# CARDIO-RHEUMATOLOGY

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# PREFACE

The intricate interplay between cardiovascular and rheumatologic diseases has emerged as a critical frontier in modern medicine. As research continues to uncover the profound connections between systemic inflammation and cardiovascular health, the importance of an integrated, multidisciplinary approach to patient care becomes increasingly clear. This book, dedicated to the evolving field of cardio-rheumatology, seeks to illuminate these intersections and provide comprehensive insights for clinicians, researchers, and students alike.

Cardiovascular diseases are among the leading causes of morbidity and mortality in patients with rheumatologic diseases. Conversely, chronic inflammation, a hallmark of many rheumatologic diseases, significantly contributes to the pathogenesis of cardiovascular diseases. A comprehensive understanding of these interconnected pathways is imperative for precise diagnosis, effective management, and the advancement of personalized medicine.

This work is the result of collaboration among experts across disciplines, reflecting a commitment to bridging gaps in knowledge and practice. It is designed to offer practical guidance grounded in the latest scientific research, covering topics from pathophysiological mechanisms to diagnostic strategies and therapeutic interventions. Each chapter is crafted to foster a deeper understanding of how rheumatologic conditions impact cardiovascular health and vice versa. We hope this book serves as a valuable resource, sparking further inquiry and innovation in this vital area of healthcare. Our ultimate goal is to enhance patient outcomes through improved awareness, early detection, and holistic care strategies.

We would like to express our profound gratitude to Associate Professor Nijad Bakhshaliyev, M.D., for his invaluable support of this book by graciously providing echocardiographic images from his extensive archive. We would also like to express our deepest appreciation to all the authors for their immense contribution to this book. This book is dedicated to all healthcare professionals who perform their duties under challenging circumstances.

As healthcare professionals and scientists, we cannot remain indifferent to wars, which are crimes against humanity. Wishing for an end to all wars and a life in peace, we respectfully commemorate the words of the great leader Mustafa Kemal Atatürk: “Peace at home, peace in the world”.

Sincerely,

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CHAPTER 1

# EPIDEMIOLOGY

*Gizem Cengiz* [1]

## INTRODUCTION

Cardiovascular diseases (CVD) affect the structures of the heart or blood vessels and are the leading causes of mortality and morbidity worldwide. Among various causes, obesity, diabetes, hypertension, malnutrition, increased cholesterol, air pollution, smoking, kidney disease, sedentary life, stressful life, smoking, and alcohol use are the leading ones. In 2019, 18.6 million deaths were caused by CVD, and 85% of these deaths were caused by ischemic heart disease and stroke (1).

Rheumatic diseases (RD) are diverse systemic and chronic syndromes that influence remaining organs and tissues with which CVD is associated or coexists. RD encompasses approximately 200 conditions and affects one-third of the world's population. Although damage caused by RD is primarily seen in musculoskeletal structures such as bones, muscles, joints, ligaments, and tendons (2), it can potentially affect all structures and functions of the heart. The estimated prevalence of RD in the general population varies between 9.8% and 33.2%. The relationship between inflammatory RD (IRD) and CVD has been investigated for decades, and interest in this subject continues to increase (3, 4). It has been known for many years that CVD is the most serious cause of morbidity and mortality in major RDs such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), psoriatic arthritis (PsA), and ankylosing spondylitis (AS) (3-6). Both disease-specific risk factors (such as inflammation, disease activity, and disease progression) and traditional cardiovascular risk (CVR) factors have a very important mission in the development of cardiac diseases (3,7,8). Especially in RA patients, mortality is twice as high as the normal population, and CVD is among the leading causes (3, 9). Common environmental and genetic risk factors, as well as the drugs that are widely used in the treatment of RD, may influence the development of CVD. The powerful association between RD and CVD development requires rheumatologists to survey patients with RD, performing CVR factors screening periodically and intervention with possible preventive methods (10, 11).

## SEX, AGE, AND ETHNICITY

RA patients who do not have CVD and maintain low disease activity, male patients have a higher risk of death and arteriosclerosis than females (12). In RA patients, the HLA-DRB1 gene, primarily HLA-DRB1*04 shared epitope alleles, are involved in both the development of RA and the occurrence of CVD (13).

Many RDs, especially RA, occur more frequently in middle age and older ages. Although "late-onset

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traditional and non-traditional atherosclerotic risk factors in a society that has been tried and is inadequate in calculating the risk of RD, and that strategies to reduce and prevent possible damages should be researched, developed and implemented (10).

## CONCLUSION

CVR factors in RD are much higher than those measured by known methods. The calculation of CVR factors and their reduction can be achieved by controlling the disease activity and by close monitoring and control of the drugs used in treatments, such as using them in appropriate doses and duration, and by using risk-measurement methods and providing better predictive data. It seems that it can be reduced by developing and using methods.

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CHAPTER **2**

# CLINICAL PRESENTATIONS IN CARDIO-RHEUMATOLOGY

*Gizem Kırmızıer* [1]

## INTRODUCTION

Rheumatic diseases are characterized by inflammation of one or more organs and can affect the cardiovascular (CV) system either directly or indirectly. Heart and blood vessel involvement can range from clinically silent to catastrophic conditions. In the CV system, rheumatic diseases involve myocardium, pericardium, vascular structures, conduction system and heart valves, resulting in higher mortality and morbidity. Although chronic inflammation may cause early atherosclerosis, the pathophysiological basis of these relationships remains unclear in most cases. Patients with particular rheumatologic diagnoses should be monitored with a focus on particular cardiac complications. In Behcet's disease, for instance, venous involvement is more prevalent, whereas atherosclerosis and ischemic heart disease are more prominent in rheumatoid arthritis.

Traditional CV risk factors play a secondary role compared to disease-related factors such as disease duration, disease activity, and antibody positivity. Reducing inflammatory activity and eliminating secondary risk factors, such as hypertension, hyperlipidemia, and obesity, play a crucial role in the treatment of CV disease. Vital to the prevention of catastrophic complications in rheumatic diseases is the early diagnosis of CV involvement.

## RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is an autoimmune disease that affects between 0.5% and 1.0% of the global population (1). RA frequently affects internal organs in addition to joints. Patients have a roughly 50% higher incidence of CV events and mortality (2,3).

Cardiac involvement owing to RA can be divided into two main categories: ischemic heart disease and non-ischemic heart disease. One category includes ischemic heart diseases which are characterized by inadequate blood flow to the heart muscle via the coronary arteries. This category includes endothelial dysfunction, atherosclerosis, aortic stiffness, angina, myocardial infarction (MI), cardiogenic shock, sudden cardiac death. Non-ischemic heart diseases is linked to alterations in cardiac architecture and contains pericarditis, myocarditis, systolic/diastolic dysfunction, conduction and valve abnormalities (1).

CV diseases are the most common cause of death among RA patients (4). Due to accelerated atherosclerosis, ischemic heart disease is the leading cause of CV mortality. In these patients, the thickness of the carotid intima-media is increased, and carotid plaques are observed more often. Conventional risk factors such as hypertension, smoking, hyperlipidemia, and male gender also lead to an increased risk of CV mortality. RF or anti-CCP positivity, a high disease activity score, elevated C-reactive protein (CRP) are disease-related risk factors (5).

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is the differential diagnosis of intracardiac masses, particularly myxoma. Intracardiac thrombus may cause superior vena cava syndrome and pulmonary embolism (43).

## CONCLUSION

In conclusion, the frequency of cardiac involvement in rheumatic diseases may vary from one disease to another. It may range from asymptomatic to severe involvement. Cardiovascular involvement may include pericardial disease, myocardial involvement associated with heart failure and arrhythmias, atherosclerotic cardiovascular disease, and pulmonary hypertension. Therefore, patients with rheumatic diseases should be regularly questioned for cardiovascular symptoms. Both symptomatic and asymptomatic cases at high risk for cardiovascular manifestations should be evaluated for cardiovascular involvement.

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CHAPTER 3

# ANTIBODIES AND BIOMARKERS IN CARDIO-RHEUMATOLOGY

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## INTRODUCTION

Since cardiovascular manifestations in patients with rheumatic diseases (RDs) cause significant morbidity and mortality, timely recognition is of crucial importance (1–3). Cardiovascular comorbidities may be overt and detected in the late course of RDs during the follow-up of patients with previously established diagnosis, but also exist in subclinical forms and may be the first presentation of a RD (1) requiring good knowledge about related antibodies and biomarkers to conduct further investigation and make a diagnose. The main mechanism underlying cardiovascular pathology in RDs is inflammation that leads to vascular damage and remodeling of cardiovascular tissue, together with activation of platelets and coagulation cascade (4). This inflammation is mediated by different types of antibodies directed against self-antigens, with the consequent cytokine release and changes in the levels of other inflammatory, hemostatic, metabolic, cellular or genetic biomarkers, as well as of those of cardiac origin such as troponin (Tn) and N-terminal pro-hormone B-type natriuretic peptide (NT-proBNP) (2,5,6). This chapter highlights the importance of these mediators in the context of currently available evidence of their association with cardiovascular comorbidities in patients with RDs to help the clinicians in the process of diagnosing and follow-up, but also gives the clue to the future directions in this field. As the modern therapeutic strategies in cardio-rheumatology are also guided by these biomarkers, good understanding of their role allows for a comprehensive approach to this heterogeneous group of diseases. However, besides the non-specificity of many antibodies detected in patients with RDs, a possible influence of simultaneously present conditions, comorbidities and traditional cardiovascular risk factors should be considered when interpreting the findings related to biomarkers. What's more, the interference between heterophilic antibodies and commercially available assays for some biochemical analyses, such as cardiac markers, should be taken into account (7).

## 1. SYSTEMIC SCLEROSIS

Systemic sclerosis (SSc) is a chronic multisystem autoimmune disease with heterogeneous clinical manifestations resulting from the small vessel fibroproliferative vasculopathy and excessive accumulation of collagen, mediated by both innate and adaptive immune system, although the pathogenesis is not

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plasma concentrations of sACE and sIL-2R in isolated CS were shown to be lower than in non-isolated CS, and therefore isolated CS cannot be excluded if the circulating levels of ACE and sIL-2R are not elevated (218,224). Regarding the specific types of cardiac involvement, sACE and ESR were not shown to be associated with increased premature ventricular contraction burden or implantable cardioverter defibrillator shocks/anti-tachycardia pacing in patients with CS (216).

Serum creatinine and eGFR have been indicated as prognostic biomarkers in patients with CS (218). Also, serum calcium and albumin are proposed as biomarkers of cardiac hospitalization-free survival in CS patients. However, further studies on biomarkers for the diagnosis and prognosis of sarcoidosis are necessary. Several biomarkers, such as serum amyloid, TNF, TN-C, TGF-β1, and genome-wide gene expression signature strategies are potential candidates (217,228). In addition, urinary 8-hydroxy-2'-deoxyguanosine has recently been reported to be a marker of inflammatory activity and may be associated with cardiovascular mortality in CS patients even after steroid therapy (216,230,231). Circulating miR-126 and miR-223 have been proposed as potential markers in CS, although it remains to be determined if their levels are increased in sarcoidosis patients without cardiac involvement (232,233). There is no correlation of these molecules with sACE, sIL2-R or NT-proBNP (232).

### 10.3. Cardiac biomarkers in CS

BNP was shown to be discriminative of cardiac involvement in sarcoidosis, with markedly higher levels in CS group, in contrast to Tn (224). A cut-off value of 40 pg/ml identified CS with the sensitivity of 85% and the specificity of 68% (218,224). What's more, NT-proBNP levels are higher in patients with definite than probable CS, suggesting more advanced myocardial disease in patients with definite CS (216). Elevated NT-proBNP in CS patients is associated with poor prognosis even after adjustment for LV ejection fraction (216). Although BNP is a predictor of HF in CS, it could be affected by several factors, such as LV hypertrophy, AF, older age and impaired renal function, which should be considered when interpreting the results (218,224). TnI is not associated with BNP in CS patients (217)-18). While TnI is a predictor of fatal arrhythmia in CS patients (218), TnT has not been shown to be associated with increased premature ventricular contraction burden or implantable cardioverter defibrillator shocks/anti-tachycardia pacing in CS population (216). High-sensitivity TnT is frequently elevated in patients with newly diagnosed CS and correlates with sACE (234,235) and disease activity (216). High-sensitivity TnT is also a useful biomarker for prediction of cardiovascular events in patients with sarcoidosis even if the cardiac involvement is not detected at the initial evaluation. Additionally, it has a predictive value independently of the renal function even if the eGFR is used to assess the renal function instead of creatinine (236). NT-proBNP and TnT are both associated with the composite end point of LVAD implantation, heart transplantation or death, indicating the prognostic role of these biomarkers (216). While BNP level does not change after steroid therapy, the changes in TnI and TnT levels indicate a favorable response to steroid therapy and are associated with prognosis (218,224,226,237,238).

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CHAPTER 4

# IMAGING IN CARDIO-RHEUMATOLOGY

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## INTRODUCTION

Cardiac involvement in systemic rheumatic disease is often an overlooked condition. Clinical presentation is highly heterogeneous and depends on the involved cardiac structures, which are determined by the underlying pathogenetic mechanism. Cardiac manifestations usually present as accelerated atherosclerosis, microvascular dysfunction, peri-/myocarditis, valvular heart disease, conduction system disorders, pulmonary hypertension and heart failure (1,2,3,4).

Common imaging techniques can be applied for identification of cardiovascular manifestation, such as echocardiography, magnetic resonance imaging, computed tomography, nuclear imaging or coronary angiography. A fundamental expertise about each diagnostic modality and its limitation is essential for the appropriate diagnostic approach (Table 1). Multimodal imaging is often required, especially in subclinical courses to detect early signs of disease manifestation (1,2,4).

**Table 1: Performance of cardiovascular imaging modalities in various manifestations of CVD in patients with autoimmune rheumatic disease**

| CVD manifestation | Echo | SPECT | PET | CT | CMR | CA |
|---|---|---|---|---|---|---|
| Myocardial Ischemia | ++ | +++ | ++++ | - | ++++ | ++++***** |
| Coronary anatomy | - | - | + | +++ | ++* | ++++ |
| Pericarditis** | +++ | - | - | ++ | ++++ | - |
| Myocarditis | +/- | - | +/- | - | ++++ | - |
| Heart failure*** | +++ | ++ | ++ | ++ | ++++ | - |
| Pulmonary hypertension | ++++ | - | - | - | +++ | - |
| Valvular disease | ++++ | - | - | - | +++ | - |
| Vascular inflammation**** | +/- | - | +++ | ++ | +++ | ++***** |

CVD cardiovascular disease; Echo echocardiography, SPECT single photon emission computed tomography, PET position emission tomography, CT computed tomography, CMR cardiovascular magnetic resonance, CA coronary angiography; * Pediatric patients; ** Particularly pericarditis without effusion can be detected by CMR by positive LGE of the pericardium; *** CMR is particularly useful for identifying the etiology of heart failure (e.g. infarction, pericarditis, fibrosis); **** Both CT and CMR do not assess vascular inflammation per se, but they can assess the structural consequences of inflammation in large vessels. In this regard both CT and CMR are equal of value; ***** additive techniques like FFR for ischemia and IVUS or OCT for assessment of inflammation
Modified from: S Mavrogeni and others, Cardiovascular magnetic resonance in autoimmune rheumatic diseases: a clinical consensus document by the European Association of Cardiovascular Imaging, European Heart Journal - Cardiovascular Imaging, Volume 23, Issue 9, September 2022, Pages e308–e322, https://doi.org/10.1093/ehjci/jeac134 (1)

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CHAPTER **5**

# ATHEROSCLEROTIC CARDIOVASCULAR DISEASES

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## INTRODUCTION

Atherosclerosis is a chronic inflammatory disease of elastic and musculoelastic arteries associated with the formation of atheromatous plaques. As a significant contributor to cardiovascular (CV) morbidity and mortality, atherosclerosis operates insidiously within arterial vasculature, resulting in a diverse range of CV sequelae. Colloquially referred to as arterial hardening or clogging, this pathological entity is responsible for a wide variety of CV disorders, including coronary artery disease, peripheral artery disease, and strokes (1).

The pathogenesis of atherosclerosis involves a series of intricate molecular and cellular events that ultimately result in the development and evolution of atherosclerotic plaques. The process of atherosclerosis begins with damage to the endothelial cells (ECs) that line the inner walls of arteries. Various risk factors such as high blood pressure, smoking, hypercholesterolemia, and inflammation can initiate this damage (2).

Once the ECs are injured, they become permeable to lipids, particularly low-density lipoprotein cholesterol (LDL-c). LDL-c infiltrates into the subendothelial space and undergoes modifications, such as oxidation and glycation, rendering it more susceptible to uptake by macrophages. Macrophages play a central role in atherosclerosis by ingesting the modified LDL-c particles and transforming into foam cells, which are laden with lipid droplets (3). The accumulation of foam cells initiates an inflammatory response, attracting more immune cells, including T lymphocytes and monocytes, to the site of injury. These immune cells release cytokines and chemokines, further promoting inflammation and perpetuating plaque formation. As the plaque grows, smooth muscle cells from the arterial wall migrate into the lesion and proliferate, contributing to the formation of a fibrous cap overlying the lipid-rich core. This fibrous cap is crucial for stabilizing the plaque and preventing rupture, which could lead to thrombosis and acute CV events (4).

Understanding the pathogenesis and molecular mechanisms underlying atherosclerosis is essential for developing targeted therapies aimed at preventing or treating this prevalent cardiovascular disease (CVD).

## ATHEROSCLEROSIS AND INFLAMMATION

In recent years, atherosclerosis has increasingly been recognized as a primarily inflammatory disorder, marking a significant paradigm shift in our under-

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sive approach that encompasses both traditional CVR assessment tools and disease-specific considerations, tailored to the individual patient's needs.

Looking ahead, further research is warranted to deepen our understanding of the underlying pathophysiological mechanisms linking rheumatic diseases and atherosclerosis, as well as to explore novel therapeutic strategies aimed at preventing or attenuating CV complications in this vulnerable population. By addressing the complex interplay between rheumatic diseases and atherosclerosis, we can strive towards improving the cardiovascular health and overall well-being of individuals living with these chronic conditions.

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CHAPTER 6

# DYSLIPIDEMIA AND CARDIOVASCULAR RISK

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## INTRODUCTION

Dyslipidemia, a term denoting the presence of abnormal lipid levels-including cholesterol and triglycerides in the blood, is a crucial risk factor for various cardiovascular diseases, including atherosclerosis and coronary artery disease. The term "dyslipidemia" refers to the presence of abnormal lipid levels, including cholesterol and triglycerides, in the blood. These abnormalities can involve either high or low quantities of lipoproteins, and they are often accompanied by functional disturbances that affect the proper metabolism of lipids. An imbalance in the composition of lipids can result in the accumulation of fatty deposits within the arterial walls, leading to the formation of plaques. Over time, these plaques can narrow and harden the arteries, thereby restricting blood flow to the heart and other vital organs. This condition increases the likelihood of adverse cardiovascular events, including heart attacks and strokes.

In both developed and developing countries, atherosclerotic cardiovascular disease (ASCVD) is the leading cause of mortality (1). Among the most significant preventable risk factors contributing to this condition is dyslipidemia, affecting approximately one in every two adults in Europe and North America (2-4). In Turkey, the prevalence of dyslipidemia has been documented in approximately 80% of the population aged 18 and above (5). The rising prevalence of dyslipidemia worldwide is multifactorial, with the increasing incidence of obesity and Type 2 diabetes mellitus (DM) being a contributing factor. However, it is important to note that dyslipidemia should not be considered exclusively as a lifestyle-related disease. Familial hypercholesterolemia (FH) is the most prevalent autosomal dominant single-gene disorder, characterized by elevated cholesterol levels and early-onset ASCVD, independent of lifestyle factors. The frequency of heterozygous FH has been reported to range from 1/100 to 1/500 in different populations (6).

Statins have consistently demonstrated their efficacy in reducing atherosclerotic cardiovascular disease (ASCVD)-related events and mortality in various studies focused on both primary and secondary prevention purposes (7,8). It has been observed that the greater the reduction in low-density lipoprotein (LDL) cholesterol (LDL-C) levels, the greater the cardiovascular benefit achieved (9). Consequently, there have been noteworthy advancements in the development of agents capable of achieving more substantial reductions in LDL-C levels, thereby leading to the emergence of treatment options that surpass the efficacy of statins (10).

Inflammation is the main feature of rheumatic diseases, and inflammation can lead to dyslipidemia. Inflammation is also associated with accelerated

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CHAPTER 7

# HYPERTENSION

*Seher Şener* [1]

## INTRODUCTION

Hypertension is a condition defined by chronically elevated blood pressure (1). It is a significant cause of cardiovascular diseases and death worldwide. While hypertension is common in general population, it is especially a concern for patients with rheumatic diseases (2). Rheumatic diseases, like systemic sclerosis (SSc), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), psoriatic arthritis (PsA), ankylosing spondylitis (AS), antiphospholipid syndrome (APS), and vasculitis are often linked to higher prevalence of hypertension due to multiple underlying causes (3). This review delves into the relationship between hypertension and rheumatic diseases, with a focus on the underlying mechanisms, clinical implications, and management strategies.

## MECHANISMS OF HYPERTENSION IN RHEUMATIC DISEASES

Hypertension in rheumatic diseases is a multifactorial condition influenced by chronic inflammation, endothelial dysfunction, renal involvement, autonomic nervous system abnormalities, and medication effects (4, 5). Chronic inflammation plays a pivotal role in endothelial dysfunction, which disrupts the normal mechanisms that regulate vasodilation (4). This phenomenon results in increased vascular resistance and elevated blood pressure. Beyond the impact of inflammation, additional factors, including renal involvement, issues with the nervous system, and the utilization of certain medications, have been identified as contributors to hypertension (5).

### Chronic inflammation and endothelial dysfunction

Inflammation is a central part of the development of many rheumatic diseases and plays a key role in the development of hypertension (6). Inflammatory substances such as cytokines (e.g., tumor necrosis factor-alpha [TNF-α], interleukin [IL]-6) and acute-phase proteins (e.g., C-reactive protein) directly affect the vascular endothelium (4). This can impair nitric oxide production, which is necessary for normal vasodilation and makes blood vessels stiffer, less flexible, and more resistant to blood flow, which can lead to hypertension.

### Renal and renovascular involvement

Many rheumatic diseases are associated with renal involvement, which can contribute significantly to the development of hypertension (7). Some examples of conditions that can cause hypertension in these diseases are lupus nephritis in SLE, scleroderma renal crisis in SSc, and glomerulonephritis in RA (7). Renal dysfunction often leads to fluid retention, electrolyte

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eration of the patient's comorbidities and current medications.

- Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs): These agents are particularly beneficial for patients with renal involvement, as they help protect kidney function and control blood pressure (43).
- Diuretics: These medications are employed to reduce fluid retention and are frequently effective in patients with hypertension due to corticosteroid use or renal dysfunction. However, diuretics may cause insulin resistance and may increase the risk of diabetes (44).
- Calcium channel blockers: These medications are particularly effective in managing hypertension, especially in cases involving Raynaud's phenomenon or other vasospastic conditions associated with rheumatic diseases (45).
- Beta-blockers: They are particularly useful for patients with a history of heart failure or arrhythmias. It should be kept in mind that beta-blockers (especially non-selective beta-blockers) may exacerbate Raynaud's phenomenon-related symptoms (46).

### Lifestyle modifications

In addition to pharmacologic treatment, lifestyle modifications play a pivotal role in the management of hypertension in patients with rheumatic disease (47).

