coronary arteries being normal.¹⁸ Microvascular disease is characteristic of SSc and can affect both the right and left ventricles, manifesting as a considerably reduced right ventricular ejection fraction with normal pulmonary artery pressures.¹⁸

Pericardial manifestations

Rheumatoid arthritis

Pericarditis is a common manifestation of rheumatological disorders and is usually secondary to underlying inflammation. In patients with RA, pericarditis is the most common cardiac manifestation,³⁸ affecting up to 50% of patients as detected on postmortem examination. However, clinical evidence of pericarditis is considerably less frequent, and generally affects 10% of patients with severe RA.^{1,69} Pericarditis is mostly diagnosed on autopsy or using echocardiography, and silent pericardial effusions are encountered frequently. Chronic pericarditis has the potential to result in pericardial calcification, and both immune complexes and rheumatoid factor can be found in pericardial fluid, which is characterized by neutrophil infiltrates, high protein levels, low glucose levels, and low complement levels.³⁸ Constrictive pericarditis can also develop in patients with RA, but is usually clinically silent.⁷⁰

Systemic lupus erythematosus

Pericarditis and pericardial effusion are the most common cardiac manifestations of SLE.⁶³ In several clinical studies, 20–50% of patients had pericardial involvement,^{38,63,71–73} and an even higher prevalence of pericardial involvement (60% of patients) has been suggested in autopsy series.⁷²

Patients typically present with chest pain, but pericardial effusions are usually mild and mostly do not result in cardiac tamponade and haemodynamic compromise.⁷¹

Constrictive pericarditis is rare in patients with SLE. Analysis of pericardial fluid has revealed exudative fluid with neutrophilic predominance, elevated protein levels, and low or normal glucose levels.⁷²

Systemic sclerosis

In patients with SSc, autopsy studies have shown pericardial involvement, but clinically relevant pericardial disease is rare. Pericardial effusions have been noted in up to 14% of echocardiographic studies.⁶⁸

Electrical abnormalities

Conduction abnormalities are an important cause of cardiovascular morbidity and mortality in patients with rheumatological disease, and predominantly affect those with RA, SSc, and ankylosing spondylitis.⁷⁴ Notably, patients with rheumatic disease have a higher incidence of conduction abnormalities and sudden cardiac death than the general population.^{74,75}

Rheumatoid arthritis

In patients with RA, underlying coronary artery disease predisposes patients to an increased risk of sudden cardiac death and ventricular arrhythmias.^{74,76} Rheumatoid nodules are also thought to predispose patients to cardiac involvement.⁷⁷ In a study to compare patients with non-nodular RA or nodular RA with control individuals, patients with nodular RA had not only larger aortic root diameter and lower ejection fraction, but also had <1 mm ST-segment depression on 24 h Holter monitoring, when compared with individuals in the control group.⁷⁷

Patients with RA can develop electrical abnormalities owing to rheumatoid nodules, underlying amyloidosis, or cardiomyopathy,⁷⁸ and are also thought to have increased sympathetic activity—a potential risk factor for ventricular tachyarrhythmias.⁷⁹ QT dispersion, a marker of cardiovascular morbidity and mortality that is useful in predicting ventricular arrhythmias, is considerably longer in patients with RA than in healthy controls, further suggesting an increase in cardiovascular risk in these patients.⁷⁸

Systemic lupus erythematosus

Sinus tachycardia, atrial fibrillation, and ectopic atrial beats are the most common electrophysiological abnormalities in SLE. Supraventricular arrhythmias are often associated with exacerbation of SLE or are caused by myocarditis.⁷⁴ Hydroxychloroquine therapy has

been associated with prolonged QT interval on electrocardiography and sinus bradycardia.⁸⁰ Patients with antibodies to small cytoplasmic ribonucleoproteins have an increased risk of sinus bradycardia and QT-interval prolongation.^{81,82} Sinus tachycardia, suggested as a marker of disease severity in patients with SLE, can be resolved with corticosteroid therapy.⁸³

Systemic sclerosis

Myocardial fibrosis predisposes patients with SSc to electrical abnormalities. Up to 30% of patients with SSc might have supraventricular arrhythmias, including atrial fibrillation, flutter, or paroxysmal supraventricular tachycardia.⁷⁴ Ventricular arrhythmias have been demonstrated in up to 67% of patients with SSc.⁸⁴ Premature ventricular contractions are associated with a 50% mortality, compared with 8% in patients without ectopy. SSc can also predispose patients to an increase in the risk of electrical abnormalities owing to fibrosis of the sinus node and bundle branches. These conditions have been explored in invasive electrophysiological studies, revealing diffuse conduction system disease and increased risk of tachyarrhythmias in patients with SSc.^{18,85}

Ankylosing spondylitis

Ankylosing spondylitis can cause conduction abnormalities primarily owing to postinflammatory scarring of the myocardium. The most common manifestation is first-degree atrioventricular block,¹⁸ and human leukocyte antigen (HLA)-B27-positive patients with spondylo arthritis are at elevated risk of developing heart block.⁸⁶

Cardiovascular care in rheumatology

The increased risk of cardiovascular disease in patients with systemic autoimmune rheumatic disease requires appropriate management. Given the increased risk of premature atherosclerosis—despite lack of traditional risk factors—in patients with RA, adherence to primary prevention guidelines is crucial.¹⁸ Patients with RA might have a lower target LDL-cholesterol level; therefore, aspirin therapy might be considered owing to the increased cardiovascular risk observed in this patient population. Nevertheless, widespread screening of patients with RA using carotid ultrasonography and calcium scoring is not currently mandated owing to limited data.¹⁸

