Cardiovascular Diseases and Rheumatology

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16.1 Introduction

The prevalence of various cardiovascular diseases (CVD) in the different rheumatologic disorders is a very important topic. Each disease has a number of unique manifestations despite the fact that an overlap is present due to shared common risk factors, which may be related to the longer life expectancy of the recent therapeutic advances. A growing understanding of the role of inflammation and immune system in the initiation and progression of atherosclerosis as well as the early detection of cardiovascular manifestations is due to the availability and use of sophisticated noninvasive cardiac and vascular diagnostic technology. Such discipline results in the detection of cardiac manifestation unique to each rheumatologic disorder. This was not possible previously due to short life expectancy, limited therapeutic interventions, vague understanding

of pathological process for each disease, and the limited diagnostic resources.

Cardiovascular diseases (CVD), including coronary artery diseases (CAD), can be present at the time of or after the diagnosis of rheumatologic disease. Cardiovascular association can be the principal introduction of the rheumatologic diseases in case of late diagnosis. The manifestations of CVD in rheumatologic diseases vary from subclinical to severe manifestations [4, 5], and they involve different structures of the heart. They can lead to significant morbidity and mortality. Therefore, we need to draw attention to their symptoms, to the risk factors that contribute to CVD development, as well as adaption of preventive measures that may control them. We will also consider the coronary artery disease (CAD), which maybe a crucial contributor to morbidity and mortality in numerous rheumatological diseases [6–9].

The prevalence of atherosclerotic CAD is increased in patients with chronic inflammatory rheumatic diseases, particularly in those with systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) [10, 11]. The increased risk of CAD results from both traditional risk factors and factors unique to these rheumatic diseases [12, 13]. For example, accelerated atherosclerosis is one of the important risk factors for the development of CAD, and it can be attributed to the prolonged inflammatory process in these diseases, vascular endothelial dysfunction, and a specific form of

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low-density lipoprotein (LDL). The importance of metabolic syndrome in various rheumatic diseases and its implications on morbidity and mortality will be discussed as metabolic syndrome, which is commonly diagnosed among those patients and also plays an important role in the CVD development [14–16].

Several medications are now used in the management of various rheumatologic diseases, which can affect the development of CAD—either by decreasing or increasing the CAD severity or by decreasing or increasing its risk factors. In fact, many discussions are held nowadays with focus on how and when to use them. For example, the use of aspirin and statins in rheumatology and their effect on CAD. We will discuss the latest guidelines for their use here.

In this chapter, we address the various cardiovascular events that patients are exposed to, with CAD as one of the major factors that increase their mortality [10]. We will also discuss the

important areas in regard to the identification of high-risk groups that need interventions, how to decrease the risk of CAD in these groups, and the way to better understand the effects of common medications on the risk of CAD in these patients.

16.2 Cardiovascular Manifestations in the Rheumatic Diseases

In this section, we look at CVD involvements in the different rheumatologic diseases and address the important issues in regard to their development (Tables 16.1 and 16.2 give a summary of the points given below).

The coronary artery disease (CAD) contributes significantly to the morbidity and mortality in various rheumatic diseases, whereas the occurrence of atherosclerotic CAD is increased in patients with chronic inflammatory rheumatic

Table 16.1 Type of CVD diseases

Disease	CVD	
RA	Atherosclerotic	<ul style="list-style-type: none"> • Myocardial infarction. • Congestive heart failure. • Peripheral arterial disease.
	Non-atherosclerotic	<ul style="list-style-type: none"> • Pericarditis. <p>It is possible to occur as an inflammatory manifestation of RA.</p> <ul style="list-style-type: none"> • Myocarditis and endocarditis. <p>They are also possible to occur as a complication in RA.</p> <ul style="list-style-type: none"> • Vasculitis. <p>(e.g., aortitis, coronary arteritis)</p> <p>It can cause neurovascular disease (e.g., mononeuritis multiplex), cutaneous ulceration, or organ infarction based on the affected artery.</p> <ul style="list-style-type: none"> • Other less common complications. <p>Conduction abnormalities</p> <ul style="list-style-type: none"> • Amyloidosis. • Pulmonary hypertension.
SLE	Pericardium	<ul style="list-style-type: none"> • Pericarditis. • Pericardial effusion.
	Myocardium	<ul style="list-style-type: none"> • ECG findings: Prolonged PR intervals. • MRI to help in diagnosis.
	Endocardium and valves	<ul style="list-style-type: none"> • Systolic murmur: Possibly from hyperdynamic state because of anemia. • Libman-sacks endocarditis .
Systemic sclerosis	Histology of CVD in SSc	<ul style="list-style-type: none"> • Hemosiderin deposits. • Involvement of subendocardial layers.
	Myocardium	<ul style="list-style-type: none"> • Fibrosis affects the myocardium in both ventricles and the conducting system. • Tricuspid regurgitation.
	Pulmonary arteries	<ul style="list-style-type: none"> • Pulmonary hypertension with irreversible fibrosis at the arterial walls, which will cause resistance against right ventricular contraction.

Table 16.1 (continued)

Disease	CVD	
Antiphospholipid syndrome	CAD	<ul style="list-style-type: none"> • MI and cardiac death with APL positive. • Unstable angina.
	Valvular disease	<ul style="list-style-type: none"> • Mitral, aortic, and less common in tricuspid valves. • It can progress to heart failure.
	Pseudo-endocarditis	<ul style="list-style-type: none"> • Vegetation commonly at the mitral and aortic valves. • High APL. • Blood culture is negative for infection.
	Peripheral artery disease	<ul style="list-style-type: none"> • At lower extremities.
	DVT	<ul style="list-style-type: none"> • Most common venous manifestation. • Pulmonary embolism is a common eventual complication.
	Intracardiac thrombus	<ul style="list-style-type: none"> • Not common and usually misdiagnosed.
Ankylosing spondylitis	Conduction defects	Inflammation and fibrosis of interventricular septum will cause damage of atrioventricular node, which can lead to first, second, and third-degree heart block and bundle branch block
	Aortic incompetence	Aortic wall inflammation (aortitis) above and behind sinuses of valsalva, and may extend below to the aortic roots and the wall of the mitral valve
	Left ventricular dysfunction	A possible increased connective tissue involvement in the myocardium
	Less common	<ul style="list-style-type: none"> • Pericarditis. • Cardiomyopathy. • Mitral valve disease. • Endocarditis .
Psoriatic arthritis	<ul style="list-style-type: none"> • CAD • Cerebral vascular disease. • Peripheral vascular disease. 	
Inflammatory myopathies	<ul style="list-style-type: none"> • Myocarditis. • CAD. • Affected myocardial small vessels . 	
Systemic vasculitis	<ul style="list-style-type: none"> • CAD • Myocardium, pericardium, endocardium, and conduction system involvements. • Peripheral vascular disease. 	

Table 16.2 Summarized types of CVD in rheumatologic diseases

Disease	RA	SLE	APS	SSc	AS	PsA
MI	✓	✓	✓	✓	✓	✓
CHF	✓	✓		✓	✓	
PAD	✓	✓	✓			✓
PH				✓		
Myocardial diseases	✓	✓		✓	✓	✓
Endocardial diseases	✓	✓	✓		✓	
Valvular disease	±	✓	✓		✓	
Pericarditis	✓	✓		✓	✓	
Arteritis (coronary, aorta)						
Conduction defects	±			✓	✓	✓

Symbol definitions, MI: Myocardial infarction, CHF: Congestive heart failure, PAD: Peripheral arterial disease, PH: Pulmonary hypertension, SSc: Systemic sclerosis, AS: Ankylosing spondylitis, PsA: Psoriatic arthritis. ±: in case of rheumatoid nodule

diseases, particularly those with SLE and RA. This again is emphasizing the importance of those conditions to the development of CAD. This increased risk is mediated by the presence of both traditional risk factors and factors unique to those with systemic inflammatory disorders. It is a matter of higher risk as well as the presentation.