- Weight management: A reduction in body weight, achieved through dietary modifications and increased physical activity, has been demonstrated to result in a substantial decrease in blood pressure (48).
- Salt restriction: Reducing sodium intake is essential in controlling hypertension, particularly in patients with renal involvement (49).
- Exercise: Regular physical activity can help improve cardiovascular health and reduce blood pressure (48).
- Smoking cessation: It is imperative for hypertension management. Smoking has been demonstrated to exacerbate vascular damage and hypertension, underscoring the importance of smoking cessation for effective blood pressure management (50).

### Addressing the underlying disease

The management of the underlying rheumatic disease is imperative for the control of hypertension (51). This management may entail the utilization of conventional and biologic DMARDs, or other therapeutic interventions aimed at mitigating inflammation and enhancing vascular function.

## CONCLUSION

Hypertension is a prevalent and grave complication in patients with rheumatic diseases, contributing to elevated cardiovascular morbidity and mortality. The interplay between chronic inflammation, renal dysfunction, medication side effects, and endothelial dysfunction leads to the development of hypertension in this patient population. Early detection, regular monitoring, and individualized management are essential for controlling blood pressure and improving long-term outcomes. The intricate nature of these diseases and their impact on blood pressure necessitates a comprehensive approach to management.

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CHAPTER 8

# HEART FAILURE

*Yusuf Ziya Şener* [1]

## INTRODUCTION

Heart failure is a major global health problem with an approximate prevalence of 1-2% in the general population, increasing significantly with age (1). The burden of heart failure is rising due to aging populations and improved survival from cardiovascular diseases.

Rheumatic diseases, including autoimmune and autoinflammatory disorders, affect a substantial proportion of the population, with varying prevalence rates depending on the specific disorder (2). They can contribute to cardiac dysfunction through direct myocardial involvement, vascular inflammation, and secondary effects of chronic systemic inflammation (3). Moreover, treatments used for rheumatic diseases may have significant cardiovascular effects, either exacerbating or mitigating heart failure risk (4).

In this book chapter, we explore the relationship between rheumatic diseases and heart failure, discussing the mechanisms of cardiac involvement, the impact of disease-modifying treatments, and considerations for managing heart failure in these patients.

## HEART FAILURE DEFINITION AND CLASSIFICATION

Heart failure is a clinical syndrome characterized by functional or structural impairment of ejection or ventricular filling, resulting in inadequate tissue perfusion (5). It is characterized by symptoms such as dyspnea, fatigue, and fluid retention, which can lead to significant morbidity and mortality if not managed appropriately (6).

Heart failure progresses due to various neurohormonal and inflammatory mechanisms, including activation of the renin-angiotensin-aldosterone system (RAAS), leading to vasoconstriction, sodium retention, and increased afterload (7). Increased sympathetic nervous system activity results in elevated heart rate and myocardial oxygen demand, contributing to disease progression (7). Endothelial dysfunction and inflammation play key roles in the development of fibrosis, myocardial stiffness, and vascular remodeling, leading to impaired cardiac function (8). Additionally, impaired calcium handling at the cellular level affects myocardial contractility and relaxation, further exacerbating heart failure (9).

There are numerous classifications of heart failure, and the most commonly used are based on left ventricular ejection fraction (LVEF) and patient's clinical status.

## CLASSIFICATION BASED ON LVEF (10)

- Heart failure with reduced ejection fraction (HFrEF): LVEF <40%. Characterized by systolic dysfunction, where the left ventricle fails to pump blood effectively.
- Heart failure with mildly reduced ejection fracti-

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CHAPTER 9

# MYOCARDIAL DISEASES

*Gökhan Aydın* [1]

## INTRODUCTION

Regardless of the frequency, almost all rheumatological diseases show varying degrees of cardiac involvement. Cardiac involvement may be one of the pathophysiological pathways of the primary disease, or it may appear as a side effect of drugs given for treatment. Primary or secondary cardiac effects of rheumatological diseases may occur with specific or nonspecific symptoms due to involvement in the pericardium, myocardium, valves, conduction system, coronary arteries, or may manifest itself as pulmonary hypertension with pulmonary vascular effects. Symptoms of rheumatic diseases due to cardiac involvement may sometimes be the first sign in the diagnosis of the disease or the involvement may have a subclinical course. Compared to the general population, early diagnosis is very important in the management of the disease because of the relatively increased morbidity and mortality in individuals with rheumatologic disease with cardiac involvement. In this article, the symptoms of relatively common rheumatological diseases due to myocardial involvement will be explained.

1. Rheumatoid Arthritis (RA)
2. Systemic Lupus Erythematosus SLE
3. Systemic Sclerosis (SSc)
4. Vasculitides
   - Takayasu Arteritis
   - Giant Cell Arthritis
   - Kawasaki Disease
   - ANCA (Anti-neutrophil cytoplasmic antibody) Related Vasculitides
   - Henoch-Schonlein Purpura
5. Behcet's Disease
6. Sjogren's Syndrome
7. Ankylosing Spondylitis
8. Inflammatory Myopathies

## RHEUMATOID ARTHRITIS

Rheumatoid Arthritis (RA) is a chronic, progressive disease that usually peaks at the age of 40-50 years and is more common in women than in men, can involve multiple organs with autoimmune mechanisms, and affects many systems, including the cardiovascular system, which is seen with a frequency of 1 in every 100 people in the community. Although it is characterized by symmetrical polyarthritis, extra-articular involvement indicates a poor prognosis, which increases the risk associated with cardiovascular morbidity and mortality (1). Although there is cardiac involvement in approximately half of the cases, with the dominant involvement in the pericardium in RA, myocardial involvement is relatively less and silent, similar to other autoimmune rheumatological diseas-

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### Sjogren's Syndrome

Clear evidence of cardiac involvement in primary Sjören syndrome is insufficient. Pericardial effusion, left ventricular dysfunction or AV node dysfunction can be seen in the acute or chronic phase of Sjögren's syndrome. However, disease-specific primary myocardial involvement is not common except in sporadic cases.

### Ankylosing Spondylitis

Ankylosing spondylitis is a joint disease that limits physical activity and contributes to cardiovascular risk factors such as hypertension, lipid profile disorders, obesity and metabolic syndrome. Therefore, it is not surprising that cardiovascular mortality was higher compared to the control groups. Myocardial involvement, which occurs in the form of valvular involvement, conduction tract disease as well as left ventricular diastolic dysfunction, is more common in both the elderly and young population than in the general population (31). A distinction should be made between the most common valvular pathologies in ischemic heart disease/myocardial involvement and ankylosing spondylitis, which may occur as a result of clinically accelerated atherosclerosis. Therefore, in these patients whose exercise capacity is reduced due to the primary disease, the differentiation of pathologies that may have silent clinical symptoms should be made with routine echocardiographic evaluation. CMR and coronary angiography can be performed for the diagnosis of myocardial disease in selected cases without valve disease.

### Inflammatory Myopathies

Cardiac involvement in idiopathic skin-muscle diseases such as Polymyositis/Dermatomyositis can be seen at rates of up to 75% depending on the diagnostic methods used, although it is often clinically silent (32). Myocardial involvement, which is mostly silent, occurs mostly in women and in the late period depending on the duration of the disease. Myocardial inflammation, myocarditis, diastolic dysfunction and heart failure are the most common clinical and laboratory findings.

## CONCLUSION

Accurate comparisons between studies are difficult, as there is great heterogeneity in the definition of cardiac involvement in rheumatic diseases. The prevalence of the primary disease and myocardial involvement at different rates among diseases and the absence of clinical manifestations of the involvement are compelling reasons for diagnosis. Although cardiac involvement and symptoms occur mostly in the late period, the fact that cardiac involvement is the most important factor determining mortality in rheumatic diseases reveals the importance of early diagnosis.

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CHAPTER **10**

# VALVULAR DISEASES

*Ahmet Anıl Başkurt* [1]

## INTRODUCTION

Rheumatic diseases are a group of inflammatory conditions that affect the joints, muscles, and other organs of the body. Some rheumatic diseases can also affect the cardiovascular system, leading to a range of manifestations including pericarditis, myocarditis, and valvular heart disease. Valvular heart disease is a common cardiovascular complication of rheumatic diseases and can lead to significant morbidity and mortality if left untreated. Valvular heart disease refers to conditions in which the heart valves are damaged or malfunctioning, leading to impaired blood flow through the heart. In this chapter; We will explain the heart valve involvement of different rheumatological diseases.

### Valvular heart disease and rheumatic disease

Rheumatic fever (RF), an inflammatory disease caused by untreated streptococcal infections, is a common cause of valvular heart disease in developing countries. Rheumatic fever can lead to rheumatic heart disease (RHD), which is characterized by fibrosis and scarring of the heart valves. RHD is a significant cause of morbidity and mortality in developing countries, particularly in children and young adults.

Carditis, which is the most important cause of mortality in the acute phase of acute rheumatic fever disease, can lead to fibrosis and permanent valve damage after the acute phase, and resistant heart failure requiring surgical intervention. Thus, the risk of mortality in RF continues with surgical complications or bacterial endocarditis (1). Carditis symptoms usually appear within 1-2 weeks following the arthritis findings. Cardiac involvement in RF is almost always accompanied by a murmur indicating the presence of heart valve inflammation (2). Endocarditis with inflammation of the mitral and aortic valve leaflets and mitral cord is the most typical manifestation of rheumatic carditis. Tricuspid and pulmonary valves are rarely affected, and these valve involvements can be encountered in patients with severe and chronic RF (3). The most commonly involved structure is the mitral valve. It can be best detected by a typical mitral regurgitation murmur that can be heard in the left lateral lying position, radiating from the apex to the left axilla, filling the entire systole (pansystolic), and a mid-late diastolic "Carey Coombs murmur" due to the relatively narrowed mitral valve opening due to edema of the mitral valve leaflets (4). The most common valve stenosis developing due to fibrosis in the long term is mitral stenosis (Figure 1) (4,5). The second most frequently involved valve is the aortic valve, and aortic valve regurgitation occurs in approximately 20% of patients with rheumatic carditis. It is often associated with mitral valve involvement. An

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hardening of the aortic root as a result of aortitis. Aortic regurgitation develops in 10% of patients with AS and may be seen at lower rates in patients with psoriatic arthritis and reactive arthritis. The severity of aortic root diseases is related to the age of the patient and the duration of the spondylitis. A murmur of aortic regurgitation is best heard at the right sternal border. Stenotic lesions of the aortic valve and mitral regurgitation are rare. In a study using electrocardiography and transthoracic echocardiography in 100 patients with spondylitis for more than 15 years, it was reported that there was no significant increase in valve disease rates (13). For this reason, routine echocardiography is not considered necessary for the development of aortitis in patients with AS, and investigation of aortic regurgitation with a careful physical examination would be a more recent approach.

Takayasu arteritis is a large vessel vasculitis and involves aorta and it's branches. Aortic regurgitation may occur in approximately 25% of the cases and it is shown to be associated with worse prognosis (Figure 2). Surgical intervention should be performed after the inflammation was controlled in elective cases (14).

Treatment of valvular heart disease in rheumatic diseases depends on the severity of the disease and the degree of valve damage. Mild valvular disease may not require any treatment, while more severe disease may require medical management or surgical and percutaneous intervention. In cases of severe valvular disease, valve replacement surgery may be necessary to improve symptoms and prevent further complications.

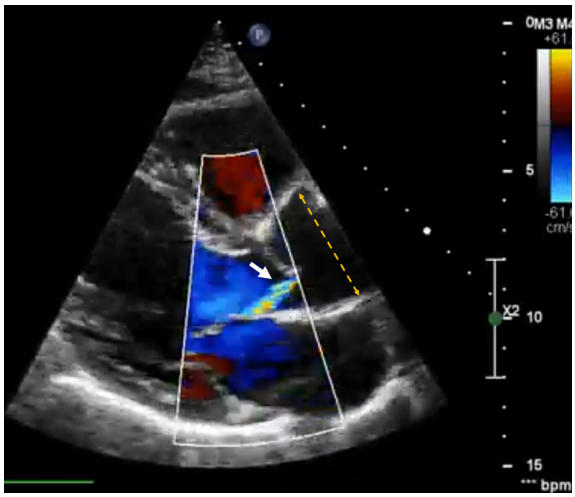


**Figure 2.** White arrow shows mild aortic regurgitation and yellow dashed arrow line shows the dilated ascending aorta in a patient with Takayasu arteritis.

## CONCLUSION

Valvular heart disease is a common cardiovascular manifestation of rheumatic diseases, particularly in cases of RHD. Mitral stenosis and regurgitation are the most common types of valvular disease seen in RHD, but valvular disease can also occur in other rheumatic diseases such as SLE and RA. Treatment of valvular heart disease in rheumatic diseases depends on the severity of the disease and the degree of valve damage and may include medical management or surgical intervention.

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CHAPTER 11

# PERICARDIAL DISEASES

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## INTRODUCTION

Rheumatologic diseases are autoimmune and autoinflammatory conditions that affect multiple organ systems and present with diverse clinical manifestations. Cardiac involvement is a common occurrence in rheumatic diseases, with etiology including the direct effect of rheumatic disease, accelerated atherosclerosis, or side effects of drugs used to treat the disease. However, it often presents atypically, requiring a clinical suspicion for diagnosis. Cardiac involvement may be either subclinical or may result in significant morbidity and mortality. The pericardium may be involved, resulting in pericarditis or pericardial effusion. The myocardium may also be involved, leading to conditions such as myocarditis, cardiomyopathy, rhythm and conduction disorders, and heart failure. Additionally, the endocardium, including the valves, may be involved, causing valve disease. The coronary arteries and great vessels may also be involved, resulting in conditions such as ischaemic heart disease and aneurysm formation. Thrombus formation may also occur. Pericardial involvement may present in a wide clinical spectrum that includes acute, recurrent, and persistent pericarditis, constrictive pericarditis, asymptomatic pericardial effusion, and pericardial tamponade (1). Therefore, early diagnosis and treatment have great importance.

## ETIOPATHOGENESIS

The pericardium is consist of two distinct layers. The lamina visceralis covers the epicardium, while the lamina parietalis is adjacent to the fibrous pericardium. There is 50-100 ml of plasma filtrate between the lamina visceralis and lamina parietalis (2,3). Pericarditis is classified according to its acute, subacute, chronic, or recurrent nature (4). Rheumatic diseases are a contributing factor in 2-7% of acute pericarditis cases and 10% of recurrent pericarditis cases (5-7). Infectious causes, including viral, bacterial, and fungal, as well as non-infectious causes such as autoimmune conditions, neoplastic, metabolic, traumatic, iatrogenic, and drug-related, may all result in the development of pericarditis. The symptoms typically include pleuritic chest pain during deep inspiration, palpitations, dyspnea, and low-grade fever (1). In most cases, the involvement of other organs is evident before the onset of pericarditis. Symptomatic pericarditis typically occurs during the active phase of the disease.

There are various underlying pathogenesis of pericarditis in the rheumatic diseases. Table 1 delineates the pathogenesis of pericardial involvement in the context of various autoimmune pericarditis entities (8).

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pericardium. This can lead to pericardial effusion or constrictive pericarditis in severe cases (35). While the primary manifestation of TAK is arterial stenosis or aneurysms, cardiovascular complications such as pericarditis are significant, requiring careful monitoring and management. The treatment approach typically involves corticosteroids and immunosuppressive agents to control the inflammatory process and prevent further damage to the heart and vascular system (35).

## CONCLUSION

Cardiac involvement in rheumatologic diseases has increasingly become a primary concern for rheumatologists. Autoimmune disease is the underlying cause of approximately 22% of acute pericarditis cases (36). Complications may include recurrent pericarditis and, less frequently, cardiac tamponade and constrictive pericarditis. Cardiology and rheumatology specialists must work closely together to ensure an accurate diagnosis. A variety of non-invasive imaging modalities, including TTE, CT, CMR, and PET, can be employed for diagnosis. It is essential to consider the respective advantages and disadvantages of these modalities and to integrate them into a comprehensive clinical diagnosis and patient follow-up plan. The cornerstone of treatment is the implementation of tailored regimens comprising immunosuppressive or antiinflammatory agents. A multidisciplinary team comprising experts in cardiology and rheumatology should undertake a comprehensive review of the patient's underlying autoimmune disorder and renal and liver function before contemplating further treatment options.

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CHAPTER **12**

# PULMONARY HYPERTENSION

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## INTRODUCTION

Pulmonary hypertension (PH) is a global health problem that is defined as mean pulmonary arterial pressure greater than 20 mmhg and may affect all age groups. Its prevalence is around 1% globally. While PH associated with left heart disease remains the most common cause, PH due to chronic obstructive pulmonary disease (COPD) represents the second most common cause (1). Pulmonary hypertension is classified under 5 groups: Group 1 PH: pulmonary arterial hypertension (PAH); Group 2 PH: PH due to left heart disease; Group 3 PH: PH due to chronic lung disease; Group 4 PH: chronic thromboembolic PH (CTEPH); Group 5 PH: Idiopathic PH.

The prevalence of Group 1 PAH is 48-55 cases/million adults and predominantly affects young women (2). Group 1 PH (PAH) is classified in the following subgroups: idiopathic PAH, PAH associated with connective tissue diseases, heritable PAH, PAH associated with congenital heart diseases, drug and toxin induced PAH and PAH associated with portal hypertension. Idiopathic PAH is the most common subtype with a prevalence of 50-60% (3). PAH is a pulmonary vascular complication of different connective tissue diseases including systemic sclerosis (SS), systemic lupus erythematosus (SLE), Sjögren syndrome and dermatomyositis. SS accounts for the 5-19% of cases with connective tissue disease related PAH. Its clinical presentation and treatment are similar to those of IPAH (4).

Patients with pulmonary hypertension present with clinical symptoms associated with right ventricular dysfunction. In the early phases of the disease, exercise induced dyspnea is observed. Other symptoms are associated with the severity and stage of the disease. The treatment goal is to be aware of the disease at an early stage, suspect PH and refer relevant patients to PH centers. The underlying disease should be detected through different diagnostic tests and the treatment should be initiated after proper risk classification (5).

## DIAGNOSIS AND TREATMENT OF PULMONARY ARTERIAL HYPERTENSION

Patients with PAH typically present to primary care physicians with non-specific symptoms in the early stages of the disease. The diagnosis is often missed because it does not come to mind and patients lose time to start treatment. Several studies have reported that it takes more than 2 years from the onset of PH symptoms to diagnosis and initiation of treatment (6). Suspicion of pulmonary hypertension is the first step in its diagnosis. In addition, patients with systemic sclerosis (SS), BMPR2 gene mutation, first-degree relatives with hereditary PAH, liver transplant

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CHAPTER **13**

# ARRHYTHMIAS

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## INTRODUCTION

Rhythm and conduction disorders and sudden cardiac death are among the important symptoms of cardiac involvement in autoimmune rheumatic diseases, resulting in morbidity and mortality. Arrhythmias may present as atrial and ventricular arrhythmias, conduction system abnormalities, biventricular heart failure, or sudden death. Among the many arrhythmogenic factors underlying arrhythmias, myocardial fibrosis plays an important role. Myocardial fibrosis constitutes the pathological substrates for reentrant circuits. The most common cause of fibrosis is inflammation or coronary artery occlusive disease, followed by supraventricular extrasystoles, tachyarrhythmias, ventricular activity, and conduction disorders. In light of this information, the first part of the article addresses the type, prevalence, and underlying mechanisms of arrhythmias in cardio rheumatology.

Rheumatic heart disease is a common cause in underdeveloped countries, contrary to developed countries, where the most common cause of atrial fibrillation is not valvular. Rheumatic heart disease is more common in young people. The onset of atrial fibrillation in rheumatic heart patients may lead to poor outcomes with increased morbidity and mortality. The risk of stroke in rheumatic atrial fibrillation has not been systematically adequately assessed using risk scores. Given the foregoing, the second part of the article addresses atrial fibrillation, an important type of arrhythmia seen in rheumatic heart disease.

## RHEUMATIC DISEASES

Rheumatic diseases (RD) involve more than one organ or system, including the musculoskeletal system. The mechanisms that affect the cardiovascular system include myocardial inflammation, fibrosis, vasculitis, thromboembolic events, and early atherosclerosis. All these mechanisms increase the frequency of altered automaticity and re-entry phenomena in patients with RD. Conduction disorders, which are more common than general rhythm disorders, usually occur during the exacerbations of RD. The mechanisms that cause rhythm disorders in autoimmune rheumatic diseases, the most important of which are myocardial inflammation and fibrosis, are different from other mechanisms and yet to be elucidated.

Inflammatory processes, oxidative stress, and cardiomyocyte necrosis can produce electrical and structural remodeling. Chronic inflammation produces sympathetic overactivation and reduced parasympathetic function. Autoantibody-mediated and drug-induced arrhythmias are also common. In systemic patients, all heart structures may be affected. Rhythm and conduction disorders can be seen in

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CHAPTER **14**

# THROMBOEMBOLIC EVENTS

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## INTRODUCTION

The role of active inflammation in the pathogenesis of thrombosis is becoming increasingly recognized (1). Inflammation induces a prothrombotic state (1,2) through the activation of endothelial cells and the increased production of tumor necrosis factor α (TNFα) and other cytokines. This causes an elevation of tissue factor (TF), a natural procoagulant, while decreasing protein C levels and promoting platelet activation (1). Table 1 shows some examples of the procoagulant effect of inflammation.

Rheumatologic diseases (RD), often occurring with inflammation, have been associated in some cases to hypercoagulability and thrombosis, both arterial and venous (1,2). A case-control study, in 2012, reported that connective tissue diseases were associated with an increased risk of venous thromboembolism (VTE), whereas diseases affecting the skin alone were not (3). In this chapter, we will review the main RD related to hypercoagulability.

## SYSTEMIC LUPUS ERITHEMATOSUS

Systemic Lupus Erythematosus (SLE) is a systemic autoimmune disease that may involve nearly every system in the human body. Cardiovascular (CV) manifestations are seen frequently (4). Incidence varies depending on sex, ethnics and age; being more frequent in non-Caucasians and urban populations.

**Table 1: Examples of the procoagulant effects of inflammation. TF: tissue factor, tPA: tissue plasminogen activator, vWF: von Willebrand factor. Adapted from (2).**

| Site | Role | Effect |
|---|---|---|
| Endothelium | Leukocyte modulation.<br>Release of inflammatory cytokines. | Increases TF and other procoagulants.<br>Decreases tPA and other anticoagulants. |
| Platelets | Release of proinflammatory cytokines.<br>Microparticle-mediated inflammation. | Platelet activation induces expression of adhesion molecules (vWF, P-selectin, fibrinogen, fibronectin...) and coagulation factors (FV, FVIII, FXI, FXIII). |
| Coagulation cascade | Activated by TF-VIIa complex. Thrombin generation. P-selectin expression. | Increased TF expression. |

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sive arteritis in the remaining third. Anastomotic aneurysm formation may occur 1-12 months after surgery or even catheterization. Recurrent surgeries increase the risk of mortality and morbidity (34). CV implication may occur as pericarditis, coronary artery disease, cardiomyopathy and, more rarely, valvular dysfunction (33,34). Patients with BD may present arterial stiffness more frequently than healthy controls, without significant CV involvement (34,39,40).