Several drugs have been suggested to be appropriate to manage cardiovascular disease in patients with autoimmune disorders. Disease-modifying antirheumatic drugs (DMARDs) were shown to reduce progression of atherosclerosis in patients with RA in several studies.^{87–89}

For example, methotrexate seemed to increase survival, potentially suggesting that early initiation of DMARD therapy might be appropriate for cardiovascular prevention, in addition to the management of the systemic disease.⁸⁷ Interestingly, a group of patients with RA, subclinical atherosclerosis, and endothelial dysfunction was reassessed prospectively after DMARD therapy: after 1 year, both the carotid intima-media thickness and endothelial-dependent flow-mediated vasodilatation were improved.⁸⁹ Anti-TNF therapies

can also reduce atherosclerosis-promoting systemic inflammation. Consequently, these agents might be associated with improvement of cardiovascular disorders in patients with autoimmune rheumatic disease. Improvement in inflammatory joint disease might also be associated with a reduction in the number of cardiac events, further supporting the use of disease-modifying agents.^{90,91}

Management of electrical abnormalities is based on the underlying pathogenesis, and is similar to the management of patients who have no rheumatic disease. Primarily, antiarrhythmic pharmacological therapy is used to manage electrical abnormalities. Digoxin is often used to decrease ventricular response in end-stage heart failure, similarly to approaches used in patients without rheumatological complications. β -Blockers are used to manage sinus tachycardia in patients with SLE but, in general, should be avoided in patients with SSc, vasculitis, and those who might have pulmonary hypertension.⁶³ Patients with a history of ventricular fibrillation undergo implantation of a cardioverter–defibrillator, and might be considered for cardiac resynchronization therapy depending on overall prognosis and degree of the myocardial dysfunction. Additionally, radiofrequency ablation can be considered for patients with symptomatic, sustained monomorphic ventricular tachycardia, especially if they are also drug-resistant, as well as for those with symptomatic, premature ventricular contractions.

Cardiovascular morbidity and mortality are recognized consequences of autoimmune rheumatic diseases, and efforts must be made to manage and treat patients with these conditions. The field of cardiorheumatology is emerging with the development of several focused clinics worldwide that indicate the increased need for cardiovascular care among patients with autoimmune inflammatory rheumatological diseases. The high prevalence of cardiovascular abnormalities and diverse sequelae require focused management and diagnosis of potential cardiovascular abnormalities to reduce cardiovascular morbidity and mortality. Whereas several cardiovascular manifestations of rheumatological diseases are clinically silent, the diagnosis and management of these disease processes is crucial. Endothelial dysfunction is a precursor to atherosclerosis, and patients with early atherosclerosis can be diagnosed by noninvasive assessment of endothelial function. Currently, no studies supporting routine screening for endothelial function exist. However, given the high risk of cardiovascular disease, noninvasive risk-factor assessment—including endothelial function assessment—might be warranted in patients with a high propensity for development of atherosclerosis, especially those with RA or SLE. Early diagnosis and appropriate preventive management are the cornerstones to reducing the burden of cardiovascular disease among patients with inflammatory autoimmune disease.

Conclusions

Autoimmune rheumatic diseases can cause a variety of cardiovascular complications that affect the vasculature, valves, myocardium, pericardium, and conduction system. Whereas many of these manifestations are often clinically silent, the high prevalence of cardiovascular disease in patients with rheumatic conditions should be recognized by clinicians and adequately managed. Early recognition and management of traditional

cardiovascular risk factors is essential, along with aggressive treatment with disease-modifying agents to improve the long-term prognosis of these patients.

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Figure 1.

Multiple cardiovascular manifestations of rheumatic diseases. Autoimmune systemic diseases can have multiple associated cardiovascular manifestations, which can largely be categorized as being vascular, myocardial, valvular, pericardial, or electrical.

Figure 2.

Common mechanisms underlying atherosclerosis and rheumatoid arthritis. Both conditions are associated with upregulation of TNF- α , metalloproteinase expression, upregulation of IL-6, T-cell activation, elevated C-reactive protein level, increased expression of adhesion molecules and endothelin, and activation of macrophages. Autoantibodies to oxLDL participate in development of both atherosclerosis and rheumatoid arthritis. Abbreviations: IL-6, interleukin-6; oxLDL, oxidized low-density lipoprotein; TNF- α , tumour necrosis factor- α ; VCAM-1, vascular cell adhesion protein 1. Reprinted with modifications with permission from Elsevier © *Am. J. Med.* 121 (Suppl. 1), Libby, P. Role of inflammation in atherosclerosis associated with rheumatoid arthritis, S21–S31 (2008).

Figure 3.

Cumulative incidence of cardiovascular manifestations in patients with or without RA.

Cumulative incidence of silent MI, sudden cardiac death, and angina in cohorts with or without RA, after adjusting for the competing risk of death from other causes.

Abbreviations: MI, myocardial infarction; RA, rheumatoid arthritis. Permission obtained from Wiley © Maradit-Kremers, H. *et al.* Increased unrecognized coronary heart disease and sudden deaths in rheumatoid arthritis: a population-based cohort study. *Arthritis Rheum.* 52, 402–411 (2005).

Figure 4.

Cumulative incidence of congestive heart failure in patients with or without RA. Patients with T2DM and patients with RA have a similar cumulative incidence of congestive heart failure, after adjusting for the risk of death from other causes, compared with individuals without RA or diabetes. Abbreviations: RA, rheumatoid arthritis; T2DM, type 2 diabetes mellitus. Permission obtained from Wiley © Peters, M. J. *et al.* Does rheumatoid arthritis equal diabetes mellitus as an independent risk factor for cardiovascular disease? A prospective study. *Arthritis Rheum.* 61, 1571–1579 (2009).