A larger proportion of patients with RA has a clinical silent CAD in comparison to demographically similar individuals in the general population. Patients with RA are also less likely to report chest pain during an acute coronary event than those without RA. It is still uncertain why this is happening, but acceptable explanations include the following: many patients with active disease and joint damage are less physically active; therefore, they are less likely to place suf-

ficient demand on the heart to elicit angina, which may attribute to RA pain. Patients with CAD tend to use nonsteroidal anti-inflammatory drugs (NSAID), glucocorticoids, or disease-modifying antirheumatic drugs (DMARDs), which can change their pain perception. Patients with rheumatoid arthritis (RA) have a reduced life expectancy when compared with the general population. Cardiovascular death is considered the leading cause of mortality in patients with RA; it is responsible for approximately half the deaths observed in RA [8]. Epidemiologic studies have shown that this increased mortality is largely attributed to cardiovascular diseases, primarily CAD. Considerable evidence suggests that inflammation plays a role in the pathogenesis of atherosclerosis [10]. The prevalence of cardiovascular comorbidity is difficult to assess accurately since CAD has a tendency to remain silent in the rheumatoid patients, but deaths from CVD occur earlier than in the general population. It has also been suggested that the increased risk of CAD in RA precedes the onset of clinical rheumatoid disease [17].

The lowering of CAD morbidity and mortality by recognizing patients at risk, and revealing their nontraditional¹ risk factors as well as their contribution in developing cardiovascular complications are important. Many rheumatic diseases have their share of these complications, e.g., RA, SLE, and vasculitis. The studies showed the importance of prevention strategies. Furthermore, many studies have been discussing various reasons of the increased in cardiac manifestations and the risk of mortality due to CAD. One could be the increase of traditional risk factors and its explanation. The second could be the special nontraditional risk factors, which are related to the pathophysiology of rheumatic diseases (See Tables 16.1 and 16.2).

Traditional risk factors include smoking,² hypertension, diabetes mellitus (DM), hyperlipidemia, and obesity [12].

The **nontraditional risk factors** are associated with elevation of CAD occurrences, which include severity of the disease, more extra-articular manifestation at presentation, corticosteroids, NSAIDs, and the low socioeconomic status. The presence of the accelerated atherosclerosis in those patients is associated with CAD development and subsequently the increased mortality from CAD in them (Tables 16.3 and 16.4).

16.2.1 Rheumatoid Arthritis (RA)

Rheumatoid arthritis is a chronic systemic inflammatory disease, which affects approximately 1% of the adult general population [18]. It has many extra-articular manifestations (e.g., heart and lung) in about 40% of patients with RA over their life time [19]. The mortality gap in comparison to the general population widened with the dramatic improvement in the overall mortality rate in the latter group [20]. For example, if we compare the general population to the patients with RA, there is an increased incidence of cardiovascular events, including myocardial infarction, stroke, and cardiac death among the patients with RA.

Cardiovascular disease is recognized as the leading cause of death in RA patients, accounting for nearly 40% of mortality [18]. Patients with RA are at twofold increased risk for myocardial infarction and stroke, with risk increasing to nearly threefold in patients who have had the disease for 10 years or more [18]. Congestive heart failure appears to be a greater contributor to excess mortality than ischemia. This increased cardiovascular disease risk in RA patients seems to be independent of traditional cardiovascular risk factors. Pathogenic mechanisms include pro-oxidative dyslipidemia, insulin resistance, prothrombotic state, hyperhomocysteinemia, and immune mechanisms, such as T-cell activation

¹Patients are exposed to both the traditional risk factors of CAD and the nontraditional risk factors related to their disease.

²Apart from the known effects of smoking on CAD, it

increases the severity of the rheumatoid arthritis, which can lead to atypical manifestation of the CAD and increasing the difficulty of the early detection (Tables 16.3 and 16.4).

Table 16.3 Prevalence of traditional risk factors

Prevalence	Smoking	Hypertension	DM	Dyslipidemia	Obesity
RA	↑↑	↑	↑↑	↑↑	↑
SLE	↑	↑↑	↑	↑	↑
General population	↑	↑	↑	–	↑

Table 16.4 Effects of traditional risk factors on RA

Effects of	RA
Smoking	↑RA development ↑ RF and ACPA-positive RA ↑worse prognosis
Hypertension	↑more than the general population, it is unclear whether it is from under diagnosis or from under treatment ↑BP from NSAIDs, chronic corticosteroids, leflunomide, and cyclosporine
DM	Possible association between RA and insulin resistance Can predict a new cardiovascular event
Dyslipidemia	↓ or ↑ Total lipid ↓ or ↑ LDL ↓HDL Can predate the diagnosis of RA
BMI	↑BMI and obesity = ↑other traditional risk factors = ↑worse prognosis = CVD ↓BMI and cachexia = acute inflammation

that subsequently lead to endothelial dysfunction, a decrease in endothelial progenitor cells, and arterial stiffness, which are the constituents of accelerated atherosclerosis observed in RA patients [18]. These patients are greatly susceptible to CAD (myocardial infarction and angina), heart failure, pericarditis, myocarditis, atrial fibrillation, valvular heart disease, and cardiac amyloidosis.

16.2.1.1 Pericarditis

Pericarditis is the most common cardiac manifestation in RA, which is usually an asymptomatic disease. Clinical pericarditis is observed in around 4% of the patients [21], which is lower than the autopsy proven one that occurs in around 30%–50% of patients with RA [22]. Patients with

RA are more likely to develop pericardial effusion than the ones without RA by ten times [23]. Most of the patients develop the pericardial effusion after the onset of the arthritis; however, RA was diagnosed after pericardial effusion in a minority of patients [3]. The variables associated with the development of extra-articular manifestations including pericarditis are as follows: male gender, presence of increased serum concentrations of rheumatoid factor, joint erosions, subcutaneous nodules, number of disease-modifying antirheumatic drugs (DMARD), presence of nail fold lesions, and any other extra-articular feature 1 year before the time of the diagnosis, or treatment with corticosteroids at the time of the diagnosis [21].

Patients with findings of edema, shortness of breath, chest pain, raised jugular venous pressure, pericardial rub, and paradoxical pulse were found to have 100% mortality rate within 2 years [4]. In patients with pericardial effusion, the diagnosis of RA was mainly clinical without the need for invasive procedure [3]. Biologic agents are now considered one of the cornerstones of RA therapy associated with the development of pericardial effusion mostly within 4 months of the start of the infliximab and etanercept [24]. Purulent pericardial effusion was reported in patients receiving infliximab and etanercept [25, 26].

Treatment: Although most of the evidence came from patients with immune-mediated pericarditis, it can be extrapolated to the RA-associated pericarditis as follows:

1. Asymptomatic disease usually diagnosed accidentally will resolve spontaneously.
2. Symptomatic disease therapy includes the following:
 - Nonsteroidal anti-inflammatory drug (NSAID) is the mainstay therapy for idio-

pathic pericarditis, and the two agents that proved their efficacy are ibuprofen and indomethacin [27].

- Corticosteroids: low- to moderate-dosage prednisone (0.2–0.5 mg/kg per day) for 4 weeks and then slowly tapered, if the patient is intolerant to aspirin or NSAID or with pericardial effusion [27].
- Colchicine: in patients with acute and recurrent pericarditis in addition to aspirin or NSAID in the dose of 0.5 mg twice daily in patients >70 kg and 0.5 mg once daily in patients ≤70 kg [27].
- If previous medical treatment fails, there is growing evidence for oral azathioprine, intravenous human immunoglobulins, and anakinra [27].
- Tocilizumab was reported to be successful too [28, 29].
- Surgical management includes pericardiocentesis, pericardiectomy, or pericardiotomy in the cases of hemodynamic compromise, cardiac tamponade, or constrictive pericarditis.
- Biologic-agents-associated pericarditis should be stopped and treated accordingly [24].
- Purulent pericarditis with biologic agents should be stopped and antibiotic therapy to be used accordingly [25, 26].

16.2.1.2 Myocardial Involvement

Myocarditis is less common than RA-associated pericarditis. It was found in 19% of patients with RA based on post-mortem study where the majority were females with active arthritis; however, most of the patients with myocarditis were clinically asymptomatic [30].

Cardiomyopathy with finding of left ventricle hypertrophy (LVH) was found in around 37% of asymptomatic RA patients by echocardiography [31]. The pathohistological finding was either diffuse or focal inflammation of the myocardium [32].

Diagnosis: The left ventricle function is usually evaluated with echocardiography, but it has a limited role in the evaluation of myocardium involvement. Cardiac magnetic resonance imag-

ing (CMR) is helpful as noninvasive evaluation tool for myocarditis as it shows increased T2-weighted edema ratio (ER) score suggesting myocardial tissue edema. It has a role too in identifying the chronicity of myocarditis [33].