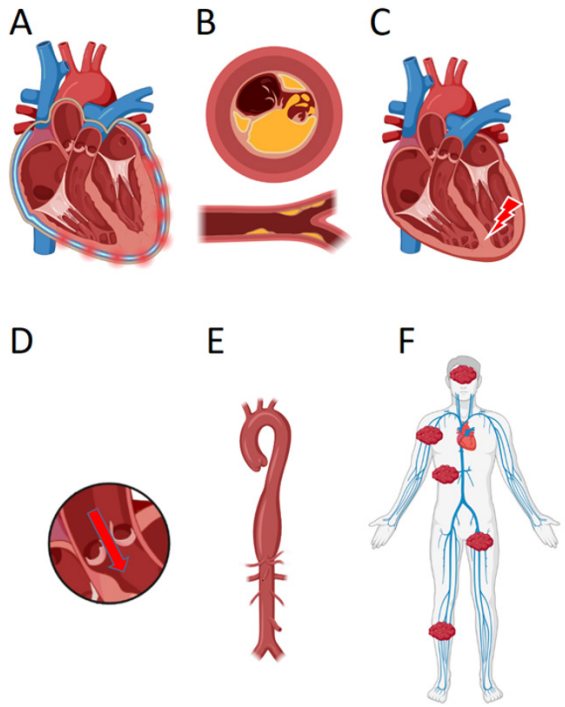


**Figure 1.** Types of cardiovascular involvement in BD. From left to right: A. Pericarditis, B. Atherosclerotic coronary artery disease, C. Cardiomyopathy, D. Valvular dysfunction, E. Arterial aneurysms, F. Venous thrombosis at usual or unusual sites. Created by the author with BioRender®.

### Management

The use of immunosuppression has been found to prevent relapse of venous thrombosis (41). Clinical guidelines currently encourage the use of immunosuppressants over anticoagulation or antifibrinolytic therapies (38). When anticoagulation is needed in BD, patients should be monitored due to the possibility of coexisting pulmonary arterial aneurysm and its bleeding risk (2). Secondary prevention also relies mainly on immunosuppression rather than anticoagulation therapies (35).

## OTHER AUTOIMMUNE DISEASES

Granulomatosis with polyangiitis has an increased risk of VTE during the first two years after the diagnosis (42). In 2015, Ungprasert *et al.* performed a metanalysis describing a statistically significant increased VTE risk in patients with Sjogren's syndrome (43). Also in 2015, Ungprasert *et al.* (44) described a higher VTE risk among patients with sarcoidosis. There are not different recommendations regarding treatment and secondary prophylaxis for patients with these diseases than those of the general population (12).

## CONCLUSION

Patients with rheumatic diseases are at increased risk of developing venous thromboembolism (VTE). The risk of VTE seems to be highest in the first year of disease and the risk of VTE seems to be related to the activity of the inflammatory disease, rather than the administered treatments. Thromboembolic events being increasingly recognized as a complication of rheumati diseases results in significant morbidity and mortality. Physicians should be aware of this risk and act accordingly.

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CHAPTER **15**

# AORTA AND PERIPHERAL ARTERY DISEASES

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## INTRODUCTION

Aorta and peripheral artery diseases (PAD) are complex conditions that can present significant challenges in their diagnosis and treatment. These diseases affect the major arteries that supply the body, including the aorta and its branches, and can lead to severe consequences if left untreated. However, recent advances in diagnostic techniques and treatment modalities have revolutionized the field of cardiology, offering new hope for patients with these conditions. Aorta is involved in large vessel vasculites (Takayasau arteritis and giant cell arteritis) and vasculitic involvement may cause both stenosis and aneurysmal dilatation. Moreover, all rheumatic diseases contributes accelerated atherosclerosis thorough the increased inflammatory state and risk of atherosclerotic aortic and peripheral artery disease is increased in patients with rheumatic diseases (1, 2). Management of aortic vasculitis are discussed in disease specific chapters. Therefore, this chapter provides an up-to-date overview of the management of aortic diseases and PAD in general.

## PATHOPHYSIOLOGY

### Atherosclerosis

Atherosclerosis is the primary underlying pathology in the development of aorta and peripheral artery diseases. It involves the progressive accumulation of lipid-rich plaques within the arterial walls, leading to vessel narrowing, occlusion, or aneurysm formation. Recent studies have elucidated various cellular and molecular mechanisms involved in atherosclerosis progression, providing insights into potential therapeutic targets. One crucial aspect of atherosclerosis is endothelial dysfunction, which is characterized by impaired nitric oxide production, increased oxidative stress, and enhanced expression of adhesion molecules. Endothelial dysfunction plays a critical role in the initiation and progression of atherosclerotic lesions. Activation of endothelial cells allows the infiltration of immune cells, such as monocytes and T cells, into the arterial wall, triggering an inflammatory response (3, 4).

Inflammation is a key driver of atherosclerosis, and recent studies have focused on understanding the complex interplay between inflammatory cells, cytokines, and chemokines in the development of atherosclerotic plaques. One notable study by Libby et al. (4) emphasized the role of innate immune cells, such as macrophages and dendritic cells, in the initiation and progression of atherosclerosis. These cells promote the recruitment of other immune cells and contribute to the formation of a lipid-rich necrotic core within the plaques (4). Moreover, the inflammasome, a multiprotein complex involved in the activation of inflammatory responses, has emerged as a key mediator in atherosclerosis pathogenesis. A study

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### *Carotid Endarterectomy*

Carotid endarterectomy is a surgical procedure performed to remove plaque and restore blood flow in the carotid arteries, which supply blood to the brain. It is indicated for patients with significant carotid artery stenosis who are at high risk of stroke. Carotid endarterectomy has been shown to significantly reduce the risk of stroke in patients with symptomatic and severe asymptomatic carotid stenosis, Cartotid artery stenting is also another option for the treatment of carotid artery stenosis and the type of intervention should be decided based on patient's surgical risk (22).

## Future Directions

Gene Therapy

Gene therapy aims to modulate gene expression to address underlying molecular defects and promote disease regression. In aorta and peripheral artery diseases, gene therapy holds the potential to target key pathways involved in plaque formation, inflammation, and vascular remodeling. Preclinical studies have shown promising results with gene therapy approaches targeting genes involved in lipid metabolism, inflammation, and neointimal hyperplasia. For example, the use of adeno-associated viral vectors to deliver genes encoding for anti-inflammatory cytokines or endothelial nitric oxide synthase has demonstrated favorable effects on plaque stability and vascular function in animal models. Clinical trials are underway to evaluate the safety and efficacy of gene therapy in aorta and peripheral artery diseases, which may pave the way for novel therapeutic strategies (23, 24).

### *Stem Cell Therapies*

Cell-based therapies involve the transplantation or modulation of cells to promote tissue repair and regeneration. In aorta and peripheral artery diseases, cell-based therapies aim to enhance angiogenesis, promote vascular remodeling, and improve blood flow. Preclinical studies have explored the use of various cell types, including endothelial progenitor cells, mesenchymal stem cells, and induced pluripotent stem cells, for therapeutic purposes. These studies have shown promising results in promoting neovascularization, improving endothelial function, and reducing atherosclerotic burden ((1)Clinical trials are ongoing to assess the safety and efficacy of cell-based therapies in patients with aorta and peripheral artery diseases (25, 26).

## CONCLUSION

Patients with rheumatic diseases are at increased risk for peripheral artery disease and aortic disease. Antiplatelet therapy, lipid-lowering therapy, and blood pressure control are key components of medical therapy. Interventional procedures such as angioplasty, stenting, EVAR, and surgery are used when medical management alone is not sufficient. Interventional procedures should be performed after inflammation has been suppressed and control of the underlying disease has been achieved. Advances in interventional techniques and devices have significantly improved outcomes, resulting in better patient outcomes. Personalized treatment plans that take into account patient-specific factors and disease characteristics are essential to optimize outcomes in aortic and peripheral artery disease.

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CHAPTER **16**

# STROKE

*Edip Varan* [1]

## INTRODUCTION

Stroke is a medical condition that causes sudden focal neurological deficit. It is classified as ischemic stroke (IS) and hemorrhagic stroke (HS) (1). Stroke recently has become an important healthcare problem. According to research conducted in 2016, stroke accounts for 10% of total deaths worldwide. It is an important physical problem for patients and causes emotional disorders (2). Therefore, it is necessary to clearly understand the risk of stroke. Modifiable risk factors constitute most of the risks in the population. These include obesity, hyperlipidemia, hypertension, diabetes mellitus, smoking, alcoholism, psychosocial factors, and cardiac causes (3).

Inflammation, the main underlying mechanims in rheumatic diseases, plays a crucial role in pathogenesis of stroke, and many other chronic diseases (4-6). Arthritis is a chronic inflammatory disease with synovial tissue inflammation (7, 8). Inflammation of the joints and other tissues induces the production of cytokines (9, 10). The main rheumatic diseases in which arthritis is the main driver of the clinical presentation are rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), and osteoarthritis (OA) (11).

Cytokines and other inflammatory mediators also contribute the pathogenesis of stroke. Proinflammatory mediators cause monocyte and leukocyte adhesion to the vascular wall, followed by chemotaxis, leading to atherosclerosis and stroke (12,13).

## RHEUMATOLOGIC DISEASES

Rheumatic diseases include a range of diseases and they may also involve outside the musculoskeletal system. There are several rheumatic diseases and RA, PsA, AS, and systemic lupus erythematosus (SLE) accounts for the majority of daily practice (14).

RA is a chronic, progressive inflammation of the small synovial joints causing deformity and pain. The annual incidence of RA, adjusted for age and sex, is 40.9 per 100,000 (15). Other manifestations of RA are keratoconjunctivitis, cardiovascular diseases, and interstitial pulmonary fibrosis (16).

RA is a risk factor for stroke. Those with rheumatological diseases die at an early age from stroke and cardiovascular diseases. Therefore, the risk of stroke in these patients should be determined to reduce the number of deaths. Higher incidence rates of stroke in patients with rheumatic disease was established in large population studies (17).

Stroke incidence increases with increasing age. Stroke is rare at early ages, but stroke occurs at younger ages in rheumatic diseases. There is no stroke risk difference over 65 years of age in patients with and without rheumatic diseases. As inflammation plasy a central role in stroke pathogenesis, the risk of stroke

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CHAPTER **17**

# RHEUMATOID ARTHRITIS

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## INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized primarily by the involvement of joints containing the synovium. Although its etiology has not yet been fully elucidated, it is thought to occur with the effect of some environmental factors based on genetic predisposition. The immune system is reactivated as a result of a complex interaction of genetic and environmental factors and impaired self-tolerance. Among the environmental factors, the most important factor that is related to RA is smoking. In addition to smoking, inhaled agents such as silica dust and air pollution, various bacterial and viral infections, obesity, vitamin D deficiency, and low education level have also been suggested to play a role in the development of RA (1,2).

As a result of autoantibody formation and abnormal intracellular signal transduction, inflammation develops in tissues under the influence of immune system elements such as cytokines, chemokines, growth factors, and matrix metalloproteinases (3). RA occurs in approximately 1% of adults and is the most common chronic inflammatory arthritis. It affects women 2 to 3 times more often than men (4). While the disease usually shows an insidious course with constitutional symptoms such as weakness, fatigue, loss of appetite, and sometimes weight loss before the overt arthritic picture develops, in some cases, it may present with an acutely severe clinic.

Although the typical joint involvement pattern is in the form of symmetrical polyarthritis of the small joints of the hands and feet, mono-oligoarticular involvement can also be seen. Morning stiffness and swelling in the affected joints are the most important features of RA (5).

The most characteristic laboratory finding is rheumatoid factor (RF) positivity. RF is an antibody against the Fc fragment of immunoglobulin G and is detected in the serum of approximately 75% of RA patients. However, the specificity of RF in the diagnosis of RA is low and it can be positive in many chronic inflammatory and some infective conditions (6). Another antibody is an anti-citrullinated peptide antibody (ACPA) (the most common of the anti-modified protein antibodies [AMPAs]) and is found in approximately 70-75% of patients with RA. AMPAs include antibodies that target citrullinated and carbamylated protein structures. In contrast to RF, ACPA has a high specificity (>90%) in the diagnosis of RA (7,8). These autoantibodies can be detected in serum years before the diagnosis of the disease. It has been shown that both RF and ACPA positivity are associated with more aggressive and erosive joint disease as well as extra-articular involvement.

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### Cardiac conduction abnormalities

Although usually clinically insignificant, conduction system abnormalities have been found in up to 50% of patients with RA through electrocardiography studies. All types of conduction abnormalities can be seen, including complete heart block. There is a twofold increase in the risk of sudden cardiac death in RA patients compared to healthy controls (21). The etiology of arrhythmia, which is more common in patients with seropositive nodular disease, includes cardiac nodulosis, amyloidosis, and HF in addition to ischemia due to atherosclerosis. On the other hand, increased sympathetic activity in RA patients may theoretically contribute to the development of ventricular tachyarrhythmias (22).

## CONCLUSION

RA is not only a joint disease but can also exhibit extra-articular involvement. Among these, the cardiovascular system has a particular importance due to its increased mortality risk. Cardiovascular structures are adversely affected directly or indirectly, especially through chronic inflammation. Controlling disease activity with effective and aggressive treatment will significantly reduce morbidity and mortality from cardiovascular disease. Considering that the chronic inflammatory process plays a major role, patients should be evaluated for cardiac risk at regular intervals determined by additional risk factors, even if they are subclinical.

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CHAPTER **18**

# SJOGREN'S SYNDROME

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## INTRODUCTION

Sjogren's syndrome (SS) is an autoimmune dissease which affects exocrine organs (lacrimal, salivary and parotid glands). SS may be seen as primary or secondary to another rheumatological disorder, the secondary form mostly accompanies rheumatoid arthritis (RA). Dry eyes and dry mouth are the most common clinical features of SS but extraglandular manifestations can also be observed. The prevalence of primary Sjögren's syndrome (pSS) is estimated to affect 0.1% to 4% of the general population, with a notable gender disparity, with females exhibiting a nine-fold greater risk than males (female to male ratio = 9:1). Primary SS typically affects females between ages 30 and 50 years (1).

Lymphocytes are the predominant cells involved in the inflammatory process in SS. In mild lesions, the predominant cell population within the affected tissue is constituted by CD4+ T lymphocytes, which account for 70–80% of the total cellularity. Conversely, in more advanced lesions, B cells emerge as a prominent cellular component (2). Immunoglobulins exhibiting reactivity to Ro52, Ro60 (Anti-SSA/Ro) and/or La (Anti-SSB/La) antigens are released from B cells and these antibodies play a pivotal role in the pathogenesis (3). Lymphocyte mediated damage is responsible for the clinical manifestations.

## CLINICAL FINDINGS

The clinical spectrum of SS, encompasses a range from dryness of the mucosal surfaces to the systemic involvement (extra glandular involvement). While the most common findings are xerophtalmia and xerostomia, patients may also present with more systemic symptoms, such as fatigue and arthralgia. Generalised pain, fibromyalgia, weakness, and sleep disturbances are common (4). Skin, joint, lung, liver, renal and neurological involvement can be seen in SS. The treatment approach is specified based on the type and severity of the involvement. Patients who have organ involvement require more aggressive therapy (Table 1) (1,5).

## DIAGNOSTIC APPROACH

### Assessment of ocular and oral dryness

*Diagnostic testing for dry eye;*

- Shirmer's test evaluates tear production with a filter paper. It is diagnostic if tear production is less than 5 mm at the fifth minute.
- Rose Bengal scoring, Lissamine green test and ocular staining scores are employed to evaluate the structural damage to the conjunctival epithelium via staining.

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single risk factor, especially in diseases in which many components play a role in etiology, such as CV diseases (33). In some studies, traditional risk factors such as hypertension, hyperlipidemia, obesity, metabolic syndrome were found more common in patients with SS, but these are conflicting results (34,35).

Some data suggest that the rate of cerebral infarction and venous thromboembolism (VTE) may be higher in the anti-Ro (SSA) and anti-La (SSB) seropositive subgroups compared to the healthy population. Although the data require confirmation, there is some evidence to suggest that the presence of autoantibodies is associated with an increased risk of cardiovascular morbidity (36). Atherosclerosis is an inflammatory process involving vessel walls, and endothelial dysfunction is the starting point of this course. An association between metabolic syndrome, dyslipidemia and serum concentration of interleukin (IL)-1β and IL-6 in SS patients is not surprising (35). Additionally, endothelial dysfunction seems more prominent in patients with active disease measured by SS activity index (37). The most supported theory is that CV risk is the consequence of a complex combination of multiple factors, including traditional risk factors and disease-related mechanisms, longer disease duration and administered treatment agents.

## CONCLUSION

In conclusion, cardiovascular involvement is not common in Sjogren's syndrome, and the most common cardiovascular manifestation is mild asypmtomatic pericardial effusion. The most significant form of involvement is fetal heart block, which can be observed as a consequence of transplacental transmission of anti-Ro (SSA) and anti-La (SSB) antibodies to infants whose mothers have been diagnosed with SS. Precautions should be taken in this regard and fetal echocardiography follow-up should be performed at 16$^{th}$ to 28$^{th}$ weeks of pregnancy. It is known that chronic inflammatory conditions are associated with increased atherosclerosis; this has also been demonstrated in patients with SS. The risk is amplified by the chronic state of the disease, the effects of aging, and the adverse effects of treatments. It is therefore recommended that patients with SS should also be monitored in terms of the components of metabolic syndrome.

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CHAPTER **19**

# RELAPSING POLYCHONDRITIS

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## INTRODUCTION

Relapsing polychondritis (RP) is a rare, autoimmune disorder characterized by recurrent episodes of inflammation targeting cartilage and proteoglycan-rich tissues throughout the body. Accordingly, the structures affected by RP include not solely cartilaginous formations, including the auricular, nasal, respiratory, and articular sites, but also extend to non-cartilaginous tissues, notably encompassing ocular, cutaneous, cardiac, and central nervous system elements (1). In more than 80% of patients, RP manifests with distinctive clinical features typified by auricular chondritis and polyarthritis, albeit with the potential for involvement of other organ systems as well (2). Moreover, up to 30% of RP patients have concurrent or associated diseases, such as rheumatoid arthritis, Sjogren's syndrome, systemic sclerosis, systemic lupus erythematosus, ankylosing spondylitis, psoriatic arthritis, vasculitis (Antineutrophil cytoplasmic antibody-associated vasculitides, polyarteritis nodosa, Behçet's disease), myelodysplastic syndromes, lymphoma, and autoimmune thyroid diseases (3,4).

Cardiovascular involvement has been reported in up to 25% of these patients. More importantly, this involvement is accepted as the second most common cause of death after respiratory system involvement. In this section, the author aims to emphasize the cardiovascular manifestations of RP, while also reviewing the epidemiology, etiopathogenesis, clinical presentations, diagnosis, and treatment approaches in patients with RP.

## EPIDEMIOLOGY AND ETIOPATHOGENESIS

The estimated yearly incidence of RP approximates 3.5 cases per one million individuals in the USA (3,5). The incidence and prevalence rates differ across various countries. In a study conducted in the UK, the authors reported 106 cases during 87 million person-years (6). However, the incidence of RP in Hungary is similar to that in the USA (7). In addition, the incidence of organ involvement is reported at varying rates according to geographical regions. For example, an article scrutinizing the clinical and prognostic features of RP within the Chinese population revealed notable distinctions. Specifically, the research delineated lower incidence rates of arthritis, auricular chondritis, ocular inflammation, and renal involvement, while concurrently indicating a higher incidence of laryngotracheal symptoms, skin manifestations, and neurological complications when compared to the corresponding parameters observed among Caucasians (8).

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adalimumab), tocilizumab, anakinra, rituximab, and abatacept, have been employed in patients refractory to conventional therapeutic approaches. The dose of these bDMARDs is similar to the dose used in patients with rheumatoid arthritis. Data are limited on some treatment approaches, such as leflunomide, high-dose intravenous immunoglobulins, anti-CD4 monoclonal antibodies, and plasmapheresis. In addition, the results of using these drugs are contradictory (2,6,12,13).

Treatment options may vary depending on the type of involvement. Managing cardiovascular complications in RP can be difficult. In addition to corticosteroids, immunosuppressants such as azathioprine, methotrexate, infliximab, and cyclophosphamide have been reported to be used in RP patients with cardiovascular symptoms. Nevertheless, it is worth noting that challenges persist in attaining treatment targets for some patients (14). According to a systematic literature review, at the time of diagnosis of aortic involvement, over half of the patients were already under corticosteroid and/or immunosuppressive treatment. Half of these patients altered their medication regimens due to the lack of efficacy. Furthermore, approximately 33% of patients required the addition of new medications or the modification of their treatment approach, even after receiving intensive therapies such as cyclophosphamide. In conclusion, these observations show the intricate nature of effectively managing the condition (15,20). Pulse corticosteroid therapy is useful to treat patients with heart block (20). Tocilizumab may be an effective treatment for patients with corticosteroid-resistant RP aortitis. In cases where aortic insufficiency and coronary stenosis reach severe levels, surgical interventions are indicated, specifically aortic valve repair for aortic insufficiency and coronary artery bypass grafting for coronary stenosis (14).

The clinical progression of RP can be systematically monitored through the utilization of a dedicated disease activity assessment tool known as the Relapsing Polychondritis Disease Activity Index (RPDAI). This evaluation tool, developed in 2012, consists of 27 items, with each item assigned a score ranging from 1 to 24. Notably, high scores indicate a poor prognosis (2).

## CONCLUSION

RP is a rare, autoimmune disorder characterized by recurrent inflammation of the cartilaginous structures of the ear, nose, laryngotracheobronchial region, and joints. RP also affects several organs such as the ocular, cutaneous, cardiac, and central nervous systems. Cardiovascular manifestations are less observed but this involvement is the second most common cause of death in RP patients. Cardiovascular involvement encompasses valvular and vascular manifestations, arrhythmias and conduction defects, and pericardial and myocardial involvement. These manifestations may be insidious. Therefore, screening of the patients with RP for cardiovascular involvement is essential. Particularly, imaging modalities including echocardiography, CT and MR angiography, and PET/CT can help define cardiovascular complications. Lastly, cardiovascular manifestations are difficult to treat. First-line treatment is generally corticosteroids. Second-line treatment encompasses immunosuppressants such as methotrexate, azathioprine, infliximab, cyclophosphamide, and tocilizumab.

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CHAPTER **20**

# SPONDYLOARTHROPATHIES

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## INTRODUCTION

A chronic inflammatory condition known as spondyloarthritis (SpA) can present in a variety of ways depending on whether it affects the axial or peripheral joints (1). In all subgroups, the prevalence of SpA varies from 0.3% to 1.9% globally. Common extra-articular symptoms of SpA include inflammatory bowel disease (IBD), psoriasis, and acute anterior uveitis (2). The subgroups of SpA include ankylosing spondylitis (AS), reactive arthritis, psoriatic arthritis (PsA), arthritis associated with IBD and undifferentiated SpA (3).

PsA, a complicated chronic inflammatory rheumatism, exhibits a wide range of phenotypic variation, including axial and peripheral joints abnormalities as well as extra-articular conditions affecting the cardiovascular (CV), dermatologic, digestive, and ophthalmologic systems (4).

The data base was highest for rheumatoid arthritis (RA) when the European League Against Rheumatism (EULAR) recently updated recommendations for managing cardiovascular disease (CVD) risk in rheumatic diseases (5). AS, is a condition with radiographic evidence in individuals with axial disease in SpA (6). PsA, on the other hand, provides evidence in individuals with peripheral SpA. Compared to other rheumatic diseases, this evidence is sparser and frequently has contradictory results (7, 8).