Treatment: Conventional therapy to support the left ventricle function is generally used. High-dose prednisolone (60 mg) daily for 2 months, tapered over 4 months followed by maintenance dose, normalizes the left ventricle ejection fraction and the gallium uptake [34].

Antimalarials-Induced Cardiotoxicity

Hydroxychloroquine and chloroquine are medications initially used as antimalarial treatment. They found to be effective as disease-modifying antirheumatic drugs. Hydroxychloroquine-induced cardiotoxicity has been reported in patients with RA [35].

Risk factors: Old age, female sex, long duration of therapy, high daily dose, preexisting cardiac disease, or renal impairment [35].

Presentation: Features of systolic dysfunction and prolonged QT interval were reported too [35].

Diagnosis:

- (a) Echocardiography shows diffuse thickening ventricular walls [35].
- (b) CMR: Shows areas of patchy gadolinium enhancement. It is important to differentiate it from other causes of cardiomyopathy [35].
- (c) Endomyocardial biopsy: Shows enlarged and vacuolated cells, and the presence of myeloid and curvilinear bodies within the cardiac myocytes [35].

Treatment: Mainly withdrawal of the antimalarial agents and conventional heart failure treatment if needed [35].

16.2.1.3 Heart Failure

It is a clinical syndrome that is two times higher in RA patients than the general population [36].

Associations: Rheumatoid factor positivity was associated with higher risk of congestive heart failure [36].

Causes: Patients with RA develop heart failure mostly due to ischemic cardiomyopathy,

drug-induced myopathy (e.g., antimalarial drugs), rheumatoid nodule, NSAID use, or amyloidosis.

Treatment: Treat the underlying cause and conventional heart failure treatment. Avoid the use of tumor necrosis factor- α (TNF α) inhibitors especially the high doses (10 mg/kg) in NYHA classes 3 and 4 heart failure [37]. In patients with congestive heart failure and RA, the combined use of synthetic DMARDs, non-TNF biologic, or tofacitinib over TNF inhibitors is recommended [38].

16.2.1.4 Coronary Artery Disease (CAD)

Patients with rheumatoid arthritis (RA) have a reduced life expectancy when compared with the general population, where cardiovascular death is considered the leading cause of mortality in patients with RA; it is responsible for approximately half the deaths observed in RA [8]. Epidemiologic studies have shown that this increased mortality is largely attributable to cardiovascular diseases, primarily CAD. Considerable evidence suggests that inflammation plays a role in the pathogenesis of atherosclerosis [10]. The prevalence of cardiovascular comorbidity is difficult to assess accurately because CAD has a tendency to remain silent in the rheumatoid patient, but deaths from CVD occur earlier than in the general population. It has also been suggested that the increased risk of CAD in RA precedes the onset of clinical rheumatoid disease [17].

Traditional risk factors for atherosclerosis, such as smoking, hypercholesterolemia, hypertension, DM, and sedentary lifestyle, may be more common in RA than in the population as a whole but do not account for all of the increase in the disease. Currently, there is a large body of evidence that a chronic inflammatory state can enhance the harmful effects of some traditional risk factors, such as the association between systemic inflammation and arterial wall stiffness in hypertension or the proatherogenic lipid profile (high LDL and lipoprotein (a) low HDL) seen with increasing rheumatoid disease activity. The burden of addressing CAD in RA is therefore divided between rigorous control of traditional

risk factors and effective disease control through immunosuppression [39]. The more extended the span of the RA and the utilization of TNF α inhibitors are, there is a chance for improvement of atherosclerosis [40]. The two are a surrogate for the seriousness of the illness and a presence of coronary calcification [41]. Male gender and severe inflammatory state (high inflammatory markers and disease activity score) are usually associated with atherosclerosis [42].

Factors influencing cardiovascular disease in rheumatoid arthritis:

- **Oxidized LDL (oxLDL)** and antibodies to oxidized LDL are both established as significant risk factors for CVD in RA. It has been consistently observed that the levels of oxLDL are higher in patients with active disease [39].
- **C-reactive protein:** Higher levels of CRP are associated with CVD in non-RA patients [39]. Treatment of CAD with statins or angiotensin-converting enzyme (ACE) inhibitors has been demonstrated to lower CRP levels [39]. Attention was specifically focused on high-sensitivity CRP (hsCRP). Raised hsCRP is found in hypertension, smoking, and DM, as well as CAD.

In RA baseline, CRP predicts cardiovascular mortality [43], and 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 activates monocyte chemotactic protein-1 (MCP-1), which can be inhibited by statins and fenofibrates [39].

- **Homocysteine:** Homocysteine is increasingly regarded as an epiphenomenon of CAD rather than a causative factor [39].

Elevated levels of homocysteine have been associated with CAD in the general population as well as in reduced levels of various vitamins including folate and B6 [39]. It has also been shown that homocysteine is present in higher concentrations in the joints of RA patients, where it may enhance production of pro-inflammatory cytokines such as IL-1 and thus act as a driver for

joint damage; it may also accelerate atherosclerosis in a similar manner [44].

- **Physical disability due to rheumatoid arthritis:** Poor functional status, especially in the lower limbs, is a powerful predictor of mortality in RA, while regular exercise is known to have beneficial effects on the cardiovascular system. Exercise capacity is also inversely related to the presence of metabolic syndrome [45]. Patients with chronic RA have physical disabilities, which prevent them from taking regular exercise. This influences CAD in several ways; the presence of CAD usually causes delay in the individual's presentation to clinician since reduced physical activity may not exacerbate symptoms. The delay in presentation would also prevent treatment at an earlier stage of CAD, even with the lack of CVD, physical disability would still stop adequate exercise.
- **Leptin and the adipocytokines:** Leptin is an adipokine that functions both as a hormone and a cytokine. It is produced by the adipose tissue, and its main role appears to be to reduce food intake and to stimulate the sympathetic nervous system. It is known to stimulate inflammatory cytokine production, and to have direct 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 [39]. Leptin has the potential to play a key role linking obesity, inflammation, and cardiovascular damage.

Prevention of CAD in RA.

Since it is generally similar to prevention in patients without RA [46], here are some important points to prevent CAD in RA patients.

One needs to:

- Stop smoking.
- Measure fasting blood glucose annually or in the event of significant weight gain especially in patients taking steroids. In already diabetic

patients, the steroids should be kept in the lowest dose.

- Monitor blood pressure for RA patients before beginning medications and then at regular intervals for patients using NSAID, cyclosporine, and corticosteroids. NSAIDs reduce the antihypertensive effects of diuretics, β -blockers, and angiotensin-converting enzyme inhibitors, but it is less likely to interfere with calcium channel blockers [47]. In those group of patients either to increase the dose of the antihypertensive medications or to use a calcium channel blocker.
- Manage hypercholesterolaemia according to recommendation for the general population.
- Manage obesity as well as weight loss.
- Supplement the diet with fish oil that is rich in omega-3 fats, because this has demonstrated efficacy in the treatment of RA, facilitated reduction of NSAIDs use and reduced cardiovascular mortality risk [48].
- Diagnose and treat RA early:
 - Methotrexate: shown to decrease cardiovascular mortality among RA patients [49].
 - TNF inhibitors: shown to decrease the risk of MI among patients who have controlled synovitis within 6 months of treatment [50].

16.2.1.5 Rheumatoid Nodule

Valvular nodule is 10 times higher in RA patients than the general population [23].

Incidence: Echocardiographic evidence of aortic valve nodule was observed less than mitral valve nodule in the rate 0.3% vs. 0.6% among RA patients [31], respectively.

Presentation: Differs according to the site of the nodule, as it causes functional impairment, such as arrhythmias and valve disease [51]. It was associated with complete atrioventricular (AV) block necessitating pacemaker as it involves the AV node [52, 53].

Treatment: According to the presentation.

16.2.2 SLE

It is a multisystem autoimmune disease with a strong female predilection.

Cardiovascular morbidity and mortality is a frequent complication, particularly in females aged 35–44 years, where the risk of myocardial infarction is raised 50-fold [54]. The cardiac morbidity is the most common cause of death in SLE patients, which is around 25% of deaths in SLE [55].

The heart is one of the most frequently affected organs in systemic lupus erythematosus (SLE), where any part can be affected, including the pericardium, myocardium, coronary arteries, valves, and the conduction system. In addition to pericarditis and myocarditis, high incidence of CAD has become increasingly recognized as cause of mortality, especially in older adult patients and those with long-standing SLE [56].