In this book chapter, we have reviewed the CVD and the risk factors that are present in patients with SpA.

## SPONDYLOARTHRITIS

Numerous research have evaluated the prevalence and risk factors for CV comorbidities (9, 10). The SPA International Society (ASAS) SPA Assessment in COMOrbidities (COMOSPA) was established to determine potential risk factors, prevalence, and treatment approaches for comorbidities in this population. The first study, which was published in 2016, found that smoking, hypertension and hyperlipidemia were the most prevalent risk factors in 34%, 29%, and 27% of patients, respectively. CV comorbidities such as myocardial infarction (MI) (2.7%) and stroke (1.3%) were identified in the ASAS-COMOSPA trial in addition to the known risk factors (11).

Patients with SpA had significantly higher risk ratios (RR) for MI and stroke than the general population, according to a recent meta-analysis that examined at CV morbidity and mortality in a large sample of people (12).

Researchers found that smoking was the most prevalent CV risk factor in ASAS-COMOSPA, occurring in 31.2% of the cohort from Northern European and Mediterranean countries. Ischemic heart disease

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the use of tofacitinib in RA, showed that tofacitinib users had significantly higher rates of MACE and cancer development than TNF-α inhibitor users. Therefore, all risks and benefits should be considered when choosing a drug and developing follow-up procedures (63).

Although it is known that SpA patients have a higher risk of CV morbidity and mortality, the therapy of the disease is still not completely clear. Therefore, it's critical to identify patients at high CV risk as early as possible. A CV risk stratification score and the use of complementary non-invasive CV imaging modalities can be part of such an approach. The most popular algorithm in European countries is the modified SCORE index. Based on the suggestions of the EULAR Task Team in 2017, the modification was made. Patients can improve their state of health by using various techniques, such as routine clinical CV risk assessment and the worldwide SCORE instrument for measuring CV risk in these people. These patients' CV risk can be reduced by lifestyle changes, such as dietary modification and smoking cessation (64, 65).

## CONCLUSION

There is increasing evidence that AS and PsA have a higher CVD burden than the general population. The presence of CV risk factors should be routinely assessed. Several non-invasive approaches can be used to measure the progression of atherosclerosis, which can be accelerated by chronic, systemic inflammation. The risk of CVD can also be reduced by appropriate and prompt treatment of the underlying disease. Patients should be educated about healthy CV lifestyle practices.

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CHAPTER **21**

# FAMILIAL MEDITERRANEAN FEVER

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## INTRODUCTION

Familial Mediterranean Fever (FMF) is an autosomal recessive autoinflammatory disease characterized by recurrent fevers and inflammatory attacks affecting serosal membranes such as the peritoneum, pleura, joints, and pericardium (1). FMF is particularly prevalent among Mediterranean populations, including Sephardic Jews, Armenians, Arabs, and Turks, and its occurrence is attributed to mutations in the MEFV (MEditerranean FeVer) gene (1,2). The diagnosis is made based on the presence of at least two of the following findings: abdominal pain, body surface temperature exceeding 38°C, chest pain, arthritis, and a family history of FMF (3). Genetic analyses have demonstrated that specific mutations, including M694V, M680I, and V726A, exert a notable influence on both the clinical progression of FMF and the response to treatment. These mutations lead to dysfunction of the pyrin/marenostrin protein, which in turn causes the uncontrolled precipitation of inflammatory processes (2,4). As a consequence of these changes, it has been shown that, although rarely, the pericardium, myocardium, coronary arteries, pulmonary vascular structures and peripheral arterial structures may be affected (5-7). Colchicine and interleukin-1 (IL-1) inhibitors used in FMF treatment are effective in modulating the inflammatory response and have potential effects on the cardiovascular system, which have been investigated in recent years.

Various studies have been conducted to examine the incidence, characteristics, and treatment of FMF (8). In a multicenter study carried out in Turkey involving 2,838 patients diagnosed with FMF, the incidence of the disease was reported to be 0.1%. In the same study, the mean age was 23 years and the incidence rate in males was 1.2:1 compared to females. Clinical features included peritonitis (93.7%), fever (92.5%), arthritis (47.4%), pleuritis (31.2%), myalgia (39.6%), and erysipelas-like erythema (20.9%). Of the 2,468 patients with sufficient data, pericarditis attacks were observed in a total of 60 (2.4%) patients (36 were definite and 24 were suspected patients), and all except two of these patients recovered spontaneously. In addition, 316 patients (12.9%) had biopsy-confirmed amyloidosis, 139 (5%) had acute rheumatic fever, 75 (2.7%) had Henoch-Schönlein purpura, 24 (0.9%) had polyarteritis nodosa, and 4 (0.1%) had systemic lupus erythematosus. In 1,090 patients who underwent genetic analysis, M694V was found to be the most common mutation (51.4%), followed by M680I (14.4%) and V726A (8.6%) mutations. Among 2,258 patients with known treatment data, 51.2% had a complete response to colchicine treatment, 46% had occasional attacks despite colchicine, and 2.8% had no response (8). This study demonstrates that FMF is not uncommon and that cardiovascular complications are frequent enough to warrant attention. Proper treatment monitoring is essential to prevent

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## VASCULITIS ASSOCIATED WITH FMF

Vasculitis is inflammation of the blood vessels and can arise due to various causes, one of which is autoinflammatory diseases. FMF, due to its autoinflammatory characteristics, can be associated with several systemic inflammatory diseases such as spondyloarthritis, inflammatory bowel disease, multiple sclerosis, and vasculitis. The presence of prolonged fever and myalgia, may indicate vasculitis in FMF cases (41). The most commonly encountered types of vasculitis associated with FMF are IgAV (formerly designated as Henoch-Schönlein purpura) and PAN (6,42). Additionally, other types of vasculitis, such as central nervous system involvement, coronary vasculitis, large vessel vasculitis, and cutaneous vasculitis, have also been reported (43–45). The incidence of IgAV in FMF patients is approximately 2.7% (8). The diagnostic criteria defined in 1990 for the disease include onset at 20 years of age or younger, palpable purpura (not accompanied by thrombocytopenia), acute abdominal pain, and demonstration of granulocytes in the walls of small arterioles or venules on biopsy. The presence of two or more of these criteria distinguishes IgAV from other forms of vasculitis with 87.1% sensitivity and 87.7% specificity (46). The course of IgAV in FMF patients differs from the norm, with a tendency to manifest at an earlier age than is typical form. In these patients, rashes may develop in unusual areas such as the face and trunk. Genetic studies on IgAV patients have shown that the MEFV genes observed in FMF patients have also been detected in IgAV patients who have not yet been diagnosed with FMF (47,48). PAN, the second most common vasculitis seen in FMF patients, occurs in approximately 0.9% of cases and affects small and medium-sized arteries (8). The main clinical features of PAN include fatigue, fever, rash, abdominal pain, arthropathy, myalgia, and hypertension. While the mean age of diagnosis for PAN in individuals without FMF is approximately 50 years of age, the mean age of diagnosis in those with FMF is notably younger, at approximately 10.5 years of age. The prognosis for FMF patients is generally better compared to those without FMF, but it still poses a risk in terms of morbidity and mortality (49). These conditions are important complications to consider in the clinical management of FMF.

## CONCLUSION

The cardiovascular implications of FMF necessitate a comprehensive approach to patient care, integrating genetic analysis, vigilant monitoring, and tailored therapeutic strategies. By addressing the inflammatory underpinnings of FMF, clinicians can better manage its cardiovascular complications, ultimately improving patient outcomes and quality of life. Further research should continue to explore the complex interactions between FMF, cardiovascular disease, and vasculitis in order to develop more effective treatment protocols and preventive measures.

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CHAPTER **22**

# SYSTEMIC LUPUS ERYTHEMATOSUS

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## INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease with an unknown etiology that predominantly affects women of reproductive age. It occurs as a consequence of immune system dysfunction and affects numerous organs and systems, leading to increased morbidity and mortality (1, 2). SLE presents with a wide range of clinical manifestations, from mild to life-threatening organ involvement. A diagnosis of SLE is frequently made on the basis of a combination of immunological markers and the presence of certain clinical symptoms (3).

SLE is a complex disease that can affect any organ system of the body, including the skin, musculoskeletal system, pulmonary system, renal system, cardiac system, and neuropsychiatric system (4). The implementation of early diagnosis and modern treatments has been demonstrated to reduce mortality rates. However, recent evidence indicates that cardiovascular mortality has emerged as the leading cause of mortality (5).

## CARDIOVASCULAR SYSTEM INVOLVEMENT

Cardiovascular involvement represents a significant cause of morbidity and mortality in patients with lupus. Cardiac involvement is observed in over 50% of SLE patients (6). Any component of the cardiovascular system may be affected in patients with SLE, including the pericardium, myocardium, valvular structures, conduction system, and coronary arteries (7, 8) (Figure 1). Pericarditis represents the most prevalent cardiac involvement of SLE. Atherosclerosis, particularly accelerated atherosclerosis, is a significant contributor to morbidity in SLE.

Cardiac complications result from a complex interplay between the primary disease, traditional risk factors, and treatment-related effects (10). Although cardiovascular involvement may be mild and asymptomatic, it can be fatal in some instances. It is therefore imperative that an early diagnosis and treatment plan must be established. The following article presents a summary of the cardiac manifestations associated with SLE.

### Pericarditis

Pericarditis, the most prevalent cardiac manifestation of SLE, is incorporated into the American College of Rheumatology (ACR), the Systemic Lupus International Clinical Conference (SLICC), and the European League Against Rheumatism/ACR classification criteria for SLE. The frequency of pericarditis varies according to whether it is asymptomatic or symptomatic. Despite the fact that only 25% of patients present with symptoms, over 50% of patients have

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CHAPTER **23**

# ANTIPHOSPHOLIPID SYNDROME

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## INTRODUCTION

Antiphospholipid syndrome (APS) is an autoimmune disease that affects multiple systems and organs; develops as a result of antiphospholipid antibodies (aPL) dependent with vascular thromboses and/ or pregnancy complications. Firstly in the early 1980s, APS was described based on the observation that thrombosis and pregnancy losses were seen more frequently in SLE patients who had lupus anticoagulant (LA), anti-cardiolipin antibodies [1]. The prevalence of APS is approximately 50/100 000 of the population [2]. The prevelance of APS increases with age; the prevelance especially high in older patients with a chronic disease [3]. Antiphospholipid syndrome can be secondary or primary; secondary APS is associated with other autoimmune disease, particularly systemic lupus erythematosus (SLE) and primary APS is assosiated no autoimmune disease [4]. Clinical thrombotic vascular complications are often associated with antiphospholipid antibodies that can occur autoimmune disease, viral, bacterial, protozoal, fungal infections, malignancies, drugs [5, 6]. Patients who have antiphospholipid antibodies (aPL) are at risk of developing thrombocytopenia, venous and arterial thrombosis, and recurrent fetal loss [7]. APS is a multisystemic syndrome that consists of these clinical events in association with aPL [8].

The types of aPL, including Lupus anticoagulant (LA), anti-cardiolipin antibodies (aCL, immunoglobulin G and immunoglobulin M), and anti–β2-glycoprotein I antibodies (IgG and IgM) are detected frequently at APS [2, 9]. Lupus Anticoagulant (LA) in vitro, LA is defined as autoantibodies that prolong phospholipid dependent coagulation tests and firstly it was demonstrated at 1952 in the presence of systemic lupus erythematosus [10, 11]. Although LA is frequently used in clinical practice, it is misnamed because it can be seen in many disesase other than SLE and it acst as an anticoagulant in vitro hemostasis tests while causing a tendency to thrombosis in vivo [12]. Anti-cardiolipin antibodies are antiphospholipid antibodies developed against cardiolipin; firstly demonstrated in the serum of patients with SLE in 1983 [1].

APL interact pathologically in various stages on primary hemostasis and secondary hemostasis that results thrombophilia and thrombosis [13-16]. APS is a prothrombotic state, associated with premature atherosclerosis as a result of factors such as endothelial and platelet activation [17-19]. In studies, it is showed that atherosclerosis was seen more significantly in APS patients than controls. Although there are various prospective and retrospective studies showing the relationship between APS and venous-arteriel thrombosis, the pathogenesis of thrombosis development in APS has not been adequately explained. In vitro studies about relationship with thrombosis in APS, procoagulant activity have been shown by activation of endotelial cells, interaction with anticoagulant

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with various thrombotic and nonthrombotic cardiac manifestations including atherosclerosis, valvular heart disesase, myocardial dysfunction, intracardiac thrombus, pulmonary hypertension. Primary and secondary cardiovascular prevention strategies should be implemented basically with lifestyle changes firstly and involved specific treatment algorithm of cardiovascular risk factors. Statins is recommended to use for primary and secondary prevention of cardiovasculary disease in all APS patients. In addition, primary prophylaxis with aspirin is indicated in asymptomatic aPL carriers with a high-risk profile or with concomitant SLE. And also aspirin could be considered in low-risk profile aPL carriers with concomitant traditional cardiovascular risk factors.

The secondary prevention approach in APS patients is based on VKA treatment and anticoagulant life-long therapy has a important to prevent recurrent pulmonary embolism. Definetely, the treatment with DOACs is not recommended in patients with APS because of the high risk of recurrent thrombosis. Overall, high quality clinical trials are needed to identify effective and safe therapeutic options to reduce thrombotic events in aPL carriers and APS patients.

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CHAPTER **24**

# SYSTEMIC SCLEROSIS

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## INTRODUCTION

Systemic sclerosis (SSc) is an immunological disease characterized by excessive fibrosis in tissues, obliterative vascular disease, and evidence of autoimmunity, primarily the production of multiple autoantibodies. Cutaneous involvement is the usual finding and eventually occurs in about 95% of cases, but the involvement of internal organs is responsible for most of the morbidity and mortality. SSc is divided into two groups according to its course:

- Diffuse SSc, which is characterized initially by diffuse skin involvement, progresses rapidly and has early visceral involvement
- Limited SSc, in contrast, typically presents with skin changes that are confined to the fingers, forearms, and face, and tends to have a more indolent course with later visceral involvement, often affecting the lungs and gastrointestinal system over time.

## PATHOGENESIS

The cause of SSc is unknown, but the disease is probably caused by three interrelated processes involving autoimmune responses, vascular damage, and collagen deposition. Microvascular disease is consistently present in the early stages of SSc. Prominent signs of endothelial activation and injury and increased platelet activation have been noted. However, the cause of vascular injury is unknown; it may be the initiating event or consequence of chronic inflammation with mediators released by inflammatory cells that damage the microvascular endothelium. This type of endothelial injury followed by platelet aggregation leads to the release of some platelet and endothelial factors which trigger endothelial proliferation and intimal and perivascular fibrosis. Eventually, extensive narrowing of the microvasculature leads to ischemic injury and scarring. The pulmonary vasculature is often involved and the resulting pulmonary hypertension is a serious complication of the disease.

Pathologic changes may affect all chambers of the heart (1). Autopsy studies have found fibrosis in cardiac tissues including the myocardium, conduction system, valves, and pericardium. (2,3,4). Microvascular changes have been noted along with contraction band necrosis (2,4), a sequela of perfusion, and reperfusion injury. Characteristically, SSc fibrosis can distribute throughout both ventricles, regardless of coronary artery distribution, and patients with patent coronary arteries have diffuse myocardial fibrosis in the SSc (2). Histopathologic studies have demonstrated intimal hyperplasia of myocardial arterioles (5), and in vivo, decreased coronary flow and resistance reserve have been noted in these patients (6).

Cardiac involvement is often clinically occult in SSc patients. Echocardiography, electrocardiography (ECG), computed tomography (CT) and magnetic

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taneously. In a single-centered study, cardiac death was found to be higher in patients with SSc compared with PAH or IHD and was higher when multiple cardiac pathologies were present. Different cardiac parameters have been found to have significant prognostic value in SSc. Among TTE parameters, LVEF <50% is the strongest predictor of mortality (42). Left ventricular diastolic dysfunction is associated with increased mortality, and in the Norwegian population study, diastolic dysfunction was associated with a risk of 3.71 for death, consistent with the single-center American cohort study (43). The presence of the right bundle branch block on ECG at baseline was found to be a significant predictor of mortality in the GENIOS cohort (44). The presence of more than 1000 ventricular ectopic beats is associated with a 6-fold increased risk of death, and this was confirmed by another study in which more than 1190 ventricular premature beats per day were found to be indicative of the need for SCD or AICD (45). Perfusion defects demonstrated by SPECT are associated with an increased risk of developing heart failure and death.

## CONCLUSION

Cardiac complications are of major importance in SSc patients, especially in diffuse cutaneous SSc, and SCD risk is high. Furthermore, although SCD is associated with malignant arrhythmias, the risk of SCD is very high and its prevalence ranges from 21% to 54%. Early diagnosis and treatment of cardiac complications can slow the development of myocardial ischemia, immunoinflammatory damage, and myocardial fibrosis. Thus, quality of life can be improved in this patient group. Despite the early detection of cardiac complications with modern imaging and biomarkers, effective treatment of these complications is still in the development phase. Currently, when faced with cardiac complications, we can provide symptomatic treatment and intervention at the early stage of the disease. However, more studies will be needed in the future on how to control and reduce the incidence of cardiovascular risk factors and prevent cardiac pathologic changes.

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CHAPTER **25**

# UNDIFFERENTIATED CONNECTIVE TISSUE DISEASE, MIXED CONNECTIVE TISSUE DISEASE, AND OVERLAP SYNDROMES

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## INTRODUCTION

Connective tissue diseases (CTDs) are systemic autoimmune diseases characterized by a variety of clinical features and multiple organ involvement, including rheumatoid arthritis (RA), systemic sclerosis (SSc), systemic lupus erythematosus (SLE), polymyositis, dermatomyositis, Sjogren's syndrome (SjS), and mixed connective tissue disease (MCTD). If the patient does not meet the criteria for a specific disease, but has the manifestations of a systemic autoimmune disease, it is referred to as undifferentiated tissue disease (UCTD). The presence of two or more specific CTDs in a patient is referred to as "overlap syndrome". A wide clinical spectrum of cardiac manifestations can be seen in CTDs. Cardiovascular involvement is important in CTDs as it may affect the prognosis and mortality of the disease. Therefore, early detection may allow early therapeutic intervention and improve patient outcomes.

## UNDIFFERENTIATED CONNECTIVE TISSUE DISEASE (UCTD)

The term 'UCTD' is used for a clinical entity that meets the serological and clinical manifestations of a systemic autoimmune disease; yet, does not fulfill the diagnostic criteria for a specific CTD (1). Primarily, the UCTD term was defined by Leroy *et al*. in 1980, as an early phase of a rheumatic disease (2).

Clinical characteristics of patients with UCTD can vary widely. The clinical spectrum of the disease includes polyarthritis, oesophageal dysmotility, serositis, lymphadenopathy, peripheral neuropathy, central nervous system involvement, interstitial pneumonitis, dry mouth, and dry eyes. Organ non-specific autoantibodies are usually present at the time of diagnosis.

Disease progression is usually slow and progressive. The majority of UCTD patients remain undifferentiated after 10 years (3). The disease is classified into 'stable' and 'early or evolving' UCTD. In the first group of patients, the disease remains mostly undifferentiated, whereas the latter has a tendency to develop a specific CTD in a short time or years after (4).

Severe organ involvement can rarely occur in stable UCTD. Pulmonary and cardiac involvement may occur in the long term disease, especially after three years of inflammation and injury (5). Lately, studies have shown accelerated atherosclerosis and cardiac involvement in several CTDs including UCTD (6,7). Traditional atherosclerotic risk factors such as low high-density lipoprotein (HDL), increased systolic blood pressure, increased serum total cholesterol level, increased low-density lipoprotein (LDL) cholesterol, and increased fasting glucose were shown in late UCTD patients. Yet, even in the absence of traditional factors, atherosclerosis, endothelial cell injury, and

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CHAPTER **26**

# BEHÇET'S DISEASE

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## INTRODUCTION

Behçet's disease is characterized by oral aphthae, genital ulcers, skin lesions, uveitis and joint involvement. Vasculitis is the main causative factor underlying Behçet's disease, but its pathophysiology has not been clearly elucidated. Although cardiovascular involvement of Behçet's disease is rare, it can lead to serious complications such as pericarditis, endocarditis, intracardiac thrombus, vascular aneurysm, deep vein thrombosis and pulmonary hypertension (1,2).

Genetic predisposition, environmental factors and immunologic mechanisms are thought to play a role. The main pathologic feature of the disease is vasculitis in large, medium and small vessels. This vasculitis can affect both arterial and venous vessels, leading to vascular aneurysm formation, stenoses, thrombosis, cardiac fibrosis and other vascular complications (2).

Cardiovascular involvement of Behçet's disease will be discussed in detail. Pathogenesis, clinical manifestations and treatment approaches will be discussed. The clinical features and treatment options of vascular aneurysms, the role of deep vein thrombosis (DVT) in Behçet's disease, the pathophysiology and clinical management of pulmonary hypertension and chronic thromboembolic pulmonary hypertension (CTEPH) will also be comprehensively evaluated. The clinical course of group 4 pulmonary hypertension associated with Behçet's pulmonary vasculitis, its relationship with cardiac fibrosis and treatment approaches will be emphasized (2).

Treatment of the cardiovascular complications of Behçet's disease is usually based on suppressing vasculitis. The prognosis of cardiac involvement is poor, and treatment options include the use of oral anticoagulants, immunosuppressive therapies and colchicine. Oral anticoagulants are used to prevent blood clots. Immunosuppressive therapies used in Behçet's disease include corticosteroids, azathioprine, cyclophosphamide and biologic agents (2). The pathogenesis, clinical manifestations and treatment of the cardiovascular involvement in Behcet's disease are summarized in this chapter.

## EPIDEMIOLOGY AND PATHOGENESIS

Major manifestations of Behçet's disease include aphthous ulcers, skin lesions (erythema nodosum), eye involvement (uveitis) presenting with recurrent visual loss, joint involvement (arthritis) and genital ulcers. The presence of these major findings plays an important role in the diagnosis of Behçet's disease. A combination of these findings and clinical evaluation is necessary for the diagnosis of the disease.

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CHAPTER **27**

# GOUT AND OTHER CRYSTAL ARTHROPATHIES

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## INTRODUCTION

Inflammation promotes the development of atherosclerosis (1). Mortality and the incidence of complications from atherosclerosis are increased in chronic inflammatory diseases such as rheumatoid arthritis, systemic lupus erythematosus and gout (2). These arguments support the contribution of inflammation due to rheumatic diseases to cardiovascular (CV) morbidity and mortality (3). There are observations regarding the association between gout and risk factors of atherosclerosis. The risk of atherosclerotic disease is increased in gout (4). Several epidemiological studies showed a positive relationship between the risk of cardiovascular disease (CVD) and elevated serum uric acid (UA) levels. However, asymptomatic hyperuricemia has not been proven as an independent risk factor for atherosclerosis. Although the underlying mechanisms are not well understood, hyperuricemia is associated with many CV risk factors such as hypertension (HT), obesity, insulin resistance and hyperlipidemia (5-6). Therefore, screening and treating CV risk factors are important in patients with gout.