Pericarditis is the most common cardiac abnormality in SLE patients, but lesions of the valves, as well as myocardium and coronary vessels, may all occur. In the past, cardiac manifestations were severe and life threatening, often leading to death. Therefore, they were frequently found in postmortem examinations. Nowadays, cardiac manifestations are often mild and asymptomatic. However, they can be frequently recognized by echocardiography and other noninvasive tests (Echocardiography is a sensitive and specific technique in detecting cardiac abnormalities, particularly mild pericarditis, valvular lesions, and myocardial dysfunction). Therefore, echocardiography should be performed periodically on SLE patients [57].

16.2.2.1 Pericarditis

The most common clinical cardiovascular manifestation of SLE.

Prevalence: Echocardiographic evidence of pericardial effusion was detected in 27% of SLE patients, where most of them had asymptomatic disease [58]. Lupus pericarditis occurs predominantly in females in around 92% [59] which is mostly due to main predominance of SLE in females.

Associations: Mostly associated with active SLE in 93% and involvement of other organs with SLE in 72% [59]. In the absence of renal failure, constrictive pericarditis or pericardial effusion is rarely reported [60]. Patients with tamponade had lower serum level of C4 in com-

parison to the ones who did not develop tamponade [61].

Clinical presentation: Ranges from asymptomatic to pericardial effusion [58] to cardiac tamponade in 16% [59].

Diagnosis: Either by the presence of pericardial effusion by echocardiography only or the presence of 2 out of 4 of the following (Retrosternal pain, pericardial friction rub, widespread ST-segment elevation, and new/worsening pericardial effusion) among SLE patients [59].

Treatment: The treatment of lupus pericarditis is mainly derived from immune-mediated pericarditis, as previously mentioned in the RA section, where it responded well to NSAID and corticosteroids [59]. High-dose corticosteroids, complete drainage, and pericardial window were used for treating patients with large pericardial effusion/tamponade [61, 62].

16.2.2.2 Myocarditis

Effects: SLE is associated with the increase in the left ventricle mass, and this would be even more if SLE was associated with hypertension (HTN) [63].

Associations: The association is strong between lupus myocarditis with the presence of myositis but weak with the presence of the antibodies to nuclear ribonucleoprotein (RNP) [64]. High SLE Disease Activity Index is an independent risk factor in the development of lupus myocarditis [5], where anticardiolipin IgG and lupus anticoagulant were positive in patients with severe symptoms [65].

Clinical features: It ranges from asymptomatic disease discovered accidentally to symptomatic heart failure and sudden death [5].

Diagnosis: Echocardiography: Most patients suffered from wall motion abnormalities (WMA), whereas less than 50% of lupus myocarditis patients showed decrease in the left ventricle ejection fraction after the exclusion of other causes of myocarditis [5].

Treatment: Conventional treatment of heart failure [5]. Immunosuppressive therapy (high-dose systemic corticosteroids with subsequent dose tapering, intravenous immunoglobulin, plasmapheresis, or cyclophosphamide) showed

improvement in heart failure symptoms, EF, and the WMA of the heart [5]. After corticosteroids therapy, the EF improved up to a mean of 49.5% after around 7 months of follow-up from a mean of 33.8% [66]; one article reported normal EF after follow-up [67]. Refractory lupus myocarditis can be treated with rituximab [68]. Intravenous “pulse” cyclophosphamide was used in patient with lupus myocarditis refractory to corticosteroids, and it showed improvement in heart failure symptoms and EF from 19% to 63% [69]. Mycophenolate mofetil was effective in a case series [70]. Intravenous immunoglobulin was effective in the treatment of patients with severe lupus myocarditis in conjunction with corticosteroids and cyclophosphamide [65]. One rare case report showed that plasmapheresis and extracorporeal membrane oxygenation (ECMO) were effective in lupus myocarditis [71].

16.2.2.3 Coronary Artery Disease (CAD)

Prevalence: The prevalence of the angina, myocardial infarction, and sudden cardiac death was found to be 8.3% as per a Johns Hopkins SLE cohort study [9]. Another study found more than 50-fold risks of MI in young women 35–44 years old when compared to the control group [11].

Risk Factors

(a) Traditional risk factors for atherosclerosis.

It has an increased prevalence in patients with SLE as hypertension, DM, premature menopause, sedentary lifestyle, and high homocysteine level [12].

(b) Inflammation-related risk factors.

- High disease activity and elevated level of CRP [13].
- In lupus nephritis, it was found that patients with long-term lupus nephritis had frequent episodes of cardiac lesions, mainly cardiac infarctions [72].
- Low serum levels of C3, antiphospholipid antibodies (APL), and elevated levels of antibodies to anti-ds DNA were found to be independent predictors of thrombosis. Hydroxychloroquine is pro-

TECTIVE against future thrombosis in those patients [73].

- Several autoantibodies such as anti-DNA, APL, anti-SSA (Ro antibodies), and anti-endothelial cell antibodies present in patients with SLE can mediate cardiac damage [74].
- Old age at diagnosis of SLE [9, 11].
- Longer duration of SLE [9, 11].
- Longer duration of steroid therapy [9].
- High levels of oxidized low-density lipoprotein cholesterol and homocysteine [9].

Preventions of CAD in SLE.

To prevent CAD, one has to:

- Control the traditional risk factors, to use the statins according to the guidelines for the general population, and to control blood pressure aggressively.
- Improve the lipid profile by using hydroxychloroquine as it lowers the level of the cholesterol in the blood, especially in patients taking steroids [75], and it is associated with a reduced risk of DM [76].
- Minimize the use of steroids.

16.2.2.4 Endocarditis (Libman–Sacks Endocarditis)

It was first described by Libman and Sacks in 1942 after they discovered valvular lesions in four patients with SLE.

Prevalence: Echocardiographic evidence was detected in around 11% of patients with SLE [77].

Associations: It was found to be associated with longer SLE duration and activity, thrombosis, stroke, thrombocytopenia, and antiphospholipid syndrome [77]. Its coexistence with antiphospholipid antibodies (APLs) increases the risk of thromboembolic complications, especially stroke [78].

Pathology: Since the main involved valve is the mitral followed by the aortic [78], the left side is mainly more involved than the right. Therefore, the main dysfunction is regurgitation; stenosis is rarely found [78].

Diagnosis: Echocardiography: It is manifested as valve vegetations, thickening, and/or

regurgitation [79]. Transesophageal echocardiography (TEE) was found to be more sensitive than transthoracic echocardiography (TTE) for the detection of echocardiographic findings [79]; for example, valvular thickening was found higher with TEE at 70% vs. 52% with TTE [79].

How to differentiate it from infective endocarditis? Infective endocarditis is an uncommon complication of SLE, yet at the same time, it should be in the differential diagnosis as both diseases can be presented with fever and valvular vegetation. Three laboratory tests can help differentiate between them to a degree, and these are the white blood cell count (WBC), the CRP level, and the antiphospholipid antibody (APL) level [80]. The test results show that the WBC is expected to be low during lupus flare and high during infection, CRP is high with infection and suppressed during lupus flare, and the aPL is high in SLE and unlikely to be positive in infection [80].

Treatment

The control of the SLE disease activity is important with the use of the corticosteroids. Although the use of corticosteroid is not beneficial for the valve lesion, it is important to control underlying diseases [78]. The corticosteroids, on the other hand, were noted to be associated with fibrosis and severe dysfunction (e.g., mitral valve insufficiency) after high doses of corticosteroid are used [81, 82]. Patients with Libman–Sacks Endocarditis, who suffered from a thromboembolic event, are recommended to be on life-long anticoagulation to prevent further episodes [78]. Accordingly, conventional treatment of heart failure and valvular lesion as needed is crucial.

16.2.3 Systemic Sclerosis (SSc)

Widespread vascular lesions, fibrosis of the skin, and internal organs characterize a connective tissue disease. More than half of the patients with SSc, who underwent autopsy, were found to have significant cardiac abnormalities [37]. Cardiac involvement is recognized as a poor prognostic factor when clinically evident, with a 5-year mortality rate is around 75% [83]. Primary myocardial involvement is common in SSc; increasingly,

evidence strongly suggests that myocardial involvement is related to repeated focal ischemia leading to myocardial fibrosis with irreversible lesions. Reproducible data have shown that this relates to microcirculation impairment with abnormal vasoreactivity, with or without associated structural vascular abnormalities. Consistently, atherosclerosis and macrovascular coronary lesions do not seem to be increased in SSc. Myocardial involvement leads to abnormal systolic, diastolic left ventricular dysfunction, and right ventricular dysfunction. Sensitive and quantitative methods have demonstrated the ability of vasodilators—including calcium channel blockers and angiotensin-converting enzyme inhibitors—to improve both perfusion and function abnormalities. By that, they emphasize the critical role of microcirculation impairment [84].