## GOUT

Gout is a metabolic disease characterized by the accumulation of monosodium urate (MSU) crystals in the supersaturated extracellular fluids in the kidney and connective tissue, particularly in middle-aged men with hyperuricemia and episodic acute and chronic arthritic flares. Research over the last 20 years has shown that gout may be an independent risk factor for CVD and mortality (7). A meta-analysis of the prevalence of CVD in gout reported a prevalence of HT of 63.7%, heart failure (HF) of 8.7%, cerebrovascular accident of 4.3%, myocardial infarction (MI) of 2.8% and venous thromboembolism of 2.1% (8). In one cohort, 8% of gout patients developed CVD after 3 years of follow-up, compared with 5% of patients in the control group. In the same cohort, 30% of patients were already diagnosed with CVD at baseline, compared with 20% in the control group (9). The incidence of CVD was even higher in patients treated by rheumatologists (47%) and this situation may be explained by the higher incidence of severe gout observed in patients followed by rheumatologists (10). Elevated serum UA concentrations (>9.1 mg/dL), disease duration (≥2 years), oligoarticular or polyarticular disease, joint damage and tophi are identified as the risk factors associated with increased CV risk.

### Epidemiology and Pathogenesis

The prevalence of gout is 5-28/1000 in men and 1-6/1000 in women. Age and gender are two irreversible risk factors affecting the prevalence

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and around the knee. It is similar to osteoarthritis. However, there is significant patellofemoral involvement and subchondral cyst formation. MRI provides great convenience in detecting articular cartilage involvement but its effectiveness is limited in meniscus involvement. Indomethacin or other NSAIDs are used to treat acute pseudogout attacks. Oral colchicine is not as effective in acute gouty arthritis. Aspiration of synovial fluid and intra-articular corticosteroids are indicated, especially when large joint involvement is present. When recurrent attacks occur and there is no response to NSAIDs, 30-40 mg of oral prednisone may be required for short periods. The steroid dose should be reduced gradually. Long-term use of colchicine at a dose of 0.6-1.2 mg/day is effective in reducing recurrent pseudogout attacks (41).

### CPPD and Cardiovascular Risk

CPP crystals activate the NLRP3 inflammasome, leading to the release of IL-1β. NLRP3 inflammasome activation results in the alteration of lipid metabolism, inflammation, and oxidative stress, which contribute to atherosclerosis. The presence of crystals alone is not sufficient to explain the increased risk of CV events. The studies have shown that CPP crystals induce IL-1β expression only in the presence of pathogen-associated molecular patterns (PAMP) or damage-associated molecular patterns (DAMPs) such as serum amyloid A. It supports that subclinical inflammation is the result of an ongoing process such as vascular calcification or long-term exposure to PAMPs/DAMPs with long-term CV consequences. Inflammation due to the exacerbations and subclinical inflammation between exacerbations may contribute to CV risk.

A cohort from the conducted in the Veterans Health Administration Corporate Data Warehouse showed an increased risk of acute coronary syndrome and stroke in CPPD after adjustment for traditional CVD risk factors. Conversely, CPPD patients exhibited a markedly reduced risk of mortality (42). A study revealed an elevated risk of MACE in patients with acute CPP crystal arthritis during the initial two years following diagnosis (hazard ratio (HR) 1.32). The risk of non-fatal cardiovascular (CV) events was elevated in the initial two-year period (HR 1.92) and the subsequent ten-year period (HR 2.18). However, there was no observed increase in the risk of death. In the outpatient-only analysis, there was a notable elevation in the risk of nonfatal CV events during the second through tenth years, with no such increase observed during the initial two-year period. The incidence rates for MACE in the first two years following the onset of acute CPP crystal arthritis were 91 per 1,000 person-years (p-y), compared to 59 per 1,000 p-y in non-CPPD cases. The incidence of MACE across years two to ten was 58 per 1,000 p-y in acute CPP crystal arthritis and 53 per 1,000 p-y in non-CPPD cases (43).

## CONCLUSION

A modest increase in the risk of cardiovascular disease may be observed in gout, independent of traditional risk factors. This effect may be related to hyperuricemia and disease-related inflammatory burden. However, it is also known that the comorbidities accompanying gout cause a significant increase in the risk of CVD. Therefore, it is necessary to be careful when monitoring gout in terms of CVD.

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CHAPTER **28**

# IDIOPATHIC INFLAMMATORY MYOSITIS

*Dilek Tezcan* [1]

## 1. INTRODUCTION

Idiopathic inflammatory myositis (IIM) is a systemic autoimmune disease with heterogeneous subgroups, mainly characterized by muscle pain and muscle weakness caused by muscle inflammation. IIM diagnoses are based on clinical, laboratory, radiological, electrophysiological, and histopathological findings. They are clinically characterized by proximal muscle weakness, elevated muscle enzymes, myopathic changes on electromyography, and abnormal muscle biopsy. IIM can be divided into subgroups in tight of new myositis-specific autoantibodies (MSA), histopathological developments, and classification criteria. These are dermatomyositis (DM), immune-mediated necrotizing myopathy (IMNM), overlap myositis (OM), inclusion body myositis (ICM), amyopathic dermatomyositis (ADM), polymyositis (PM), and cancer-associated myositis. Different subgroups have different clinical, histopathological findings, autoantibody profiles, prognosis, and treatment responses (1-3).

## 2. EPIDEMIOLOGY

The incidence of various subgroups of IIM vary by ethnicity, age, and gender. The estimated prevalence for PM and DM is between 5-22/100.000, and the annual incidence is between 1.2-19/1000000. Epidemiological data on new IIM subgroups are lacking. The overall female-male incidence rate is 2.5/1; this rate is lower in childhood disease and malignancy (1/1) but very high in OM (10/1). The only exception is ICM, which men are more commonly affected by. DM has biphasic peaks in childhood and middle age, whereas PM peaks in middle age. ICM is common after the age of 50. Age increases when associated with malignancy or in cases of ICM (1-6).

## 3. ETIOLOGY AND PATHOGENESIS

### 3.1 Genetic Risk Factors

HLA-DRB1*0301 and HLA-DQA1*0501 haplotypes appear to be the strongest genetic risk factors. However, different phenotypes of HLA, genes that regulate cytokines and receptors, have additional risk and protective factors. The HLA-B8/DR3/DR52/DQ2 haplotype is found in many ICM patients. Recent studies have identified the HLA-DRB1 alleles HLA-DRB1*01:01 and HLA-DRB1*13:01 as risk factors for ICM. (1).

### 3.2 Environmental factors

The prevalence of IIM in Europe increases significantly from north to south. Among the agents playing a role in IIM; viruses, bacteria, parasites, drugs (statins, fibrates, chloroquine, l-tryptophan, D-penicillamine, pembrolizumab, ipilimumab, nivolumab, growth

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nerstones in the treatment of myocarditis. In addition to immunosuppressive therapy, the management of cardiac involvement may require personalized cardiac-specific therapy. The immunomodulatory role of intravenous immunoglobulin is present in moderate-to-severe heart disease; however, this can be potentially dangerous in heart failure due to fluid overload (17,18).

## CONCLUSION

IIM is related to an increased risk of heart disease, but the prevalence remains unclear. Approximately 70% of patients may have only subclinical symptoms. It has been estimated that cardiovascular involvement is responsible for 10-20% of deaths in patients. The three main causes of cardiac mortality in IIM patients are congestive heart failure, myocardial infarction, and arrhythmias. The main mechanisms responsible appear to be atherosclerosis and myocarditis. Evaluation of cardiac function at the time of diagnosis and during follow-up in every patient with myositis is important for early diagnosis and treatment, even in patients with remission.

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CHAPTER **29**

# CARDIAC SARCOIDOSIS

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## INTRODUCTION

Sarcoidosis is a multi-organ system disease characterized by the infiltration of different organs by non-necrotizing granulomas. It generally affects adults aged 25 to 50, and women are more at risk than men. Sarcoidosis typically occurs in the mediastinal lymph nodes and lungs, but may also affect the skin, eyes, and liver. The underlying cause is not completely understood, but theories suggest that, in individuals with a genetic predisposition, an unknown antigenic trigger stimulates an inflammatory cascade that results in granulomatous inflammation followed by fibrosis and scarring in tissue (1,2).

## EPIDEMIOLOGY

The annual incidence of sarcoidosis in the United States is 10 per 100,000. The highest prevalence was reported in African ancestry and Northern European. Cardiac involvement is noted in 3% to 10% of patients although autopsy studies reported cardiac involvement in up to 46.9% of cases (3,4). Cardiac sarcoidosis (CS) is more frequently reported in Japanese patients as compared to African-American and Caucasian patients. More recent data suggest that cardiac involvement is has common in male sarcoidosis patients (5). CS incidence have been rising as a result of the increasing recognition and interest for the disease, the development of new imaging techniques, and the publication of related guidelines. Cardiac involvement may occur with systemic sarcoidosis, or it may be the first and only finding of the disease in nearly half of the cases (6).

## PATHOGENESIS

Several factors play a role in the pathophysiology of CS, including immune dysregulation as well as genetic susceptibility, previous infection history, and occupational or environmental factors. Human leukocyte antigen (HLA) alleles are effective in the course of the disease. For example, HLA-DR17 (3) is most associated with sarcoidosis in the White population, DRB1*03 is associated with spontaneous resolution, and HLA-DR15 (2) or DR14 (6) is associated with a chronic disease course (7). Related infectious agents include mycobacteria, Propionibacterium, Borrelia burgdorferi, Rickettsia helvetica, Epstein-Barr virus, and human herpes virus 8 (8). Workers in the lumber and woodworking industries exposed to industrial organic dust are at increased risk of sarcoidosis (9). The formation of discrete non-caseating granulomas consisting of multinucleated giant cells and epithelioid histiocytes surrounded by fibroblasts is the histological feature of sarcoidosis. Multinucleated giant cells are initially foreign body type (with nuclei

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CHAPTER **30**

# SECONDARY AMYLOIDOSIS

*Ferit Böyük* [1]

## INTRODUCTION

Cardiac amyloidosis is characterized by the accumulation of amyloid fibrils in the extracellular space. Amyloid fibrils are rigid, non-branching, and 7-10 nanometers in size. There are different types of cardiac amyloidosis, with 95% of cases being light chain (AL) and transthyretin (ATTR) type amyloidosis. In addition, chronic inflammation, chronic infection, and chronic malnutrition are also associated with amyloidosis. Secondary amyloidosis (AA) results from the accumulation of serum amyloid A (SAA) proteins synthesized in response to proinflammatory signals.[1,2] AA amyloidosis can develop as a result of chronic infection, rheumatoid arthritis, familial Mediterranean fever, and chronic inflammatory bowel disease.[3,4] It is important to note that amyloidosis is no longer a rare disease; the number of diagnosed patients is increasing every year. Despite the paucity of epidemiological studies, there is evidence that the incidence of AA amyloidosis is rising in developing countries. It is crucial to diagnose amyloidosis at an early stage, as survival rates decline significantly following cardiac involvement.[5]

## CARDINAL MANIFESTATIONS AND DIAGNOSIS

Cardiac amyloidosis may mimic other cardiac diseases, such as left ventricular hypertrophy (caused by various factors), hypertrophic cardiomyopathy, and hypertensive heart disease. The majority of cases of cardiac amyloidosis are attributed to primary amyloidosis (AL type) and transthyretin amyloidosis. However, despite its rarity, secondary amyloidosis (AA type) may also affect the heart.The usual clinical manifestation of cardiac amyloidosis is heart failure with preserved ejection fraction (HFpEF). It is very distinctive for primary (AL) amyloidosis when HFpEF is combined with macroglossia and periorbital purpura. The red flags that should raise concerns about amyloidosis can be listed as follows;

- Low voltage on ECG and thickening of the septum/posterior wall >1.2
- Thickening of the right ventricular free wall
- Intolerance of beta-blockers and ACE inhibitors
- Low blood pressure in patients with a previous history of hypertension
- History of carpal tunnel syndrome (Particularly in TTR amyloidosis).[6 7,8]

Investigation should be done in patients with red flags seen for cardiac amyloidosis. ECG, detailed echocardiography, cardiac biomarkers (troponin and BNP), and cardiac magnetic resonance (CMR) evaluation should be performed in patients suspected of cardiac involvement. In that case, serum kappa/lambda light chain ratio, and serum/urine immunofluorescence electrophoresis should be considered,

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matory cytokines such as TNF-α and IL-6.[19,20] Studies evaluating anti-TNF therapy in AA amyloidosis mainly include patients with rheumatoid arthritis and spondyloarthritis. In a retrospective series including 15 patients treated with anti-TNF, amyloidosis progressed in seven patients (46.7%), stabilized in five patients (33.3%), and there was a decrease in proteinuria in three patients (20%) within 10 months.[21] Various reports also showed improvement in AA amyloidosis with tocilizumab (anti-IL-6 receptor monoclonal antibody) treatment. Anti-TNF agents are also used to treat inflammatory bowel diseases, and it has been reported that AA amyloidosis is resolved in these patients.[22,23]Given the significant role of IL-1, blocking IL-1 has become a major focus. Anakinra (a synthetic version of human IL-1 receptor antagonist), rilonacept (a fusion protein targeting IL-1 receptor), and canakinumab (an antibody against IL-1β) are effective in treating genetic inflammatory diseases like FMF and NLRP3-related autoinflammatory disorders.[24,25] Both dialysis methods and kidney transplant are suitable for patients with AA amyloidosis and kidney failure. However, survival is poor in dialysis patients, especially when cardiac involvement is prevalent. Particularly, cardiovascular amyloid accumulation and the tendency for hypotension due to nephrotic syndrome can be a significant problem in these patients. Kidney transplant is the optimal treatment option for these patients, however, survival rates are low. The mortality rates associated with cardiovascular involvement after transplantation are high, therefore detailed cardiac examination is important.[7,26]The use of Anti-TNF in kidney transplant recipients (KTRs) has been associated with better control of inflammation at the expense of increased infection rates and remission of the underlying disease.[27]Anakinra and canakinumab are effective; resulting in longer renal graft survival and lower rejection rates, however, an increase in the number of deaths was observed; this may be due not only to infections but also to the progression of amyloid fibril accumulation in the cardiovascular system. Colchicine was reported to be safe in kidney transplant recipients.[28,29]

Cardiac involvement in secondary (AA) amyloidosis is a rare phenomenon, and cardiac MRI findings may assist in differentiating it from other forms of cardiac amyloidosis. Diffuse late gadolinium enhancement, a characteristic feature of primary and TTR cardiac amyloidosis, is not observed in AA type cardiac amyloidosis.[30] The median survival rate in patients with cardiac AA amyloidosis has been reported to be approximately two years. There is no specific treatment for cardiac involvement; the primary objective is to control the underlying inflammatory disease with appropriate immunosuppressive treatment regimens, as abovementioned.[31]

## CONCLUSION

AA amyloidosis occurs as a result of chronic inflammation and primarily affects the kidneys. The frequency of AA amyloidosis is decreasing due to the diagnosis and treatment of chronic inflammatory conditions. The diagnosis of AA amyloidosis still relies on histology. In addition to traditional treatments, anti-TNF, IL-1, and IL-2 antagonists are important treatment options. When end stage kidney disease develops, the treatment is kidney transplantation. Experimental studies aimed at completely removing amyloid deposits from tissues currently appear to be unsuccessful.

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CHAPTER 31

# LARGE VESSEL VASCULITIS

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## INTRODUCTION

There is an increased risk of cardiovascular disease (CVD) and mortality, especially in large vessel vasculitides (LVV) such as Takayasu arteritis (TAK) and giant cell arteritis (GCA). Cardiac manifestations in LVV may be associated with hypertension, pathological involvement of the pulmonary or coronary arteries, myocardial infiltration, and aortic regurgitation. Furthermore, the correlation between chronic inflammation and accelerated atherosclerosis is well documented (1). Endothelial dysfunction resulting from the action of inflammatory cytokines and oxidative stress is a primary cause of early atherosclerosis (2). It is important to diagnose the disease at an early stage, rapidly suppress vascular activity, and prevent damage to improve the prognosis.

## TAKAYASU ARTERITIS

TAK is a granulomatous vasculitis that predominantly affects the aorta, its principal branches, and the pulmonary arteries. This leads to a range of ischemic symptoms, including stenosis, thrombosis, and, in some cases, aneurysm formation in the major vessels (3). It is primarily observed in females of reproductive age. The manifestations of the disease are variable, contingent upon the arteries involved and the degree of inflammation. The clinical manifestations of the disease can range from non-specific symptoms such as fever, myalgia, arthralgia, and weight loss to those related to ischemia, including claudication, hypertension, carotid body tumors, syncope, stroke, and abdominal angina (4). The tissue-level process commences with granulomatous inflammation of the medial wall and adventitia of the affected vessels. Over time, the disease may progress to fibrosis, resulting in stenosis or occlusion. In the advanced stage of the disease, dilatation or aneurysmal changes may occur due to damage to the elastic fibers of the medial wall (5).

Although cardiac involvement can be seen in all primary vasculitides, this complication is more common in TAK, eosinophilic granulomatous polyangiitis (EGPA), and polyarteritis nodosa (PAN) (6). Cardiac involvement can manifest as palpitations, angina, dyspnea, myocardial infarction (MI), or heart failure (7). The pericardium, myocardium, coronary arteries, and/or heart valves may be affected in TAK (6). Patients with TAK frequently exhibit cardiac abnormalities, especially those with a Numano-type V angiography pattern (8). Therefore, echocardiography should be performed at the time of diagnosis. The Framingham Risk Score and cumulative cardiovascular events (CVE) incidence were significantly higher in patients with TAK compared to the control group (9). Echocardiography is an indispensable tool for assessing and following cardiac involvement in TAK.

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the coronary vessels. In addition to coronary artery vasculitis, it can manifest clinically as valve disease, pericarditis, and myocarditis. The early diagnosis of cardiac involvement due to vasculitis has a significant impact on the selection of an appropriate treatment plan and the prognosis.

It is of the utmost importance to control vascular inflammation rapidly, as this is a significant factor in mortality. Moreover, it is recommended that patients be encouraged to cease smoking, adopt a healthy diet, and engage in low-intensity exercise. It is also imperative to ensure that traditional risk factors are effectively managed.

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CHAPTER 32

# ANCA-ASSOCIATED VASCULITIS

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## INTRODUCTION

Vasculitides define the presence of inflammation and necrosis of blood vessels, resulting in damage to the vessel wall. This damage can lead to aneurysm, perforation or thrombosis (1). In the revised Chapel Hill 2012 classification of vasculitides, vasculitides were classified as large, medium and small vessel vasculitides based on the involved vessel diameter. ANCA-associated vasculitides (AAV) were classified in small vessel vasculitides (2). In the Chapel Hill 2012 classification, names of AAV were also revised. Granulomatous polyangiitis (GPA) was used instead of Wegener's granulomatosis (WG), and eosinophilic granulomatous polyangiitis (EGPA) was proposed to be used instead of Churg-Strauss syndrome (CSS) (2). After a brief summary of the pathogenesis and clinical manifestations of AAVs, cardiovascular involvement in AAV was discussed in this chapter.

## ETIOPATHOGENESIS

AAV is uncommon, with an annual incidence of 20 per million and a prevalence of up to 100 per million. Progress is being made in understanding the pathophysiology of AAV, but its etiopathogenesis remains complex and multifactorial (3). AAV develops in genetically susceptible individuals with the interaction of environmental (silica, asbestos, drug exposure) and infectious (*S. aureus*) factors. Autoimmunity induced by these factors initiates the process with autoantibody production, tissue damage and the appearance of disease findings. Activation in the monocyte-macrophage system leads to activation and proliferation of Th1 cells. Neutrophils and macrophages are activated by TNF-alpha and IFN-gamma mediators released from these cells. The interaction of stimulated neutrophils and monocytes with ANCA triggers inflammatory cascades. ANCAs formed against MPO and PR3 antigens in the cytoplasm of neutrophil and monocytes are important in the pathogenesis (4).

## CLINICAL FINDINGS AND CLASSIFICATION

AAV is divided into three subgroups including GPA, EGPA, and microscopic polyangitis (MPA). Renal limited ANCA-associated vasculitis can be considered as a fourth subgroup, but ultimately corresponds in practice to the kidney-restricted forms of MPA or GPA. Systemic signs of inflammation such as weight loss, weakness, fatigue, arthralgia and myalgia can be observed in AAV. Especially in elderly patients, it can be confused with infection, malignancies, depression or osteoarthritis (5).

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ing the cardiac involvement in EGPA. Cardiac MRI may reveal myocardial edema and the presence of late gadolinium enhancement which represents the tissue scar formation. CMR might be used also in evaluating the treatment response (32).

Systemic inflammatory diseases are a risk factor for atherosclerotic cardiovascular disease (33). Arterial inflammation is caused by lipid deposition, systemic inflammation resulting from increased production of tumor necrosis factor (TNF)-a and interleukin (IL)-6 (34). Glucocorticoid therapy causes diabetes and hypertension, and as a result, the development of atherosclerosis and cardiac dysfunction is accelerated (35). Therefore, the increased risk of atherosclerotic cardivascular disease in AAVs should be kept in mind beyond cardiac involvement.

### Definition of cardiac involvement

Patients with one or more of the following findings were defined as having cardiac involvement: (36)

| |
|---|
| 1. Major ECG abnormalities (ECG) |
| 2. Pericardial effusion (echocardiography or CMR) |
| 3. Myocarditis (EMB) |
| 4. LGE and/or oedema (CMR) |
| 5. Regional or global wall motion abnormalities (echocardiography or CMR) |
| 6. Significant valvular regurgitation (grade ≥ 3) (echocardiography) |
| 7. Pulmonary hypertension (sPAP > 45 mm Hg) (echocardiography) |
| 8. Significant coronary lesion(s) (CT-angiography and/or coronary angiogram) |

EMB: Endomyocardial biopsy LGE: late gadolium enhancement

### Treatment of Cardiac Involvement

The main goal of treatment of cardiac involvement is to induce remission and control disease activity. Therefore, corticosteroids in combination with other immunosuppressive agents (mainly cyclophosphamide) are considered the hallmark of treatment. In addition, cardiac manifestations should be treated according to the type of heart disease, as in the general population. If heart failure is present, heart failure treatment (beta-blockers, renin-angiotensin system inhibitors, etc.) should be given. In the case of advanced heart block, pacemaker implantation should be considered (37). The risk of sudden cardiac death should be assessed with Holter rhythm monitoring and cardiac MRI findings, and implantation of an implantable cardioverter defibrillator should be considered to prevent sudden death.

## CONCLUSION

AAVs are rare rhumatic diseases and the most common manifestations are lung, kidney, upper respiratory tract, skin involvement. Cardiac involvement is relatively less than other organs involved. Cardiac involvement, especially in AAV subgroup EGPA, is associated with poor prognosis and increased mortality risk. If cardiac involvement is suspected, echocardiography and electrocardiography should be performed. Cardiac MRI is the best imaging modality for both diagnosis and assessment of treatment response in cardiac involvement. Treatment should aim to control the underlying vasculitis with immunosuppressive therapy and treatment with cardiovascular drugs or interventions depending on the type of cardiac involvement.

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CHAPTER 33

# POLIARTERITIS NODOSA (PAN) AND DEFICIENCY OF ADENOSINE DEAMINASE 2 (DADA2)

*Sema Nur Taşkın* [1]

## INTRODUCTION

Polyarteritis nodosa (PAN) is a rare systemic necrotizing vasculitis that predominantly affects medium-sized arteries in childhood. PAN can involve any system of the body and lead to significant morbidity and mortality. In 2014, the discovery of adenosine deaminase 2 deficiency (DADA2) significantly changed our perspective on childhood-onset PAN. DADA2 has provided an explanation for familial PAN and resistant cases of childhood-onset PAN. In this chapter, PAN and DADA2 will be discussed in light of the current literature.

## POLYARTERITIS NODOSA (PAN)

PAN is a systemic necrotizing vasculitis predominantly affecting medium-sized arteries. It can involve any system of the body, leading to thrombosis or aneurysm, and can cause significant morbidity and mortality (1,2). PAN was first described in 1852 by Karl Rokitansky, a pathologist at the University of Vienna (3). PAN, which can affect almost any system, was deadly before the discovery of steroid therapy. Today, it is known that although the prognosis improves with advanced treatment methods, it can still be mortal in severe cases. The presentation of the disease ranges from a relatively benign cutaneous form that may resolve even untreated to a serious systemic form that may be fatal. Cutaneous PAN is defined as vasculitis in which small and medium-sized arteries are involved, as in systemic PAN, but vasculitis is limited to the skin (4).

## EPIDEMIOLOGY

Epidemiological studies on PAN are very limited, especially in childhood. In studies involving the adult age group, the annual incidence is reported as 1.6-9 cases/million, and the prevalence is approximately 31 cases/million persons (5,6). It has been documented to be the 3rd most frequent systemic vasculitis in childhood after IgA vasculitis and Kawasaki disease in some regions (7,8). However, after the identification of DADA2, which mimics PAN and is histologically indistinguishable, it became clear that PAN is even rarer than previously thought in childhood (9,10). Considering the gender distribution, although male gender is more common in adults, no differentiation was detected in children. (6) There is a wide distribution in age of onset in both adults and children. While the most frequently seen age group in adults is 25-50 years, the most frequently seen age of onset in children is around 9-10 years of age (8,11). It is thought that patients with familial Mediterranean fever (FMF) gene (MEFV) mutations are predisposed to develop PAN. In countries like Turkey where MEFV gene mutations are common, PAN is considered a disease

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are less common, but idiopathic thrombocytopenic purpura and Evans syndrome have been reported as features of DADA2 (60,63).

## LABORATORY, RADIOLOGICAL, AND HISTOPATHOLOGICAL FINDINGS

There is no specific laboratory finding of DADA2. High acute-phase reactants are common during exacerbations. Transaminase elevation is a common finding. Its characteristic histopathological changes are severe inflammatory response around or inside the vessel wall and fibrinoid necrosis of the vessel wall. Acute or chronic lacunar ischemic infarcts in the deep brain nuclei and/or brain stem can be visualized with MR angiography. Angiography is the best method for demonstrating aneurysms and stenoses in medium-sized arteries (29,30).

## DIAGNOSIS

The diagnosis of DADA2 should be suspected in children and young adults presenting with PAN, such as vasculitis and ischemic or hemorrhagic stroke, especially in the presence of livedo, systemic inflammation, cytopenias, and hypogammaglobulinemia. It is confirmed by genetic studies that identify biallelic deleterious ADA2 variants, or by a biochemical analysis showing nearly absent levels of ADA2 activity in plasma or serum (64).

## TREATMENT AND PROGNOSIS

In the treatment of DADA2, immunosuppressive agents are used to reduce and control inflammation. Although high doses of steroids may provide temporary relief, the disease usually flares up during dose reduction. Azathioprine, methotrexate, calcineurin inhibitors, cyclophosphamide, mycophenolate mofetil, and sirolimus failed to consistently control inflammation. It was found to be insufficient to achieve remission with anti-interleukin-1 therapy (44). Anti-TNF-α agents give very good results in the treatment of vasculitis in patients with DADA2. It has been demonstrated that acute phase levels of patients and skin rashes decrease with anti-TNF-α therapy. In addition, it has been demonstrated to reduce ischemic stroke and alleviate immunodeficiency, hepatosplenomegaly, and neutropenia. Fresh frozen plasma infusions have been tried to maintain enzyme levels; however, the half-life of plasma ADA2 is short (49,65). Publications are showing that hematopoietic stem cell transplantation is successful in DADA2 patients presenting with hematological findings (54,61). Disease-related mortality was reported as 8% before age 30; the cause of death includes complications from recurrent stroke or infection (50).

## CONCLUSION

Although PAN and DADA2 have common findings, they are two very different diseases. Both diseases must be carefully evaluated in the differential diagnosis, especially in patients with livedo reticularis-like skin lesions and necrotizing vasculitis. However, stroke at an early age, family history of similar disease, unexplained immune dysregulation, and hematological findings should primarily suggest DADA2.

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CHAPTER **34**

# IgG4-RELATED DISEASE

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## INTRODUCTION

IgG4-related disease (IgG4-RD) is a disorder that was very lately discovered and is now generating a lot of attention across many medical specialties (1, 2). The observation of high blood IgG4 concentrations in individuals with sclerosing pancreatitis served as the first tip-off to its discovery (3, 4). Formerly known as Mikulicz disease, characterized by bilateral swelling of the salivary and lacrimal glands, and autoimmune pancreatitis (AIP) are two diseases now associated with high blood IgG4 concentrations (5). The retroperitoneum, lung, central nervous system, liver, thyroid, prostate, gastrointestinal tract, lymph nodes, kidney, skin, breast, and arteries are among the many organs that IgG4-RD can affect synchronously or metachronously.

Extrapancreatic lesions such as sclerosing cholangitis, sialadenitis, and dacryoadenitis are all linked to AIP (6). On the other hand, interstitial pneumonia, interstitial nephritis, and AIP are usually linked to sialadenitis and dacryoadenitis (also known as Mikulicz disease) (7). The idea of a systemic disease with a high blood IgG4 level was developed as a consequence of these discoveries, and several publications from Japan and other nations have characterized IgG4-related disorders using various nomenclatures. At the first international meeting on this disease, it was decided to use the term "IgG4-related disease" as a standard (8). Additionally, the chosen nomenclature for certain organ presentations of IgG4-RD was approved by the organizing committee of IgG4-RD.

## EPIDEMIOLOGY

Due to the paucity of global cohort studies and the fact that IgG4-RD was just recently recognized, the epidemiology of the condition is still poorly known. Japan's IgG4-RD teams reported a reported prevalence of 0.28 to 1.08/100,000 people (1). According to a 2011 national study conducted in Japan, the prevalence rate for AIP was 4.6/100,000 (9).

## CLINICAL PRESENTATION

### Type 1 autoimmune pancreatitis (AIP) and sclerosing cholangitis

Types 1 and 2 of AIP have been identified (10). The prototype of IgG4-RD, type 1 AIP, has served as the foundation for the idea of IgG4-RD (3, 4). Clinically, individuals exhibit obstructive jaundice as a result of intrapancreatic bile duct constriction; nonetheless, pancreatitis attacks with severe abdominal pain are uncommon. Increased levels of bilirubin and biliary

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operate on since its wall is thicker and attaches to the surrounding tissue. Therefore, before undergoing surgical therapy, AAAs should be evaluated to determine whether or not they are inflamed. IAAA may first be treated with medicine. When the inflammation subsided, surgical treatment for extremely big aneurysms would be taken into consideration. Although endovascular aneurysm repair has fewer postoperative consequences than surgical repair, it is less effective than open repair in reducing inflammation around inflammatory AAA. Even after therapy, it is impossible to conclude if inflammatory AAA has a better prognosis than atherosclerotic AAA since the real natural course of the condition is still poorly known. When an aneurysm ruptures, surgery may be considered, but the prognosis is poor (56). Due to the adhesion of intra-abdominal organs, it can be more challenging to conduct in an IgG4-related aneurysm than in an atherosclerotic one. After an aneurysm ruptures, coil embolization of the artery may be used to control the bleeding.

## CONCLUSIONS

Even though the strong clinicopathological correlation is the cornerstone for confirming IgG4-RD, tissue biopsy remains the gold standard for diagnosis. Clinicians' attention and rate of fast diagnosis, which is necessary to avoid harm to vital organs, will rise if they are aware of this disease. The diagnosis of this disease has been significantly hampered by the absence of valid biomarkers. However, recent strides in understanding the etiology of the disease, particularly the function of plasmablasts and the interplay between T and B cells, have generated intriguing and promising theories that may lead to new biomarkers and innovative therapeutic approaches. Due to the limited availability of randomized controlled studies, the efficacy of steroid-sparing drugs in IgG4-RD remains uncertain. Nevertheless, as a result of greater awareness and worldwide cooperation, the field is poised to advance and undertake additional clinical studies to demonstrate the effectiveness of drugs for maintenance treatment in IgG4-RD.

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CHAPTER **35**

# KAWASAKI DISEASE

*Zafer Kök* [1]

## INTRODUCTION

Kawasaki Disease (KD) is systemic inflammatory vasculitis that influences the arterial system mainly medium-sized arteries (1). First described in 1967 in Japan by Dr. Kawasaki. Initially described as mucocutaneous lymph disease (2).

KD is most prevalent under five years of age and this rate is approximately 85%. KD is 1.5 times more common in boys contrary to girls. Recently KD has been the leading cause of acquired cardiac disease at a young age in Western countries. Fatality of disease in Japan is 0.015% (3). The prevalence was very high among Asian children, especially those of Japanese ancestry.

## DIAGNOSIS

KD is diagnosed clinically, there is no unique diagnostic laboratory test for the disease. There are two sets of most commonly used diagnostic criteria.

| |
|---|
| 1: Kawasaki Disease Research Committee (Japan) guidelines 2002 (4). |
| 2: American Heart Association (AHA) guidelines, 2004 (5). |

The diagnostic criteria of the KD are summarized in Table 1.

**Table 1. Diagnostic criteria of Kawasaki disease**

| **Criteria** | |
|---|---|
| Fever | Fever for 5 days (typically high spiking, remittent) |
| Conjunctivitis | Bilateral conjunctival injection (typically sparing the limbic region, non-exudative) |
| Mucosal changes | · Erythema & peeling of lips<br>· Strawberry tongue<br>· Erythema of oral cavity |
| Lymphadenopathy | Cervical located, >1,5 cm in diameter, firm, nonfluctuant nodes bilaterally |
| Mucosal changes | In different forms: commonly maculopapular, may be urticarial, erythrodermic, or erythema multiforme-like |
| Extremity changes | In the acute phase; induration and erythema of extremity<br>In the subacute phase; periungual desquamation may seen |

Main difference between two diagnostic criteria is in AHA guideline fever is cornerstone, fever must be present (4). Additionally, 4 out of 5 criteria must be met (4).

In Japan guideline fever is not necessary. 5 out of 6 criteria must be met (5).

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CHAPTER **36**

# ADULT-ONSET STILL'S DISEASE

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## INTRODUCTION

Adult-onset Still's disease (AOSD) is a rare systemic autoinflammatory disorder that can affect numerous organ systems. The prevalence of the disease is estimated to be between 0.16 and 0.4 cases per 10,000 individuals. AOSD affects men and women equally and is most prevalent among patients between the ages of 15 and 25, as well as those between 36 and 46. The precise etiology of this disease remains uncertain. However, a multitude of factors, including environmental exposures, genetic predispositions, viral and bacterial infections, neoplasms, and inflammatory processes, have been identified as potential contributors to its development (2). Given the involvement of numerous cytokines, including interleukins (IL-1 and IL-6), in the pathogenesis of AOSD, the use of biological drugs targeting these cytokines represents a rapidly expanding area of medical practice (3).

The Yamaguchi and Fautrel criteria are employed for the diagnosis of AOSD (Tables 1 and 2). The most commonly reported symptoms of AOSD are persistent high fever, arthralgia or polyarthritis, salmon-colored pink skin lesions, leukocytosis, and elevated ferritin levels (6). Additionally, other rare manifestations have been documented during patient follow-up (7). Additionally, complications may arise in the form of reactive hemophagocytic lymphohistiocytosis, neurological issues, lung disorders, liver or renal failure, and cardiac dysfunction (8).

Complications affecting the heart may manifest in any layer and can have a potentially life-threatening outcome, including myocarditis (9), tamponade (10), or endocarditis (11). A recent study comprising 96 patients revealed that 29% exhibited cardiac involvement. Cardiac complications were present at diagnosis in 89% of patients, with pericarditis being the most common diagnosis. Other cardiac complications included cardiac tamponade, rare myocarditis, and one case of noninfectious endocarditis. AOSD patients with cardiac complications tended to have a severe inflammatory response syndrome, resistance to standard conventional therapies, a higher rate of intensive care unit admission, and a higher rate of biotherapy treatment (12).

**Table1: Yamaguchi's criteria**

A minimum of 5 criteria is required, at least 2 of which must be majör

**Major criteria**

- Fever over 39°C for more than a week
- Arthralgia or arthritis lasting more than 2 weeks
- Rash that is specific to adult-onset Still disease
- Leukocytosis >10000/mm3, >80% polymorphonuclear cells

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and provide relief from severe disease manifestations, including cardiac involvement (13, 14).

For cardiac complications such as endocarditis, the treatment approach depends on whether the condition is infectious or related to systemic inflammation (28, 29). While bacterial endocarditis is rare in AOSD, when it occurs, intravenous antibiotics are required. In contrast, if the endocarditis is non-bacterial and associated with AOSD, immunosuppressive therapy (such as corticosteroids or biologics) is used to manage the underlying inflammatory process (28, 29). Regular monitoring of cardiac function is essential, and in cases of severe complications such as valvular dysfunction or myocardial involvement, further interventions, including surgical options or mechanical support (e.g., ECMO), may be needed in refractory cases (18).

## CONCLUSION

Cardiac involvement in AOSD is not a common occurrence, yet it can prove fatal if caused by acute myocarditis or associated with significant mortality. The standard treatment for AOSD is the administration of high doses of corticosteroids. The prognosis is favorable; however, approximately 33% of patients are unresponsive or refractory to standard treatment or require intensive care. In cases of severe illness, it is advisable to commence treatment with anti-IL1 or IL-6 agents at the earliest opportunity. Cardiac manifestations may serve as indicators of disease activity, severity, and the potential for a refractory form of AOSD, which would necessitate treatment with biologic DMARDs. All individuals diagnosed with AOSD must undergo cardiac screening.

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CHAPTER 37

# MULTISYSTEM INFLAMMATORY SYNDROME IN ADULTS (MIS-A)

*Firdevs Ulutaş* [1]

## INTRODUCTION

The post-infectious hyperinflammatory syndrome, designated as multisystem inflammatory syndrome in children (MIS-C), was initially delineated in the pediatric population in April 2020 [1]. This clinical emergency is frequently observed in children in the weeks following infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It frequently affects the cardiovascular and gastrointestinal systems. A comparable multisystem hyperinflammatory state has been identified in adults with coronavirus disease 2019 (COVID-19), designated as the multisystem inflammatory syndrome in adults (MIS-A) [3]. A distinct clinical hyperinflammatory condition, MIS-A, was described in patients up to age 50 years with severe extrapulmonary system dysfunction (including thrombosis) without severe respiratory disease. Although MIS-A shares certain characteristics with MIS-C, cardiac dysfunction, thromboembolic events, and an elevated risk of mortality have been observed more frequently in MIS-A.

The true prevalence of MIS-A is uncertain, but it is rarely observed as a complication of SARS-CoV-2 infection. The Centers for Disease Control and Prevention (CDC) has defined MIS-A as a hyperinflammatory state with multiorgan (≥2) dysfunction in individuals (>21 years of age) with current or antecedent evidence of an asymptomatic and symptomatic SARS-CoV-2 infection within 12 weeks [4]. In addition to SARS-CoV-2 infection, the SARS-CoV-2 Pfizer-BioNTech mRNA has been identified as a potential contributing factor in a 44-year-old patient [5]. The Brighton Collaboration Case criteria, which classify MIS-A cases as "definite," "probable," or "possible," have recently been updated. To diagnose a patient with MIS-A, it is necessary to consider the laboratory evidence of severe inflammation and the recent infection with SARS-CoV-2, as well as the clinical presentations. Currently, there is no specific diagnostic test for MIS-A [6].

Although the precise pathophysiology of MIS-A remains unclear, it is believed to be caused by a delayed and dysregulated immune response involving both innate and adaptive immune cells that occurs weeks after recovery from a SARS-CoV-2 infection. Potential underlying mechanisms include (i) the generation of autoantibodies, (ii) antibody recognition of persistent viral antigens on infected cells, and (iii) a hyperinflammatory response to viral superantigens and a systemic cytokine storm. This uncontrolled immune response results in systemic inflammation, endothelial dysfunction, and a procoagulant state. Patients with MIS-A frequently present with elevated acute inflammatory markers, including C-reactive protein, interleukin (IL)-6, ferritin, and erythrocyte sedimentation rate. Additionally, they often exhibit

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dex of suspicion for MIS-A among patients for whom a history of illness is not available. These patients should undergo evaluation for current or previous SARS-CoV-2 infection, utilizing methods such as RT-PCR, rapid antigen tests, or serologic tests for antibodies, including measuring titers. Additionally, evaluation for severe inflammation and/or coagulopathy is recommended, with particular attention paid to elevated C-reactive protein, ferritin, interleukin 6, or D-dimer levels.

The optimal treatment for MIS-A remains uncertain. However, anti-inflammatory drugs, including intravenous immunoglobulin (IVIG) and pulse glucocorticoids, are frequently employed. In select cases, immune modulators (e.g., tocilizumab or anakinra) may be employed. In numerous studies, concomitant antibiotics are frequently employed for the treatment of acute febrile bacterial infections, and heparin is utilized for thrombosis prophylaxis without any evidence-based guidelines. The aforementioned therapeutic regimen can also reverse cardiac dysfunction by alleviating excessive inflammation [21]. Patients who are severely ill and experiencing shock or hypotension may require supportive management, including the use of vasoactive medications such as inotropes, intra-aortic balloon pump (IABP), or extracorporeal membrane oxygenation (ECMO). In some cases, mechanical ventilation may be necessary.

In accordance with the recommendations set forth by the American College of Rheumatology (ACR) about the treatment of MIS-C, immunomodulatory therapies, including glucocorticoids and/or IVIG, are to be regarded as the preferred initial treatment modality. The ACR guidelines for MIS-C recommend anticoagulation in patients with one or more of the following conditions: documented thrombosis, moderate-to-severe left ventricular dysfunction, and [22].

## CONCLUSION

The present paper addresses a topic of great importance: the serious sequelae of the novel COVID-19 that may be poorly understood, underreported, and, most worrisome of all, not diagnosed promptly. Cardiac dysfunction represents a prominent feature of the sequelae of COVID-19, due to the abundance of ACE2 receptors in cardiac tissue. A delayed diagnosis may result in heart failure and shock, which could ultimately lead to the development of chronic cardiac disease. The avoidance of complications and chronic illness is possible with the administration of prompt early corticosteroid therapy. Despite a patient's recovery to their pre-disease baseline level of function, it is advisable to conduct cardiac function surveillance to screen for the potential development of chronic cardiac disease during the follow-up period.

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CHAPTER **38**

# JUVENILE IDIOPATHIC ARTHRITIS

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## INTRODUCTION

Arthritis is defined as joint inflammation. It is characterized by inflammatory processes affecting multiple joints, manifesting as swelling, redness, elevated temperature, and impaired functionality.[1,2] In arthritis, the primary symptoms are joint swelling and morning stiffness. The temperature of the joint surface is elevated.

The National Institute for Health and Care Excellence (NICE) recommends performing a paediatric gait, extremities and vertebral column (pGALS) examination to effectively assess a child presenting with arthritis or arthralgia.[3,4] The pGALS examination commences with a comprehensive examination of the child's front, back, and sides. The examination should include an assessment of joint swelling, muscle mass, scoliosis, flexion deformity of the hip or knee, rashes, and bruises.[5]

The term "acute arthritis" is used to describe arthritis in the same joint that lasts less than one and a half months. A condition that persists for a period exceeding one and a half months is classified as chronic arthritis.[6] The classification of arthritis is based on the number of joints involved. Monoarthritis is characterized by involvement of a single joint, oligoarthritis by involvement of four or fewer joints, and polyarthritis by involvement of five or more joints.[7] Enthesopathy is defined as an inflammatory response occurring in the area where tendons attach to bone. It is most prevalent in the Achilles tendon.[8]

Juvenile idiopathic arthritis (JIA) represents the most prevalent underlying cause of chronic arthritis in childhood. Juvenile idiopathic arthritis (JIA) is a childhood diagnosis of arthritis that manifested before the age of 16 years, persisted for more than six weeks, and could not be attributed to other causes.[9]

In subtypes such as oligoarticular and polyarticular JIA, an antigen-mediated autoimmune process is identified as a key element in the pathogenesis. In the case of systemic-onset JIA, an autoinflammatory process occurs with the uncontrolled activation of the innate immune system.[10] There are seven recognized types of JIA, as defined by the International League of Associations for Rheumatology (ILAR).[9] These subgroups are: systemic-onset, oligoarticular, rheumatoid factor (RF) positive polyarticular, RF negative polyarticular, psoriatic arthritis (PsA), enthesitis-related arthritis, and unclassified arthritis.[11]

The mean age of onset was found to be six years for the systemic-onset and polyarticular type; for the oligoarticular type, a mean age of four years has been reported for girls and 10 years for boys.[11] While the oligoarticular type is more common in girls, the enthesitis-related type is more prevalent in men. Systemic-onset JIA manifests in both boys and girls with equal frequency.[12]

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acteristics that are similar to those observed in other conditions, such as Kawasaki disease (KD) and multisystem inflammatory syndrome in children (MIS-C). Cardiac manifestations in systemic-onset JIA include coronary arteritis, myopericarditis, congestive heart failure, valve abnormalities, and conduction system abnormalities.[38] Coronary artery aneurysms are more common in KD.[39] Myocarditis is observed in approximately 5% of cases of systemic-onset JIA. Congestive heart failure is a relatively uncommon occurrence in patients with systemic-onset JIA. However, immunosuppressive therapy is beneficial in this regard. Intravenous immunoglobulin (IVIG) has been demonstrated to be an effective treatment for restoring left ventricular function and for acute myocarditis due to systemic-onset JIA.[38] In the coronary circulation, aneurysmal changes, similar to those observed in KD, can be encountered in patients with systemic-onset JIA, though this is an uncommon occurrence.[38,39]

Systemic inflammation has been demonstrated to increase the risk of atherosclerosis. Consequently, patients with JIA are at an elevated risk of developing cardiovascular disease (CVD).[41] However, this risk can be mitigated through the use of anti-TNF-α therapy, which has been shown to effectively reduce cardiovascular risk in JIA patients.[42]

It has been demonstrated that inflammatory mediators such as IL-18 in JPsA play a role in the development of CVD. In individuals with PsA, cardiovascular events are the leading cause of mortality in those with advanced age.[43]

In the group of seronegative spondyloarthropathies, the disease with the most pronounced cardiac involvement is enthesitis-associated arthritis. While aortic regurgitation, hypertension, ventricular diastolic dysfunction, conduction blocks, and atherosclerotic and ischemic events resulting from prolonged exposure to inflammatory processes have been frequently described in adult studies, cardiac involvement is rarely observed in juvenile AS or enthesitis-associated arthritis.[44]

## CONCLUSION

JIA is a chronic disease. Among the various subtypes of JIA, those with the highest prevalence of cardiac involvement are systemic-onset JIA and SpA, which encompasses enthesitis-associated arthritis and PsA. The regression of cardiac findings in response to appropriate treatment of the primary disease underscores the importance of maintaining control of the disease process.