Asymmetric hypertrophy of the interventricular septum with signs of sub-aortic obstruction consistent with hypertrophic obstructive cardiomyopathy was evident in echocardiogram in patients with diffuse SSc. Hypertrophic cardiomyopathy is associated with the human lymphocyte antigen HLA DR3 [85], and this may provide a possible link with SSc as this HLA phenotype is common in the latter condition [85].

16.2.3.1 Myocardial Fibrosis

Prevalence: Around 66% of patients with SSc based on MRI [86]. The presence of the left ventricle (LV) dysfunction (ejection fraction (EF) <55%) was reported in around 5.4% among SSc patients [1].

Pathology: Patchy distribution of myocardial fibrosis is pathognomonic [87]; Foci of contraction band necrosis (mostly due to the recurrent vasospasm of the small vessels of the heart) is found in all parts of the myocardium mainly in the subendocardial area [88]. Asymptomatic patients with impaired coronary flow reserve did not show stenotic lesions of the major epicardial coronary arteries [89]. Contrarily, symptomatic patients (e.g., angina) with SSc had evidence of CAD in similar rate to the symptomatic ones without SSc [90].

Associations: There is association between the high volume of fibrosis and Raynaud's phenomenon duration of 15 years or more and

abnormal Holter study results [86]. Male sex, old age, presence of digital ulcerations, and myositis were associated with higher prevalence of LV dysfunction [1].

Diagnosis

- (a) Echocardiography: Most patients had LV hypertrophy in around 22.6%, followed by LV diastolic dysfunction in around 17.7%, and a rare percent of LV systolic dysfunction in around 1.4%, in the absence of the pulmonary arterial hypertension [91].
- (b) Heart MRI: Delay enhancement MRI can identify areas of fibrosis in a significant number of patients [86].

Treatment

Vasodilators (e.g., calcium channel blockers and angiotensin-converting enzyme (ACE) inhibitors) showed improvement of the myocardial perfusion and halting of the disease progression [92]. Patients showed radiological improvement in myocardial perfusion and function after the administration of nifedipine (60 mg daily) for 14 days [93]. Among SSc patients, it was found that the ones treated with calcium channel blockers (CCB) have less reduced LVEF [1]; the cardiac protective effect of CCB still needs to be established.

16.2.3.2 Myocardial Ischemia

SSc is an independent risk factor for acute myocardial infarction with no protective effect was noted with the immunosuppressive therapy [6].

16.2.3.3 Pericarditis

Prevalence: Symptomatic pericardial disease is observed in around (5–16%) of the patients, which is lower than the autopsy proven one and was demonstrated in around (33–72%) of SSc patients [94]. Symptomatic pericarditis in patients with limited scleroderma is more than the patients with diffuse scleroderma, which was observed at the rate of 30% vs. 16%, respectively [2].

Associations: Symptomatic pericarditis is associated with pulmonary hypertension [95],

while cardiac tamponade and heart failure are associated with poor prognosis [87].

Presentation: It is usually asymptomatic [2], yet it can rarely be present with large symptomatic pericardial effusion [2]. The large pericardial effusion usually occurs after the clinical and laboratory manifestations of the scleroderma [2], but still it can happen before, so it is part of the differential diagnosis of pericardial effusion [96]. Renal failure can be presented in the setting of large pericardial effusion and constrictive pericarditis [87].

Laboratory: exudative pericardial effusion pattern with predominance of mononuclear cells [97].

Treatment: In the setting of pericarditis, NSAID and corticosteroids were effective [94], and with the presence of active inflammation, immunosuppressive therapy may have a role [94].

Conventional heart failure treatment is helpful [94]. Cardiac tamponade is to be treated accordingly, e.g., pericardiocentesis [87]. Constrictive pericarditis is to be treated accordingly, e.g., diuretics, sodium and fluid restriction, and/or pericardial stripping [87].

16.2.4 Antiphospholipid Syndrome

Antiphospholipid syndrome (APS) is a systemic autoimmune disease associated with arterial and venous thrombotic events and recurrent fetal loss. The heart is a target organ in APS.

Endocardial disease, intracardiac thrombosis, myocardial involvement including CAD and microvascular thrombosis, as well as pulmonary hypertension, have all been described in APS patients. Valvular involvement is the most common manifestation with a prevalence of 82% detected by transesophageal echocardiography. Symmetrical—nodular thickening of the mitral and/or aortic valves—is characteristic. Anticoagulant/antiplatelet treatment is ineffective in terms of valvular lesion regression [98]. Some patients require cardiac valve replacement. However, patients with APS have shown an increased perioperative morbidity and mortality. Intracardiac thrombosis,

although a rare complication, can cause pulmonary and systemic emboli [98].

16.2.4.1 Aspirin and APS

The primary prophylaxis of thrombosis with low dose aspirin (81 mg) in asymptomatic, persistently antiphospholipid antibody (APL)-positive individuals was not beneficial when compared to placebo [99]. SLE patients with persistent positive lupus anticoagulant (LA) antibody are at high risk of thrombosis, and primary prophylaxis with low-dose aspirin and hydroxychloroquine is recommended [100].

16.2.5 Ankylosing Spondylitis (AS)

It is a chronic inflammatory condition that usually affects young men, mainly affecting the spine and the sacroiliac joints and, to lesser extent, the peripheral joints. Cardiac dysfunction and pulmonary disease are well known and commonly reported extra-articular manifestation associated with ankylosing spondylitis (AS). The cardiac manifestations were reported in around 2–10% [101], and it may reach up to 30% [102] of patients with AS—mostly conduction defects and aortic insufficiency [101]. The cardiac manifestation is mostly observed in patients with long-term AS and peripheral joint involvement [103]. AS has also been reported to be specifically associated with aortitis, aortic valve diseases, conduction disturbances, cardiomyopathy, and CAD. There is no difference between the type of rheumatic therapy and its use among patients with AS, who have myocardial infarction versus who does not [101].

16.2.5.1 Aortic Involvement

It was first described in 1973 AD by Bulkley and Roberts during autopsy examination of patients with AS that had congestive heart failure due to severe aortic regurgitation [104]. It is an important topic, because if patients with AS developed chest pain, you should rule out aortic dissection.

Prevalence: Echocardiographic evidence of aortic regurgitation was mostly mild and was observed in around 3–13% of patients with AS

[60]. Positive HLA-B27 patients with aortic regurgitation around half of them do not have clinical features of rheumatic disease [105].

Pathology: Arteritis around the aortic root and valve due to inflammatory process with platelets aggregation lead to tissue thickening [104]. There is fibrous growth of the intimal layer that leads to aortic root dilatation [104]. Increase in stiffness of the aorta and decreased global myocardial performance are features of AS and correlate with the disease activity and its duration [106].

Diagnosis: Echocardiography: TEE showed aortic root thickening, increased stiffness, dilatation, and nodularities of the aortic cusps. The first two were the most common findings [107]. Valve regurgitation was seen in around half of the patients [107].

16.2.5.2 Myocardial Involvement

Prevalence: Diastolic dysfunction was found at the rate of 20% [108] ranging to 50% [109], while systolic dysfunction was affected less than that in around 18% of AS patients [110].

Pathology: It was found to have an increase in myocardial inflammation and the connective tissue/myocyte rate, which will give the picture of the increase in diffuse interstitial connective tissue [110].

Presentation: Diastolic dysfunction in AS is usually not severe enough to cause diastolic heart failure [111]. Rarely, were LV systolic dysfunction and hypertrophy reported in the absence of significant aortic regurgitation [48].

16.2.5.3 Conduction Abnormalities

It is the most common finding in AS patients, and it usually precedes the other cardiac findings [102].

Prevalence: Conduction abnormalities were observed in around 2–20% of AS patients [60]. Around half of the positive HLA-B27 patients with conduction abnormalities do not have clinical features of rheumatic disease [105].

Pathology: Inflammatory process leads to damage of the interventricular septum wall, and AV node dysfunction is secondary to the compromise of the arterial supply to the AV node [112].

Another factor is the autonomic nervous system abnormalities that can lead to conduction defects and arrhythmias at the end [113].

Associations: Disease duration is associated with the prolongation of the PR and the QRS intervals [112]. Conduction abnormalities occur more frequently in patients with positive HLA-B27 [105].

Types:

1. Supraventricular extrasystoles and ventricular extrasystoles are very common findings among AS patients [102].
2. Prolonged QRS interval in about 29.2% of AS patients [112].
3. First-degree atrioventricular (AV) block in around 4.6% of AS patients [112].
4. Complete right bundle branch block (RBBB) in around 0.8% of AS patients [112].
5. Left anterior hemiblock 0.8% of AS patients [112].

16.2.6 Psoriatic Arthritis

The increased risk of clinical and subclinical CVD is mostly due to accelerating atherosclerosis, and the incidence of mortality in CAD was similar to that of RA [114]. Patients with psoriatic arthritis have higher occurrences of CVD risk factors and CAD, peripheral vascular disease, and congestive heart failure [115].

16.2.6.1 Arrhythmias

Incidence: Patients with psoriasis were found to have higher risk of developing arrhythmia than the normal population at the rate of 15.41 per 1000 person-years, and this was even higher among patients with psoriatic arthritis [116].

16.2.6.2 CAD:

Incidence: The incidences of myocardial infarction is 5.13 per 1000 person-years, while it is 5.13 for severe psoriasis, which is higher than the general population [7]. The new events of heart failure were higher among psoriasis patients, especially among the severe psoriasis group than the general population [117].

Associations: Severe psoriasis is associated rationally with a higher risk of death, specifically cardiovascular being the most common cause [118]. CAD is associated with young patients [7, 119], psoriatic arthritis [119], and/or severe psoriasis [7, 119]. Severe psoriasis has higher risk of CAD and stroke [119].

Pathology: Metabolic diseases, such as obesity and diabetes mellitus, are more among psoriasis patients, which may play a role in the development of atherosclerosis in addition to the inflammatory process [120].

Prevention: Treatment with methotrexate and TNF alpha inhibitors therapy appears to lower the rates of CAD among patients with psoriasis [120].

16.2.7 Systemic Vasculitis

CVD is significantly involved in different types of systemic vasculitis, ranging from large to small vessel vasculitis (see Chap. 20 on “Vasculitis and Rheumatology”).

16.3 The Accelerated Atherosclerosis Effects on CAD in Rheumatologic Diseases

This can be called an immune system-mediated inflammatory process as the immune cells can be found within atherosclerotic plaques, and inflammation activates this process.

(Table 16.5 shows the major contributing factors for atherosclerosis in different rheumatologic diseases).

16.4 Metabolic Syndrome and Rheumatological Diseases

The concept of metabolic syndrome was first recognized by Raven when he discussed that insulin resistance has a central role in type 2 DM, hypertension, and CAD [121]. Later, it became known as metabolic syndrome. The major components

Table 16.5 : Atherosclerosis in rheumatologic diseases

Disease	Contributed factors	
All	<ul style="list-style-type: none"> • Active prolonged inflammatory process. • Vascular endothelial dysfunction and injury. • ↑ Oxidized LDL (oxLDL) engulfed by macrophages to form foam cells • Immune dysregulation by ↑ CD4+ T cells that lack surface CD28 molecule (CD4 + CD28–), which infiltrate the atherosclerotic plaques and display a high pro-inflammatory and tissue-damaging potential; this promotes vascular injury. • ↑ Beta 2 glycoprotein I (B2GPI) is present along with CD4 lymphocytes in the plaque cells which increase the lesion area. • The plaque secretes interleukins, tumor necrosis factor-α (TNF), and platelet-derived growth factor for more expansion of the lesion. • ↑ Anti-oxLDL, (aCL) antibodies, anti-β2GPI antibodies when there is extensive atherosclerosis. 	
Disease	Contributed factors	Subclinical detection
RA	<ul style="list-style-type: none"> • Endothelial dysfunction. • Traditional risk factors. • Depletion of endothelial progenitor cells. 	Preclinical atherosclerosis can be detected by: <ol style="list-style-type: none"> 1. B mode-carotid ultrasound: <ul style="list-style-type: none"> • IMT (intimal medial thickness). • See atherosclerotic plaque by echolucency and calcific acoustic shadowing. 2. CT scan of coronary arteries: <ul style="list-style-type: none"> • Presence of calcification. • Extent of calcification. 3. Arterial stiffness: <ul style="list-style-type: none"> • Pulse wave velocity (PWV). • Pulse wave analysis (PWA). 4. Elevated CRP.
SLE	<ul style="list-style-type: none"> • Traditional risk factors. • Depletion of endothelial progenitor cells. • Inflammation. • Metabolic changes in SLE: Renal dysfunction and early menopause. • Antiphospholipid antibodies. 	
APS	<ul style="list-style-type: none"> • Possible involvement of antiphospholipid antibodies (APL) in the pathogenesis of atherosclerosis. • Positive APL is associated with arterial atherosclerosis which will develop into thrombosis at coronary, carotid, and lower peripheral arteries. • Positive lupus anticoagulant (LA) is associated with venous thrombosis. 	
Systemic sclerosis	<ul style="list-style-type: none"> • Endothelial injury and its activation can lead to loss of vasomotor function and vasoconstriction. • Myofibroblasts develop from activated vascular muscles and cause thickening of the intima, lumen narrowing, and irreversible fibrosis. • It may also induce formation of intravascular thrombosis. 	
Ankylosing spondylitis	<ul style="list-style-type: none"> • There are very limited studies. • Inflammation is a possible contributed risk. • Endothelial dysfunction. 	
Vasculitis	<ul style="list-style-type: none"> • There is inflammatory cells infiltration in the layers of arterial wall. 	<ul style="list-style-type: none"> • Variable.

of metabolic syndrome include dyslipidemia, central obesity, insulin resistance, and hypertension [122]. The major components are not occurring concurrently; as it was found that insulin sensitivity will predict the increase in waist circumference (obesity), and the latter will predict the remaining components, e.g., dyslipidemia and hypertension [123]. The adipose tissue is acting as endocrine organ by the secretion of the pro-inflammatory factors called adipokines.

Insulin resistance has a role in the development of CVD (probably due to the adipokines from the adipose tissue) [124] as it has a role in the enhancement of vascular inflammation and endothelial dysfunction [125]. Different adipokines have been recognized in metabolic syndrome with rheumatic diseases, and their effects were emphasized (see Table 16.6).

Patients with rheumatic diseases are under the pressure of chronic inflammation mainly with

Table 16.6 The effects of different adipokines on rheumatologic diseases [154]

Rheumatic disease	Adipokines			
	Leptin	Adiponectin	Visfatin	Resistin
RA	↑, pro-inflammatory	↑, Synovitis	↑, Radiographic joint damage	↑, Disease activity and joint destruction
PsA	Controversial	Controversial	Controversial	–
PsA	–	–	–	–
AS	Marker of disease activity??	–	Controversial	–
Gout	–	–	–	–
OA	↑, cartilage destruction	Controversial	↑, degradation of collagen	–

RA and SLE. Many patients with rheumatic diseases—mainly RA, SLE, and AS—have been diagnosed with metabolic syndrome [14–16].

Here, we will discuss the rheumatic diseases and its relationship with metabolic syndrome.

16.4.1 RA

It was initial to associate insulin sensitivity to be lower in RA patients compared to osteoarthritis patients [126]. Later, it was found that the main factors of insulin resistance in RA are obesity and disease activity [127]. The prevalence of metabolic syndrome among RA patients ranges from 44% to 53% [15, 128]. Such patients were found to have higher disease activity than those without metabolic syndrome with low level of high-density lipoprotein cholesterol [15]. Its presence is associated with higher systemic inflammatory marker and glucocorticoids use [129]. Patients with RA, who were diagnosed with metabolic syndrome, were found to have higher risk of coronary artery calcification [128].

16.4.2 SLE

Non-diabetic patients with SLE were found to have significant decrease in sensitivity to insulin, and around 18% of them were diagnosed with metabolic syndrome [130]. The prevalence of metabolic syndrome among SLE patients ranges from 16% to 32.4% [14, 131, 132]. SLE patients have higher fasting insulin level, and cardiovascular risk factors

were also elevated among the last group [133]. Metabolic syndrome was associated with higher level of C-reactive protein, homocysteine, lipoprotein, and cholesterol [14]. Metabolic syndrome and CVD among SLE patients were associated with prolonged SLE duration and increased cumulative organ damage [131]. Lupus nephritis, high corticosteroid doses, Korean and Hispanic ethnicity were associated with metabolic syndrome in SLE patients [132]. The use of hydroxychloroquine was associated with protective effect of CVD [131].