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CHAPTER **39**

# JUVENILE SYSTEMIC LUPUS ERYTHEMATOSUS AND ANTIPHOSPHOLIPID SYNDROME

*Sema Nur Taşkın* [1]

## INTRODUCTION

Systemic lupus erythematosus (SLE) represents the archetypal chronic systemic autoimmune disease. SLE is a rare but serious multisystemic disease. It is characterized by the presence of multiple autoantibodies, which can frequently affect a number of organ systems, including the skin, hematological, cardiovascular, and nervous systems, joints, and kidneys. The damage caused to these systems and organs can be significant, and in some cases, it can result in death. The onset, progression, and outcome of SLE are unpredictable. The disease process is typified by periods of exacerbation and, less frequently, remission. It is established that the primary mechanism underlying the progression of the disease is the production of autoantibodies. The autoantibodies most frequently associated with SLE are antinuclear antibodies (ANA) and anti-double-stranded (natural) DNA (anti-dsDNA). SLE is classified as juvenile SLE (jSLE) if it manifests before the age of 18 (1). Although jSLE appears to be essentially the same disease with similar etiology, pathogenesis, and laboratory findings as in adults, there is some variation in the severity and frequency of clinical symptoms. Children with SLE exhibit greater disease severity and earlier disease-related organ damage than adults with SLE. If left untreated, the five-year mortality rate reaches 95.3% (1).

Antiphospholipid syndrome (APS) is a systemic autoimmune disease that is characterized by thromboembolic events, pregnancy morbidity, hematological, dermatological, neurological, and other organ manifestations that are present in the presence of persistent antiphospholipid antibodies (APLA) (2). APS can occur without any underlying disease (primary APS) or with an underlying disease such as SLE, infection or malignancy (secondary APS). The form that manifests before the age of 18 is referred to as pediatric APS (2).

If left undiagnosed and untreated, both diseases (SLE and APS) have the potential to be fatal. In this chapter, the pathophysiology, clinical findings, and treatment approaches of SLE and APS in children will be discussed in accordance with the concepts presented in this book, with a particular focus on the cardiovascular system.

## 1. SYSTEMİC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that affects multiple systems in the body. It is associated with a high prevalence of morbidity and mortality (1). The development of SLE is influenced by a complex interplay of genetic, immunological, endocrine, and environmental factors. These factors contribute to the loss of immunological tolerance against self-antigens, leading to the formation of pathogenic autoantibodies that cause tissue damage through various mechanisms.

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CHAPTER **40**

# AUTOINFLAMMATORY DISEASES

*Şeyda Doğantan* [1]

## INTRODUCTION

Autoinflammatory diseases are a group of disorders caused by abnormalities in the immune system, characterized by repetitive episodes of systemic inflammation. These diseases occur due to overactivation of the innate immune system, which is the body's first line of defense against infectious agents. Key elements of innate immunity, including neutrophils, macrophages, and natural killer (NK) cells, exhibit phagocytic activity, allowing them to engulf and neutralize harmful pathogens.

Phagocytes can recognize structures associated with external pathogens (PAMPs, pathogen-associated molecular patterns) and endogenous molecules (DAMPs, danger-associated molecular patterns) released from damaged or stressed cells. The recognition of these patterns is mediated by pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs) and stimulator of interferon genes (STING) located on the cell surface, and nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) found in the cytosol. Once these receptors recognize PAMPs or DAMPs, they trigger intracellular signaling pathways that result in the production of pro-inflammatory cytokines and interferons, initiating the inflammatory response (1,2).

Autoinflammatory diseases arise when there is excessive activation of the innate immune system, independent of infection or autoimmunity. This leads to inflammation and an increase in acute-phase reactants during episodes. While most autoinflammatory diseases are monogenic (caused by mutations in a single gene), a few display multifactorial inheritance patterns (3,4).

When the classification of autoinflammatory diseases was made according to molecular pathways (5,6,7,8), it was as follows:

**1. Inflammasomopathies:**

- Familial Mediterranean fever (FMF),
- Mevalonate kinase deficiency (MKD) or hyper-immunoglobulin (Ig) D syndrome (HIDS),
- Cryopyrin (NLRP3)-associated inflammasomopathies,
- Pyrin-associated autoinflammation with neutrophilic dermatosis (PAAND),
- NLRC4-related macrophage-activation syndrome (NLRC4-MAS)
- NLRP1-related disease
- NLRP12-related disease

**2. Actinopathies:**

- Pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome
- Periodic fever immunodeficiency and thrombocytopenia (PFIT)
- ARPC1B deficiency

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CHAPTER **41**

# PEDIATRIC VASCULITIS

*Yasemin Nuran Dönmez* [1]

## INTRODUCTION

The term "vasculitis" refers to an inflammation of the blood vessels. Vasculitis is mainly classified according to the size of the vessel it affects (1). The organs affected by vasculitis and the presentation vary greatly depending on the type of vasculitis, the size of the affected vessel, the age of onset, and the response to treatment. Diagnosing vasculitis in children can be challenging due to several factors, including the lack of a reliable laboratory test, the disease's low incidence, and the wide variety of clinical presentations. When it comes to surviving, preventing lasting damage (renal failure, heart failure), and coping with a miserable prognosis, an early diagnosis is important. Undiagnosed renal failure, hematuria/proteinuria, elevated inflammation indices, multiorgan involvement with constitutional findings, and radiographic evidence of involvement of major vessels may all point to a diagnosis of vasculitis (2). Table 1 displays the different types of vasculitis based on the size of affected blood vessels. Even though cardiac involvement in vasculitis is less frequent than cutaneous or renal involvement, it is nevertheless crucial to understand the serious consequences. Arrhythmias, pericardial involvement, congestive heart failure, myocardial ischemia, or valve involvement can all be seen in vasculitis. Cardiac damage may be due to vasculitis-related or ischemic changes. Steroids and immunosuppressant medicines should also be considered for potential cardiotoxic effects. Kawasaki disease and Takayasu arteritis are two examples of vasculitis that are associated with an increased risk of cardiovascular complications such as coronary artery dilatation and aortic aneurysm. Furthermore, all vasculitis has a risk of atherosclerosis effect in the years following persistent vascular inflammation, arterial intimal media thickness, endothelial injury or circulating endothelial cells, free radicals, and vascular cell adhesion molecule (3, 4). To recognize potential risk factors like obesity, and dyslipidemia for cardiovascular illness and to provide modification with early diagnosis and treatment, it becomes essential to be aware of cardiac involvement in vasculitis.

**Table 1. Classification of childhood vasculitis (5)**

| |
|---|
| **I Predominantly large vessel vasculitis** |
| · Takayasu arteritis |
| **II Predominantly medium sized vessel vasculitis** |
| · Childhood polyarteritis nodosa |
| · Cutaneous polyarteritis |
| · Kawasaki disease |
| **III Predominantly small vessels vasculitis** |
| · Immunoglobulin A vasculitis / Henoch-Schoenlein Purpura |

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profile and risk factors for the metabolic syndrome (3). It's also important to note that the cardiovascular system may be affected by certain medicines used to treat vasculitis. There is an elevated risk of hypertension and dyslipidemia from steroids, as well as cardiomyopathy from cyclophosphamide and arrhythmia from mycophenolate mofetil (3). Sudden cardiac arrest or death is significantly associated with coronary artery involvement in vasculitis. PAN, Kawasaki disease, and Takayasu arteritis are the most common causes of involvement (33).

## CONCLUSION

As there is currently no definitive diagnostic approach for primary systemic vasculitis in children, clinicians must maintain a high index of suspicion to ensure timely identification. Given the heterogeneity of vasculitic disorders and their often nonspecific presentations, a comprehensive evaluation—including clinical assessment, laboratory markers of inflammation, imaging studies, and, when necessary, histopathological confirmation—is essential. Early diagnosis and prompt initiation of immunosuppressive therapy are critical in improving outcomes by controlling inflammation and preventing irreversible organ damage. This is particularly important as certain vasculitis subtypes, such as PAN, Kawasaki disease, and Takayasu arteritis, have a predilection for cardiac involvement, potentially leading to long-term cardiovascular complications.

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CHAPTER **42**

# KAWASAKI DISEASE AND MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN

*Kutay Sel* [1]

## INTRODUCTION

The disease, which was defined by the coronavirus disease 2019 (COVID-19) pandemic in the world and known as multisystem inflammatory syndrome (MIS-C), was remarkably similar to Kawasaki disease (KD) in terms of its clinical presentation and symptoms in the early days. Although the etiology of KD has not been fully elucidated, it has been a well-known disease for years. MIS-C, on the other hand, appears sometime after the COVID-19 viral infection and treatment protocols continue to evolve. This chapter discusses the similarities and differences between these two diseases.

## KAWASAKI DISEASE (KD)

KD is a systemic vasculitis seen in childhood that can affect all three layers (endocardium, myocardium, and pericardium) of the heart (1). When coronary artery involvement occurs, it can lead to mortality and morbidity. It usually occurs in children younger than five years and is more common in males. The disease was named by Dr. Kawasaki who described it for the first time in 1967 (2). Since then, awareness has increased and the number of diagnosed patients has grown rapidly, especially in Japan. Studies of the disease and research into treatment have also accelerated. In 1970, patients who died of KD were found to have coronary artery involvement at autopsy (3). Although the disease is well recognized today, its etiology has not been determined and there are no specific diagnostic laboratory tests. The diagnosis is made on the basis of clinical findings. Because the symptoms of the disease are similar to those of most childhood diseases, errors and delays in diagnosis may occur.

The incidence of KD is reported as 4-25/100000 in children ≤ 5 years in the United States, Austria, and Europe. It is reported about 1-20 times more in Northeast Asian countries (4). Especially in Japan, the incidence is highest and occurs in the form of periodic epidemics (5). The incidence is also high in Korea and Taiwan and increasing rapidly in industrializing countries such as India and China (4). Recurrence can also occur in KD, while the rate of recurrence is 1% worldwide, this rate rises to 3% in Asian countries and especially in Japan (6). Recurrence is more common in the first two years following the disease. Although the incidence also shows seasonal variability, this variability differs according to the countries (4).

Although KD can be seen frequently between the ages of 6 months and 4 years (7), it has also been reported in quite different age groups, from newborns to adults, especially in human immunodeficiency virus (HIV)-positive adults (8). It is more common in

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The American Society of Rheumatology (ACR) recommends IVIG 2 gr/kg and methylprednisolone 1-2 mg/kg/day as initial treatment. In cases resistant to first-line therapy, methylprednisolone 10-30 mg/kg/day IV or high-dose anakinra (recombinant IL-1 receptor antagonist) or infliximab (TNF-alpha antagonist) is recommended (47). The introduction of IVIG in treatment was initially due to its similarity with KD. However, the benefit of IVIG in myocarditis is unclear. Corticosteroid therapy was added to the treatment as it was tried in resistant KD. In many studies, positive results have been reported in combination of IVIG with corticosteroids instead of IVIG treatment alone (48). In patients with MIS-C, high-dose steroids are recommended if inotropes or vasopressors are used (32). Serial laboratory tests and cardiac evaluation guide the decision to reduce immunomodulatory therapy. To prevent rebound inflammation after treatment, immunomodulatory therapy should be continued for at least 2-3 weeks.

Another step in the treatment is antiaggregant and anticoagulant therapy. ASA treatment is recommended because of endothelial damage (7). A low dose (3-5 mg/kg/day) is started in MIS-C patients who do not have active bleeding or bleeding risk. This is continued until the platelet count returns to normal and coronary arteries appear to be normal four weeks after diagnosis. In patients with coronary artery aneurysms or severe left ventricular dysfunction, different treatment methods are created according to the patient's condition.

With appropriate treatment, MIS-C is a manageable disease. A 99% improvement was reported in the 90-day follow-up of patients with initially impaired cardiac systolic functions (49). Acute kidney injury, which was reported in 25-40% of patients, was also mostly fully recovered in the follow-up (50). In patients with neurological involvement, 90% complete recovery is observed at discharge (51). However, long-term data are not yet sufficient.

As a result, although the clinical course of MIS-C patients is troublesome and tiring, with effective and rapid treatment most of the patients recover completely without sequelae. Despite this, deaths have been reported, albeit at a low rate. In a study involving a total of 655 patients with MIS-C, mortality was calculated as 1.7% (32). According to CDC data, mortality is less than 1% among more than 7400 patients.

## CONCLUSION

Although KD and MIS-C share certain similarities, they represent distinct clinical entities with notable differences. Both conditions are associated with hyperinflammation and immune dysregulation, but their presentations and underlying mechanisms differ significantly. A key distinguishing feature of MIS-C is its association with SARS-CoV-2 infection, as most affected patients have a history of serology positivity for the virus, indicating a potential post-viral immune response. In contrast, KD remains idiopathic, with no definitive etiological factor identified despite extensive research. In addition, MIS-C tends to present as a more severe clinical picture with significant cardiac involvement and additional complications such as shock, prominent gastrointestinal symptoms, an increase in acute phase reactants, and hematological abnormalities.

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CHAPTER **43**

# JUVENILE DERMATOMYOSITIS AND SCLERODERMA

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## INTRODUCTION

Dermatomyositis is an autoimmune inflammatory disorder primarily affecting the skin and skeletal muscles (1). The juvenile form is a multisystem disease characterized by small-vessel vasculitis (2,3) and is classified under idiopathic inflammatory myopathies (4). Juvenile dermatomyositis is a rare autoimmune condition, with an estimated incidence of 2–3 cases per million children per year in the United States (1). It predominantly affects females, with a female-to-male ratio of 2:1 (5). The average age of onset is approximately 7 years, although cases in children younger than 3 years have been reported (6).

Scleroderma is a connective tissue disease characterized by progressive fibrosis of the skin and underlying tissues. It exists in two main forms: systemic sclerosis (SSc) and localized scleroderma (LS). SSc involves fibrosis of the skin, blood vessels, and internal organs, whereas LS primarily affects the skin and subcutaneous tissues, with minimal systemic involvement. In children, scleroderma is usually localized and carries a favorable prognosis (7). However, SSc in pediatric patients is associated with a higher risk of severe cardiomyopathy and a poorer prognosis (8). Pediatric scleroderma is rare. The annual incidence of LS is estimated at 1–3 cases per 100,000 children, whereas SSc is reported in approximately 1 per 1,000,000 children (14). LS predominantly affects females, with a female-to-male ratio of 2.4:1, while SSc exhibits an even stronger female predominance, with a ratio of 4:1 (7,9). The mean age of onset ranges from 7.3 to 8.8 years, although cases have been documented as early as the neonatal period (7,9). While fewer than 5% of SSc cases have a pediatric onset, the majority of LS cases are present in childhood (8).

In this book chapter, the cardiac manifestations of juvenile dermatomyositis and scleroderma will be discussed in detail.

## JUVENILE DERMATOMYOSITIS

### Etiology

Juvenile dermatomyositis is a multifactorial disease with a complex etiology involving genetic, environmental, and immunological factors. Among these, genetic predisposition plays a crucial role, with the human leukocyte antigen (HLA) region, located within the major histocompatibility complex (MHC), being one of the most polymorphic regions of the human genome. This region carries alleles that increase susceptibility to various autoimmune diseases, and a well-established association exists between juvenile dermatomyositis and HLA-DR3, suggesting its significant contribution to disease risk (1,2).

Environmental factors are also critical in juvenile dermatomyositis pathogenesis, with infections, medications, vaccines, and ultraviolet (UV) radiation

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CHAPTER **44**

# JUVENILE SARCOIDOSIS

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## INTRODUCTION

Sarcoidosis, also known as Besnier-Boeck-Schaumann disease, was first described as a systemic granulomatous disease in the 19th century. This complex disease has a multifactorial origin and an unclear underlying cause. It begins with an inflammatory and granulomatous process triggered in individuals with a genetic predisposition. Although the etiology is not fully understood, there is a genetic susceptibility that contributes to its development. (1,2). Sarcoidosis is more common in adults and is approximately 10 times more common in this age group than in children. Although the likelihood of sarcoidosis in children tends to increase with age, the disease can affect children of any age (3). In contrast to adults, pediatric cases of sarcoidosis primarily present with skin, joint, and eye symptoms in children under the age of 5 years of age. This presentation differs from that observed in young and older adults, where lung and lymph node involvement is more common. It's worth noting that early-onset sarcoidosis associated with the *NOD2* mutation is referred to as Blau syndrome, and while this chapter maintains a distinction, historical cohorts often combine Blau syndrome and juvenile sarcoidosis, leading challenges in differentiation [4-6].

Sarcoidosis is a disease characterized by the involvement of multiple organ systems, and the clinical symptoms can differ depending on the age of onset. The presentation of this disease can be highly variable, encompassing a wide range of manifestations. Given its tendency for an often subtle progression and occasional sudden, life-threatening onset, it is crucial to comprehensively review the cardiovascular involvement in pediatric sarcoidosis (7-8). This chapter aims to provide an up-to-date overview of the cardiac implications in childhood sarcoidosis.

## EPIDEMIOLOGY

There is limited data regarding the incidence of sarcoidosis. The annual incidence of combined granulomatous disorders, which includes conditions such as Blau syndrome, early-onset sarcoid and sarcoidosis, occurring before the age of 18 is reported to be between 0.06 and 1.02 per 100,000 people (9,10). The incidence rate in Danish children under 15 years of age has been reported to be between 0.22 and 0.27 per 100,000 children per year, and in French series it has been reported to be between 0.4 and 0.8 per 100,000 children per year (11,12). In both Blau syndrome and juvenile sarcoidosis, the ratio of females to males is approximately 1:1 (9,13,14).

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CHAPTER **45**

# ACUTE RHEUMATIC FEVER AND RHEUMATIC CARDIAC DISEASE

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## INTRODUCTION

Acute rheumatic fever (ARF) is a disease that manifests itself two to three weeks after exposure to Group A ß-hemolytic streptococcus (GAS) or *Streptococcus pyogenes* in genetically susceptible individuals. After acute pharyngitis, impetigo, or scarlet fever, ARF might arise as a result of a GAS infection. Since 1944, the Jones criteria have been utilized as diagnostic criteria for ARF. The last time it was changed was in 1992, but in 2015 it was finally modified to broaden the application of echocardiography all over the world and raise awareness of the need to take preventative measures against ARF (1). More than 33 million cases of ARF, one of the most frequently acquired heart disorders in children and young people, have been reported across the world. Diagnosis, risk assessment, and treatment are of extreme importance because ARF and its long-term cardiac consequences can be preventable and treatable with intervention at the appropriate time.

The improved quality of life and the use of antibiotics for GAS are credited for the decline in incidence and prevalence observed in recent years (2). As a result of migration from developing to developed countries and poor refugee living conditions, ARF remains a worldwide problem despite reports of a decline in incidence in industrialized nations. The incidence of ARF/Rheumatic heart disease (RHD) differs from one country to the next and also from one set of living conditions and socioeconomic status to another. Some countries (New Zealand, Australia, Pacific Islands) and populations (some Asian and Middle Eastern) have a greater incidence of ARF than others (1). The incidence is predicted to be 8.84 per 100,000 people in Turkey. According to the Jones criterion, Turkey is classified as a high-risk country. The eastern Anatolian region is claimed to have the greatest number of regional differences among the states in our country. (3). Those who are genetically predisposed and who live in overcrowded households, who live in areas with difficult access to a health center, or who have a low socioeconomic status with poor hygiene issues or overcrowding are at risk for developing acute rheumatic disease after having GAS infection (4, 5). Its occurrence may be affected by demographics, economics, malnutrition, sanitation, climate (it is more common in the fall and winter), cultural practices, and healthcare services (2). High temperatures, such as those experienced during the summer, along with high humidity, poor hygiene, and malnutrition, may increase the prevalence of impetigo.

## PATHOGENESIS

Acute pharyngitis is predominantly caused by GAS among children aged 5-15 years old, accounts for

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(18). Neither a new case of carditis nor a worsening of an existing case has been documented in patients on ASA or NSAIDs (19). Keep in mind that ASA has been linked to an elevation in liver enzymes, compliance problems, and nausea or vomiting. ASA and NSAIDs might cause gastrointestinal side effects, so a proton pump inhibitor may be added to the treatment (19). Because of the risk of the rebound effect, anti-inflammatory medicines should be taken cautiously. Anti-inflammatory medication typically results in clinical improvement within one to two weeks. It's important to keep up with treatment for at least 6-12 weeks. Weaning off the medicine is recommended rather than abruptly stopping treatment (12). NSAIDs (naproxen, ibuprofen) - Oral dosing at a rate of 10–20 mg/kg every 12 hours up to a maximum of 1,000 mg daily is recommended. Acetylsalicylic acid (aspirin) can be used 80–100 mg/kg/day (maximum 3,5 g/day) four to five times a day.

c. **Chorea:** Involuntary motions may be treated with sodium valproate or carbamazepine. Because of the risk of extrapyramidal side effects, neuroleptics should be used with caution (9). Risperidone, haloperidol, and levetiracetam are some more options.

## LONG-TERM CARDIAC OUTCOME

Most individuals with chronic rheumatic heart disease have no history of ARF, according to reports (8). To put it another way, ARF attacks are being overlooked. Both the degree to which the heart is affected initially and subsequent recurrences of the disease are major contributors to the development of chronic rheumatic fever. Within a few weeks or months, mild to moderate carditis usually gets better. Conditions such as valvular stenosis or regurgitation, heart failure, pulmonary hypertension, pregnancy complications, infective endocarditis, and arrhythmia due to chronic rheumatic heart damage may develop. Valve repairs or valve replacement may be required due to valvular problems.

## CONCLUSION

ARF presents a significant challenge for global health, as it can lead to severe long-term cardiac issues if not appropriately managed. Despite being a preventable disease, ARF continues to have a high prevalence, particularly in low- and middle-income countries and can result in lifelong heart complications. Understanding the diagnostic criteria, maintaining a low threshold of suspicion, and managing treatment effectively are crucial for preventing long-term consequences. In this context, controlling GAS infections is key to improving outcomes and preventing future complications. Screening high-risk populations with echocardiography for early detection of rheumatic heart disease is recommended. In symptomatic patients, initiating treatment promptly and ensuring continued penicillin prophylaxis are essential strategies for preventing recurrence and cardiac damage. Moreover, educating patients and their families about the importance of adherence to penicillin therapy and proper management can play a pivotal role in controlling ARF and its associated cardiac risks.

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CHAPTER **46**

# NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

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## INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a type of medications known for their anti-inflammatory, analgesic, and antipyretic efficacies (1). NSAIDs are one of the most commonly used type of medications, with approximately 5-10% of all medications prescribed each year being NSAIDs (2). These medications are used for the management of various conditions including, but not limited to, muscle pain, dysmenorrhea, osteoarthritis, spondyloarthritis, rheumatoid arthritis, pyrexia, gout, migraines, while they are also used as opioid-sparing agents in some cases of acute trauma (1).

### Sneak peek on NSAIDs – representatives, indications, and potential risks

The dosage of NSAIDs across the different indications, and particularly the analgesic versus the anti-inflammatory dosage, vary highly, as presented in Table 1. Currently, there are approximately 20 medicines approved by the Food and Drug Administration (FDA) (1). As their effectiveness and safety is generally recognized, commonly used NSAIDs, such as aspirin, can be accessed without a prescription i.e. over-the-counter (OTC) in many countries (4). However, that does not apply to higher doses of these drugs or specific NSAIDs (1).

Their mechanism of action mainly pertains to their ability to inhibit enzyme cyclooxygenase (COX), which are rate-determining enzymes for prostanoids synthesis and prostaglandins (1) (2). COX is essential in order to convert arachidonic acid into thromboxanes, prostaglandins, and prostacyclins; the therapeutic effect of NSAIDs lies in the lack of these eicosanoids (1). The anti-inflammatory effect of NSAIDs lies in the inhibition of cyclooxygenase/prostaglandin-endoperoxide synthase (PGHS-1 and PGHS-2), which play a vital role in the biosynthesis of prostaglandin, which in turn is strongly implicated in inflammation, particularly PGHS-2 (5). Some NSAIDs are nonselective inhibitors of both enzymes, while others are specific ("coxibs"), which specifically inhibit PGHS-2 (5).