16.4.3 AS

The prevalence of metabolic syndrome among AS is around 45.8% [16], whereas low AS disease activity is not associated with accelerated atherosclerosis [134].

16.4.4 Psoriasis

Psoriasis is associated with DM. The prevalence of DM was higher with severe psoriasis than mild psoriasis in the rate of 7.1% vs. 4.4%, respectively [135]. The prevalence of metabolic syndrome among psoriatic patient ranges from 15% to 35.5% [136–138]. Psoriatic patients are prone to the development of the main components of metabolic syndrome (e.g., DM and hypertension) [139]. Treating psoriasis was found to be associated with improvement in the metabolic risk biomarkers, such as high-sensitivity CRP, adiponectin, and the oral glucose tolerance test [140].

16.4.5 Gout

The initial association of gout with metabolic syndrome was with the close association of hyperuricemia and the components of metabolic syndrome (e.g., hypertension, insulin resistance, and obesity) was noted [141]. Elevated uric acid levels among gout patients can be associated with insulin resistance since renal clearance is inversely related with insulin resistance [142]. The prevalence of metabolic syndrome among gout patients ranges from 44% to 88% [143–145].

16.5 The Various Medications that Are Being Used in the Management of Rheumatologic Disease that Have Variable Effects on CAD

It is important to mention these factors because managing clinicians may not pay attention to these effects as they focus mainly on the activity of the rheumatologic disease.

16.5.1 NSAIDs³

- The risks of major cardiovascular events—such as myocardial infarction, stroke, and death—appear to increase to a similar degree by the use of most nonselective NSAIDs at high doses. The exception is naproxen, which does not increase such risk [146].
- All of the COX-2 selective inhibitors (coxibs) appear to increase the risk of ischemic cardiovascular disease in a dose-dependent fashion. Recent data showed that naproxen, celecoxib, and ibuprofen did not differ in the risk of the cardiovascular mortality, but naproxen was less than the last two for the risk of the gastrointestinal bleeding [147]. Certain COX-2

inhibitors are associated with twofold increase in CAD risk.

- COX inhibition leads to CAD with two possible mechanisms:
 - It can interfere with normal platelet and endothelial vasodilator functions.
 - It can cause hypertension.
- All (NSAIDs) can increase blood pressure in both normotensive and hypertensive individuals. Its use may reduce the effect of all antihypertensive drugs except calcium channel blockers.

(Figure 16.1 summarizes the effects of NSAIDs on the cardiovascular system)

16.5.2 Glucocorticoids (GC)

This medication is known to have serious noxious effects by increasing blood pressure, insulin resistance, body weight, and fat distribution. There is an excess risk of cardiovascular morbidity and mortality when the drug is used in high cumulative doses and for a long duration. There is 68% of increased risk of myocardial infarction among RA patients treated with GCs [148]. Cushing disease is associated with accelerated atherosclerotic vascular disease [149].

16.5.3 Methotrexate

Many studies have demonstrated that its use has been associated with a beneficial reduction in CVD events among patients with systemic inflammation diseases primarily from RA [49]. It is known to decrease homocysteine level. RA patients who used methotrexate have lower LDL levels, significant increase in mean HDL, and decrease in carotid artery intima-media thickness, compared with baseline values.

16.5.4 TNF Biologic DMARDs

- A large study showed significant reduction in fatal and nonfatal CVD outcomes associated

³The association of nonsteroidal anti-inflammatory drugs (NSAIDs) with cardiovascular morbidity and mortality in patients with RA is still controversial.

Fig. 16.1 NSAIDs and risk of CVD

- with TNF inhibitors, but this remains controversial.
- The cardiovascular benefit of TNF inhibitors may be limited to patients with RA whose synovitis responds to these agents. Patients whose disease activity was reduced by TNF inhibitor therapy within the first 6 months of treatment had markedly decreased risk of myocardial infarction compared with those who continued to have active disease.
 - It was associated with a significant increase in both total cholesterol and HDL with no change in regard to the atherogenic index [150].

16.5.5 Non-TNF Biologic DMARDs

- Rituximab has no significant effect on CVD, with no positive outcome on lipid profile or endothelial dysfunction.
- Tocilizumab is associated with beneficial low CRP after early introduction, but it has unclear worse effect regarding elevation of total cholesterol, LDL [151, 152] when used for years, even though it does not increase CVD events. Tofacitinib is also associated with increased level of LDL [153].

In summary, for the prevention of CAD in rheumatologic diseases, we should do the following:

- Traditional CAD risk factors control.
- Early diagnosis and management of CAD.
- Long follow-up for CAD complications.
- Early diagnosis and management of rheumatologic disease with strict control of the disease activity.

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Appendix 1

Note about tables and figures

* **Diagnostic markers of CVD in rheumatologic disease** (including CAD): we have a table that summarizes the workup needed for the detection of CVD in each group of patients with rheumatologic disease (Table 16.A.1).

* **Management and control of CVD risk factors** (Including CAD): The control and the prevention of the risk factors for CVD and what we also call traditional risk factors for CAD are summarized in Table 16.A.2.

Table 16.A.1 Diagnostic markers of CVD in rheumatologic disease

AIRDs	Diagnosis of CVD	
	Disease	Investigation
RA	MI	<ul style="list-style-type: none"> • ECG and cardiac enzymes: Mainly troponins and CK MB. • Echocardiogram.
	Congestive heart failure	<ul style="list-style-type: none"> • Echocardiogram. • Chest X-rays. • CBC, serum electrolytes, BUN, creatinine, liver function test, and fasting blood sugar. • Elevated B-type natriuretic peptide (BNP) levels are not specific for left ventricular systolic dysfunction, and may be reduced by concomitant diuretic and angiotensin-converting enzyme inhibitor therapy, limiting sensitivity [155] • Exercise stress tests.
	Peripheral arterial disease	<ul style="list-style-type: none"> • Clinical investigation of arterial stiffness to look for incompressibility and obstruction and performing: <ul style="list-style-type: none"> – PWV: Pulse wave velocity. – PWA: Pulse wave analysis. • Ankle-brachial systolic pressure index (ABI), • Exercise testing (ABI) if rest (ABI) is normal. • Contrast arteriography is the gold standard.
SLE	• Pericardium: Mostly asymptomatic, pericarditis or effusion.	<ul style="list-style-type: none"> • ECG findings: Diffuse ST-elevation and T-wave abnormalities. • Pericardiocentesis if significant pericardial effusion, fever (to rule out concomitant infections) or failed medical treatment. • Low antinuclear antibodies (ANA), phagocytic cells containing nuclei (LE cells), low complement levels, and immune complexes in effusion.
	Myocardium: Mainly myocarditis	<ul style="list-style-type: none"> • ECG findings: Prolonged PR intervals, ST and T-wave abnormalities. • Echocardiography. • MRI. • Myocardial biopsy.
	Endocardium and valves	<ul style="list-style-type: none"> • Echocardiography if a new murmur is detected or changing in cardiac function. • Blood culture and echocardiography if fever or new heart murmur. • Transesophageal Doppler echocardiography produces high-resolution images of the cardiac valves and is superior to transthoracic echocardiography in the detection of valve abnormalities. • Libman-sacks endocarditis is typically asymptomatic. However, the verrucae can fragment and produce systemic emboli, and infective endocarditis can develop on already damaged valves [156].
	Conduction defects	<ul style="list-style-type: none"> • Preconception or early prenatal testing for anti-Ro/SSA and anti-La/SSB antibodies and periodic monitoring for the development of heart block in the fetus.
Systemic sclerosis	Pulmonary arterial hypertension	<ul style="list-style-type: none"> • ECG: Look for tachyarrhythmia. • Chest X-ray. • Doppler echocardiogram: <ul style="list-style-type: none"> – Rhythm. – Conduction disturbance. – Cardiac chambers and valves (morphology and function). – Pulmonary arterial pressure. • Cardiac pulmonary stress test. • Cardiac catheterization for better diagnosis of pulmonary hypertension. • MRI. • Nuclear studies of myocardial function and perfusion .
	Myocardium	
AS & PsA	Different CVDs	<ul style="list-style-type: none"> • Clinical assessment. • ECG. • Cardiac enzymes. • Echocardiogram.

(continued)

Table 16.A.1 (continued)

AIRDs	Diagnosis of CVD	
	Disease	Investigation
APS	IHD	<ul style="list-style-type: none"> • Clinical assessment. • ECG. • Cardiac enzymes.
	Valvular disease	<ul style="list-style-type: none"> • Clinical: Asymptomatic regurgitation. • Echocardiogram: Vegetation and marked thickening.
	Pseudo-endocarditis	<ul style="list-style-type: none"> • Clinical: Fever, murmur, and splinter hemorrhage. • Echocardiogram with the presence of mitral valve nodules and mitral regurgitation. • High APL titer. • Blood culture is negative for infection.
	Peripheral artery disease	<ul style="list-style-type: none"> • Ankle-brachial index at lower extremities is abnormal.
	DVT	<ul style="list-style-type: none"> • Clinical assessment. • Duplex ultrasound. • D-dimer for exclusion in low probability cases..
	Intracardiac thrombus	<ul style="list-style-type: none"> • Not common and misdiagnosed. • Clinical: Angina-like pain. • Exercise test: Positive. • Angiogram: Normal coronary arteries.
Inflammatory myopathies	CVDs are rare	<ul style="list-style-type: none"> • ECG: Conduction defects and arrhythmia. • Specific marker is the level of cardiac isoform troponin-I. • Creatine kinase (CK)-MB is not a specific cardiac marker, so it is not helpful.
Vasculitis	According to the type	<ul style="list-style-type: none"> • ECG and echocardiogram. • Contrast-enhanced cardiac MRI. • BNP. • ANCA.

Table 16.A.2 Management and control of CVD risk factors [157]

Health parameters	Maintenance
Dyslipidemia	<ul style="list-style-type: none"> • Annual lipid profile screening is recommended. • Statin use decreases TC and LDL levels, which lower the risk of cardiovascular events; give if it is indicated. • In high-risk patients who use statins, the goal of LDL-C level: < 70 mg/dL. .
DM	<ul style="list-style-type: none"> • Monitoring of blood glucose (fasting and random). • Annual screening of hemoglobin A1c in patients with active disease and chronic corticosteroid use. • Treatment of DM as guidelines.
Hypertension	<ul style="list-style-type: none"> • Early blood pressure monitoring when there is a risk from medication. • Regular monitoring of blood pressure and start treatment as guidelines. • Control level of blood pressure, the goal: <140/90 mmHg.
Smoking	<ul style="list-style-type: none"> • Cessation is strongly recommended to improve disease activity and therapy effectiveness of RA, and its benefit on lowering CVD events is probable.
Obesity	<ul style="list-style-type: none"> • Regular monitoring of BMI. • Waist to hip ratio. • Encouragement of healthy diet. • Body mass index goal: 18.5–24.9 kg/m². • Waist circumference goal: Women 35 inches (89 cm), men 40 inches (102 cm).
Physical activity	Goal: At least 30 min per day, minimum 3–4 times a week

*** Preventive tips for using common medications in rheumatologic disease:** As we recognize the numerous and various medications that are being used in the management of rheumatologic diseases that are being associated with adverse effects on the CV system and CAD so here we tried to have a summary of preventive tips to use while using them in those patients as shown in Table 16.A.3.

* The use of **aspirin**: there are no specific rules for its use in rheumatologic disease as the

rules applied in those patients are the same as the general population. Figure 16.2 is a simple diagram showing the approach to use it.

* The use of **statins**: There are no specific rules for its use in rheumatologic disease as the rules applied in those patients are the same as the general population. We have here a simple diagram based on the latest guidelines from the American Heart Association (AHA) that was released in 2013 (Fig. 16.3).

Table 16.A.3 Medications of rheumatologic disease and the preventative measures

Medication	Disease	Effects on CVD
Glucocorticoids	RA SLE	<ul style="list-style-type: none"> • Reduced doses will lower the risk of CAD. • Calcium and vitamin D should be given. • Since the risk is dose-dependent, it is a must to keep the duration of using steroids as short as possible and the dose as minimal as possible. • A close surveillance of blood pressure and modification of antihypertensive regimens is recommended when the patient is hypertensive and is receiving moderate to high doses of GCs. • Increased cardiovascular disease was associated with glucocorticoid use at doses ≥ 7.5 mg/day of prednisone or its equivalent [158].
Methotrexate	RA	<ul style="list-style-type: none"> • Folic acid supplementation to correct homocysteine level. • It is advisable to continue using it as indicated as a DMARD. • Its CVD benefit is not fully approved, but a definitive result will come out from further studies which may prove the hypothesis of CVD as an inflammatory mechanism, and it can be beneficial in chronic CVD management.
TNF blockers	RA AS	<ul style="list-style-type: none"> • Annual lipid screening is recommended when the risk of lipid disturbance is there. • Inpatients with RA, it is recommended to continue using TNF inhibitors as biologic DMARD therapy. • Anti-TNF biologic (infliximab) is not recommended in patient with NYHA class 3 or 4 cardiac failure with an ejection fraction of $\leq 50\%$ due to a worsening effect of infliximab on the cardiac function. • Check pulse wave velocity and analysis for possible transient improvement of vascular morbidity. • TNF blockers may decrease CVD involvement and atherosclerosis in ankylosing spondylitis, but no strong evidence.
Non-TNF	RA	<ul style="list-style-type: none"> • More, larger studies are needed to clear the risky-beneficial nature of these medications and their effects over the CVD.
NSAIDs	RA AS	<ul style="list-style-type: none"> • Effective for pain management, but it is wise to be cautious about the cardiovascular side effects of NSAIDs especially in patients with high CVD risk factors. • Extra caution regarding the dose, risk factors, and comorbidity status.
Statins	SLE	<p>For primary and secondary prevention (as evident by the last AHA guidelines 2013) [159]</p> <ul style="list-style-type: none"> • Anti-inflammatory effect. • Lowering LDL-C and CRP. • Antithrombotic effect. • Immuno-modulating effect.
Aspirin	SLE APS	<p>Should be indicated in SLE if no contraindication:</p> <ul style="list-style-type: none"> • History of CAD. • Ongoing risk factors like HTN, DM, high cholesterol, and smoking. • Prophylactic low-dose aspirin in patients with thrombosis-free and -positive APL.

(continued)

Table 16.A.3 (continued)

Medication	Disease	Effects on CVD
Anticoagulation therapy	APS	<ul style="list-style-type: none"> • In patients with first event of venous thrombosis (INR: 2.0–3.0). • In patients with recurrent venous or arterial thrombosis, give intensive therapy (INR: 3.0–4.0). • It is recommended to give antiplatelet therapy with anticoagulation therapy (controversial).
Antimalarial agents	SLE APS	<ul style="list-style-type: none"> • Anti-inflammatory effect. • Anticoagulant effect. • For lipid profile improvement. • Prophylactic dose in patients with thrombosis-free positive APL in APS.
Cyclophosphamide	SLE	<ul style="list-style-type: none"> • It is the standard treatment of severe SLE with organ involvement, e.g., myocarditis. • It is recommended to give pulse steroids and pulse cyclophosphamide.
Calcium channel blockers	SSc	<ul style="list-style-type: none"> • Nifedipine and Diltiazem use with caution as they are contraindicated in MI and angina as they are causing reflex tachycardia.
Endothelin receptor antagonist	SSc	<ul style="list-style-type: none"> • Bosentan for relieving dyspnea and improvement of 6 min walk test (6MWT) [160].
Prostacyclin analogues	SSc	<ul style="list-style-type: none"> • Iloprost for widening narrow blood vessels and better blood circulation. • Ventavis inhaled solution for stage 3 or 4 pulmonary hypertension.
Sildenafil	SSc	<ul style="list-style-type: none"> • For improvement of hemodynamics .

Fig. 16.2 The use of aspirin for primary and secondary prevention of CAD [161]

High Intensity Statins Therapy

- Atorvastatin 40–80 mg
- Rosuvastatin 20–40 mg

Moderate Intensity Statin Therapy

- Atorvastatin 10–20 mg
- Rosuvastatin 5–10 mg
- Simvastatin 20–40 mg
- Pravastatin 40–80 mg
- Lovastatin 40 mg
- Fluvastatin XL 80 mg
- Fluvastatin 40 mg
- Pitavastatin 2–4 mg

Fig. 16.3 The use of the statins for management of CAD [159]

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