**There are three main ways to categorize NSAIDs:**

- according to their chemical structure into NSAIDs of acidic and non-acidic origin (6). The former are further sub-categorized based on the name of the organic acid which forms the basis of the structure of the medicine (7). The differences between these drugs are small, but they can sometimes be relevant to clinical practice in the presence of hypersensitivity to NSAIDs (8).

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Cohort studies involving elderly individuals or patients hospitalised for significant congestive heart failure (CHD) found no difference in the incidence of MI, stroke, or recurrent CHD between celecoxib and diclofenac, ibuprofen, or naproxen. Furthermore, according to real-world findings, most commonly used NSAIDs, including celecoxib, diclofenac, ibuprofen and naproxen, have similar cardiovascular safety profiles, even in patients with hypertension, with a low-to-moderate daily dose and a short-term treatment period (83). Lastly, an observational analysis of Canadian and European healthcare databases found that celecoxib was not associated with an increased risk of MI compared to diclofenac, ibuprofen, or naproxen in the general population (69).

While waiting for more and stronger evidence, to the best of the author's knowledge, ibuprofen and naproxen are currently the safest NSAIDs when seen through 'cardiovascular lenses'.

## CONCLUSION

NSAIDs are one of the most commonly used medicine categories, intended to treat particularly pain and inflammation. While their benefits for patient health and quality of life are recognized and established, NSAIDs are also associated with various AEs, including, among else, GI AEs, hepatic AEs, hematologic AEs, renal AEs, and cardiovascular AEs. According to published literature, a number of factors influence the risk that NSAIDs pose for the cardiovascular system, including treatment dose and duration, patient history and features etc. Moreover, each specific NSAID is associated with different AEs and a different level of risk for the development of cardiovascular AEs. In conclusion, in order to preserve patient health and quality of life, all the aforementioned factors and each medicine's safety profile have to be considered, so that the optimal treatment strategy is chosen.

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CHAPTER 47

# CORTICOSTEROIDS

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## INTRODUCTION

Corticosteroids are drugs that are structurally and functionally similar to the hormone cortisol secreted by the adrenal glands. This group of drugs has strong anti-inflammatory, immunosuppressive and antiallergic properties. Therefore, corticosteroids are widely used in the treatment of many rheumatological, dermatological, pulmonary, hematological and neurological diseases.

The synthesis and clinical use of cortisol is one of the most important advances in medicine. In 1948, the use of cortisol in a patient with rheumatoid arthritis led to its recognition as a "miracle drug" in the pharmaceutical world. However, various side effects of steroid therapy soon began to be recognised.

## CLASSIFICATION OF CORTICOSTEROIDS

Corticosteroids are divided into three groups according to their duration and potency:

1. Short Acting Corticosteroids
   - Duration of action: 8-12 hours
   - Impact strength: Low-medium
   - Examples: Hydrocortisone (Cortisol), Cortisone acetate
2. Corticosteroids of Intermediate Action
   - Duration of action: 12-36 hours
   - Impact strength: Medium-high
   - Examples: Prednisolone, Methylprednisolone, Triamcinolone
3. Long Acting Corticosteroids
   - Duration of action: 36-72 hours
   - Power of influence: High
   - Examples: Dexamethasone, Betamethasone

## MECHANISMS OF ACTION

The cardiovascular effects of corticosteroids are mediated through genomic and non-genomic mechanisms.

Genomic Effects: Corticosteroids pass through the cell membrane and bind to glucocorticoid receptors in the cytoplasm. This steroid-receptor complex enters the cell nucleus, binds to DNA and stimulates or represses the transcription of certain genes. These genomic effects lead to anti-inflammatory, immunosuppressive and metabolic changes [1,2]. Genomic effects usually require hours or days to take place and these effects include

1. Suppression of the production of pro-inflammatory cytokines (e.g. IL-1, IL-6, TNF-α)

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CHAPTER **48**

# COLCHICINE AND CARDIOVASCULAR DISEASES

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## INTRODUCTION

The majority of epidemiological and clinical studies suggest a strong contribution of inflammation to the development of atherosclerosis and other cardiovascular (CV) diseases, and anti-inflammatory drugs have shown potential therapeutic benefit in CV contexts. In recent years, interest in colchicine has again increased and that its potential role should be reappraised in cardiovascular diseases (CVD). Colchicine has been widely prescribed for pericarditis and post-pericardiotomy syndrome. Results from recent studies suggest that patients with gout treated with colchicine have a reduced rate of cardiovascular events. Emerging cardiological uses include the atherosclerosis, atrial fibrillation (AF) and heart failure (HF).

Also, because of its widely available, at low cost and favorable and well-known side effects, colchicine is most probably cost-effective therapeutic targets the inflammatory pathway to prevent and/or treat CVD.

Lower dose colchicine has been approved as the first anti-inflammatory drug to reduce the risk of CV death, myocardial infarction (MI), coronary revascularization and stroke in patients with high risk for CVD or known coronary heart disease according to US Food and Drug Administration.

## PHARMACOLOGY AND MECHANISM OF ACTION

Colchicine is an anti-inflammatory and it exerts its effects on microtubule functions contrary to non-steroidal anti-inflammatory drugs and glucocorticosteroids, which affect the arachidonic acid pathway (1,2). While, low dose colchicine inhibits microtubule polymerization, higher doses promote microtubule depolarization. This effect at the cellular level significantly impacts different processes ranging from the regulation of ion channels to cell division and migration (3). Through these effects on the cytoskeleton, colchicine particularly affects actively dividing cells (4). In addition, colchicine has therapeutic effect on gout,familial Mediterranean fever (FMF) and pericarditis by inhibiting the expression of interleukins (IL) including IL-1β, IL-6 and IL-18 (5).

Colchicine is predominantly metabolized in the gastrointestinal tract and is a substrate of cytochrome P450 3A4 (CYP3A4) and also P-glycoprotein (P-gp). Colchicine could be taken up by the cells such as endothelium and leucocytes. The pharmacological effects of colchicine are related to intraleukocyte concentrations rather than plasma concentrations (6-8). Colchicine has been shown to inhibit the directed migration of neutrophils to an inflamed focus and decrease adhesion of neutrophils to inflamed endothe-

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### Acute Myocarditis

Myocarditis shares common etiological factors with pericarditis, and intersecting conditions could be facing frequently in clinical approach (81). A double-centre retrospective cohort study analysed a total of 175 succesive patients with myopericarditis assigned to treatment with colchicine plus standard therapy or standard therapy alone. Results showed the efficiency and safety of colchicine in treating pericarditis with concominant myocarditis. Colchicine treatment led to lower recurrence rates and longer event free survival (82).

### Peripheral Artery Disease

Inflammation is central to the initiation, progression, and destabilization of atherosclerosis. Peripheral artery disease (PAD) usually manifests with a larger burden of atherosclerosis in contrast to lone CAD. The decreased impact of colchicine on PAD in some studies compared to studies involving patients with CAD may be attributed to this situation. The capability of colchicine to reduce major adverse limb events and major adverse cardiovascular events in individuals with lower extremity PAD is still uncertain. Two randomized trials are currently being enrolled to measure the potential of colchicine in secondary prevention of atherosclerotic events in PAD, a serious vascular disorder that has not been studied adequately (83,84).

## CONCLUSIONS

Inflammation plays a significant role in the majority of cardiovascular diseases and colchicine use seems to be safe and effective in different cardiovascular diseases. Colchicine is a cornerstone treatment in pericardial diseases and it is beneficial in secondary prevention in coronary artery disease. While low-dose colchicine has shown significant benefits in stable CAD, its efficacy in acute coronary ischemia remains unproven. Colchicine may also attenuate the development of postoperative atrial fibrillation and reduce the recurrence of atrial fibrillation following pulmonary vein isolation. Further studies will clarify the efficacy of colchicine in various cardiovascular diseases.

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CHAPTER **49**

# CONVENTIONAL DISEASE-MODIFYING ANTI-RHEUMATIC DRUGS (DMARDS)

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## INTRODUCTION

Cardiovascular diseases (CVD) are among the leading causes of death in individuals with rheumatic disease (1) This heightened risk is connected to both genetic susceptibility and conventional risk factors, along with systemic inflammation (2). Side effects of antirheumatic drugs and decreased mobility and exercise are also among the speculated causes of cardiovascular mortality. For this reason, it is important to know the favorable effects of the drugs to be used in the treatment that may prevent the development of CVD or the adverse effects that may lead to increased CVD risk.

Disease-modifying anti-rheumatic drugs (DMARDs) affect the course of rheumatological diseases and are classified as conventional synthetic, targeted synthetic, and biological DMARDs. Conventional synthetic DMARDs commonly consist of methotrexate, leflunomide, sulfasalazine, and hydroxychloroquine (3). In this book section, conventional DMARDs and their cardiovascular effects will be discussed.

## METHOTREXATE

Methotrexate is commonly employed in the treatment of certain autoimmune inflammatory diseases, primarily among patients diagnosed with rheumatoid arthritis (RA). Methotrexate is a folic acid antagonist. By inhibiting dihydrofolate reductase, it decreases the synthesis of purine metabolites which are important in cell proliferation (4). It is started at a dose of 7.5-12.5 mg once a week. The dose can be increased by 2.5-5 mg per month up to 20 mg once a week until an adequate clinical response is obtained. It is metabolized in the liver.

Methotrexate and its metabolites are excreted from the kidney by both glomerular filtration and proximal tubular secretion (5). Plasma half-life is less than 10 hours but may increase in renal failure. Since its absorption with food is not significantly affected, it can be used with food or in fasting. Side effects such as oral ulcers (mucositis), nausea, hepatotoxicity, pneumonia, and bone marrow suppression may be observed. The addition of 1-4 mg of folic acid daily reduces the occurrence of side effects. Due to possible adverse effects on the fetus, appropriate contraception should be recommended to women in the reproductive age group with methotrexate treatment (6), and it is not used in breastfeeding women (7).

The cardiovascular effects of methotrexate have been the subject of many studies. Although methotrexate is used in many rheumatological diseases, its

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## CONCLUSION

Most patients with rheumatological diseases are at increased risk of CVD. Inflammation is the main factor contributing to this increased risk. Therefore, it is important to reduce inflammation with appropriate treatments. Conventional DMARDs are drugs that may have positive effects on the cardiovascular system both through their anti-inflammatory properties and through different pathophysiological pathways, but in some cases, negative effects may also occur. The short and long-term results of all these positive and negative effects should be investigated in controlled clinical studies.

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CHAPTER **50**

# BIOLOGIC DISEASE-MODIFYING ANTIRHEUMATIC DRUGS (DMARDS)

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## INTRODUCTION

The heart is often affected in rheumatic diseases due to the direct effect of the disease, accelerated atherosclerosis or deleteriuos effects of the pharmacological agents used for treatment. Biologic disease-modifying antirheumatic drugs (bDMARDs) are widely used for disease control in rheumatic diseases. Biologic DMARDs encompass a range of therapeutic agents, including tumour necrosis factor (TNF) inhibitors, interleukin-6 (IL-6) inhibitors, B-cell depletion therapies and B-cell activation inhibitors, co-stimulation blockers, IL-17 inhibitors, IL-12/23 inhibitors, and IL-1 inhibitors.

## TNF INHIBITORS AND CARDIOVASCULAR DISEASES

### Atherosclerotic Cardiovascular Diseases

There are five TNF inhibitors in use, including etanercept, infliximab, adalimumab, certolizumab and golimumab. Anti-TNF agents are used in the treatment of various rheumatic diseases, including rheumatoid arthritis (RA), spondyloarthritis (SpA), and psoriatic arthritis (PsA). In addition to conventional risk factors; drugs (eg steroids), chronic inflammation, and disease activation increase the risk of atherosclerosis in rheumatic diseases. Chronic inflammation may increase the risk of cardiovascular disease (CVD) by altering traditional risk factors (eg, lipid profile), leading to endothelial dysfunction and microvascular disease (1). Proinflammatory cytokines, including TNFα, not only plays an important role in pathogenetic mechanisms of RA, but also leads to progression of atherosclerosis (1). CVD has been identified to be related to increased mortality rate in RA (2). Additionally, the risk of ischemic stroke and myocardial infarction (MI) has been shown to increase in systemic lupus erythematosus (SLE) (3). Effective treatment of inflammation can decrease the risk of cardiovascular events (CVE). According to European League Against Rheumatism (EULAR) recommendations, CVD risk evaluation is advised at least every 5 years in patients with RA, ankylosing spondylitis (AS), and PsA, and disease activity control should be achieved optimally to decrease the risk of CVD (4). Anti-TNF treatments have been shown to reduce carotid-intima-media thickness, improve endothelial functions including flow-mediated vasodilation, and decrease CRP and IL-6 levels (5). The above-mentioned mechanisms suggest that anti-TNF therapies may reduce the risk of CVD. In a meta-analysis of observational cohorts of RA patients, anti-TNF therapy was associated with a reduced risk of CV events and myocardial infarction (MI) (6).

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ally, ustekinumab-induced fatal acute HF has been reported in a case (42).

### IL-1 Antagonists:

It would be more appropriate to discuss about the studies conducted in heart diseases rather than the cardiac side effects of IL-1 antagonists in this section. Anakinra is a recombinant human IL-1 receptor inhibitor. It blocks IL-1 alpha and IL-1 beta. Canakinumab is a mAb developed against IL-1 beta. Rilonacept is the receptor fusion protein of IL-1. Preclinical and clinical studies suggest that IL-1 has an pivotal role in the pathogenesis of atherosclerosis, acute MI and HF. IL-1 triggers the formation of the atherosclerotic plaque and promotes its progression (43). In the The Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS), the risk of non-fatal MI, non-fatal stroke, or cardiovascular death was decreased by 15% with canakinumab 150 mg compared to placebo in patients with prior MI and high CRP level (>2 mg/L). It was also reported that the need for coronary revascularization was reduced in canakinumab arm (43). There are conflicting results in studies with IL-1 inhibitors after acute coronary syndrome (42). Anakinra treatment was associated with lower CRP levels and improvement in peak oxygen consumption in patients with chronic systolic HF and high CRP (>2 mg/L) levels (44). A further study comparing the impact of anakinra versus placebo on cardiovascular outcomes in patients with acute decompensated heart failure reported that anakinra resulted in improvements in peak oxygen consumption and NTproBNP levels (45).

Data from randomized and observational studies support the use of an IL-1 inhibitor (rilonacept or anakinra) in recurrent pericarditis (46, 47). In a double-blind, randomized study of rilonacept involving 86 patients with symptomatic recurrent pericarditis, after 12 weeks of rilonacept treatment, patients were randomized to the rilonacept and placebo arms. Relapse occurred in 23 (74%) patients in the placebo arm compared to two patients (7%) both of whom temporarily stopped treatment, in the rilonacept arm (46). In 2021, the FDA approved the use of rilonacept for the treatment of recurrent pericarditis aged 12 years and older.

There is substantial evidence to support the role of IL-1 in the pathogenesis of heart diseases. As the evidence for the use of IL-1 blockers in treatment continues to accumulate, it will become increasingly feasible to utilize them as a treatment option on a broader scale.

## CONCLUSION

Biologic DMARDs has become the cornerstone of treatment in many rheumatic diseases and are widely used. Disease activity control in rheumatic diseases is important in terms of reducing the risk of CVD. Biologic DMARDs are efficacious in disease control; however, they may precipitate cardiovascular complications. Clinicians should be aware of the cardiovascular side effects of these drugs and implement preventive measures in patients with increased cardiovascular risk.

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CHAPTER **51**

# INTRAVENOUS IMMUNOGLOBULIN (IVIG)

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## INTRODUCTION

Intravenous immunoglobulin (IVIG) is a purified concentrate of immunoglobulins (Ig) derived from the pooled plasma of more than 1000 healthy donors (1). It primarily consists of more than 90% immunoglobulin G (IgG), although the exact composition may vary depending on the manufacturer and the purification process used (1). In addition to IgG, IVIG preparations contain small amounts of immunoglobulin A (IgA) and traces of other immunoglobulin isotypes, as well as various cytokines, soluble receptors, and other plasma-derived proteins. These additional components, while present in minor quantities, may contribute to the immunomodulatory effects of IVIG therapy.

Although the mechanism of action of IVIG is not clearly known, it is thought to act through multiple mechanisms given its multiple anti-inflammatory effects (1). Mechanisms of action include: 1. blockade of Fc receptors in macrophages and effector cells, 2. antibody-dependent cellular cytotoxicity, 3. induction of inhibitory FcgRIIB receptors, 4. reduction of complement-mediated damage, 5. reduction of immune complex-mediated inflammation, 6. induction of anti-inflammatory cytokines, 7. inhibition of endothelial cell activation, 8. control of bone marrow B-cell reservoirs, 9. selective enhancement and reduction of antibody production, 10. neutralisation of autoantibodies by anti-idiotype antibodies, 11. regulation of T-helper cell-derived cytokines, 12. neutralisation of T-cell superantigens, 13. regulation of dendritic cell functions involved in antigen presentation (2).

IVIG therapy is frequently used off-label in rheumatology and cardiology. IVIG therapy has been approved by the FDA (U.S. Food and Drug Administration) for several conditions, including primary immunodeficiency, hypogammaglobulinemia, chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy, and thrombocytopenia in patients with idiopathic thrombocytopenic purpura (3, 4).

This book chapter provides a comprehensive overview of IVIG, beginning with its mechanisms of action and general clinical applications.

## THE USE OF IVIG IN CARDIOVASCULAR DISEASE

### Kawasaki disease (KD)

KD is a common vasculitis in childhood. KD can contribute significantly to morbidity and death because it can lead to coronary artery aneurysms, coronary occlusions, and cardiac ischemia (5).

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CHAPTER **52**

# CARDIOVASCULAR ASSESSMENT BEFORE PYSIOTHERAPY

*Yasemin Özkan* [1]

## INTRODUCTION

One of the most effective treatments that a physical therapist can prescribe is an effective exercise program. In the acute care setting, this is often called mobilization, while in the outpatient setting, this is called exercise prescription and education. The extremely low exercise tolerance and complexity of health conditions in rheumatic diseases may preclude the use of training regimens designed for healthy individuals or cardiovascular patients; however, many of the basic training principles apply (1).

Cardiac involvement, which is the most important extra-articular involvement in rheumatic diseases, can negatively affect the daily life activities of these patients. Increasing mobility and exercise in these patients can have many positive effects on the body. Because these patients may have concomitant involvement of other systems, the therapist should be more careful when prescribing exercise to such patients than in the outpatient clinic. Regardless of the severity and complexity of the patient's condition, the effects of prolonged bed rest and immobility are more detrimental than early mobilization or short-term bed rest (2).

## PHYSIOLOGICAL CHANGES AND CONSEQUENCES OF DECREASED ACTIVITY

### Cardiovascular system

- Decrease in total blood and plasma volume
- Decrease in red blood cell mass and hemoglobin concentration
- Increase in basal heart rate
- Decrease in maximum oxygen uptake and fitness level
- Decrease in vascular reflexes and response to constriction of blood vessels in the lower extremities, leading to postural hypotension, fainting, dizziness
- Increased risk of deep vein thrombosis and pulmonary embolism

### Respiratory system

- Decrease in arterial oxygen levels
- Decrease in lung volumes
- Changes in blood flow and ventilation distribution in the lungs
- Accumulation of secretions in dependent parts of the lungs after closure of small airways, increasing the potential for infection
- Increased aspiration of food and stomach contents

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individuals where heart rate is an unreliable indicator, such as those on rate-limiting medications.

Oxygen saturation is recommended to be monitored during exercise to assess cardiopulmonary function and identify exercise-induced desaturation. This is especially recommended for individuals with severe pulmonary conditions or cardiac diseases associated with dyspnea.

In addition to the abovementioned baseline screening, advanced evaluation should be performed in patients with cardiovascular symptoms. Echocardiographic assessment should be considered in patients with suspicion of heart failure or valvular heart disease. Coronary imaging may be considered in patients with angina or suspected significant coronary artery disease prior to initiation of physical therapy. The type and intensity of exercise should be based on the patient's cardiovascular status, and preventive measures should be taken to reduce exercise-related cardiovascular complications (9).

## CONCLUSION

Cardiovascular problems are the most important sign of extra-articular involvement in rheumatic disease. This includes significant mortality and morbidity on the secure containment system. With individual, applicable and compatible programs, there will be improvements in the mortality and morbidity rates associated with this complex. Contribution of this patient to maintaining independence of daily living activities and improving quality of life.

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CHAPTER 53

# CARDIOVASCULAR RISK ASSESSMENT IN RHEUMATIC DISEASES

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## INTRODUCTION

Various cardiac involvement can be seen in rheumatologic diseases including cardiovascular disease (CVD), arrhythmias, heart failure, valvular disease, pericarditis-pericardial effusion, and myocardial involvement (1). Cardiovascular risk (CVR) is increased in inflammatory rheumatic disease (2). Cardiovascular (CV) involvement in rheumatic diseases has been related to risk factors of conventional CVD leading to various CV events such as underlying autoimmune-inflammatory mechanisms, ischemic stroke, coronary vascular disease, myocardial pathologies, and arrhythmia (3,4). The high CVR in rheumatic diseases cannot be explained by differences in the prevalence of conventional CVR parameters (5-9). Chronic inflammation has a basic role in the pathogenesis of CVD (10). When the relation between inflammation, cardiometabolic factors, and immunity was explored (11), the effectiveness of drugs targeting inflammatory pathways in the general population (12,13,14) and its correlation with C-reactive protein (CRP) levels were shown (15,16). Immunomodulators and steroids are the main treatment regimens in rheumatic patients. Although better control of inflammation reduces CVR (13,14) it is unknown whether some of the adverse effects of these drugs may override any anti-inflammatory effects and thus increase CVD.

There are not any cardiovascular risk assessment tools specific for rheumatic diseases and tools used in general population (SCORE2 e.g.) are used to estimate CVR in cases with rheumatic diseases. Cardiovascular risk assessment via using SCORE2 is discussed in "Dyslipidemia and Cardiovascular Risk" chapter. In this chapter, literature regarding CVR in rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS), systemic sclerosis (SSc), Sjogren's syndrome (SS), ankylosing spondylitis, psoriatic arthritis (PsA) and gout will be summarized.

## RHEUMATOID ARTHRITIS (RA)

RA is characterized by hyperplasia of the synovium in the joints causing symmetrical polyarthritis. Also can involve the lungs, skin, eyes, and heart. The prevalence of RA varies between 0.5-1.0% (17,18). CVD risk is increased by RA in studies. Meta-analyses have reported a 48% higher risk of CVD, a 68% higher risk of coronary artery disease (CAD), and a 41% higher risk of stroke when compared with all populations (19). In the Trans-Atlantic Cardiovascular Consortium for RA, about 49% of CVD events in RA were caused by conventional CVD risk factors (mainly smoking and hypertension) and 30% were caused by RA features (high DAS28, rheumatoid factor/anti-citrullinated

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myocardial infarction (14%) and heart failure (11%) (133). Elevated serum urate levels have been related to increased incidence and mortality from coronary heart disease (134). This may be due in part to the association between hyperuricemia and conventional risk factors (135).

Hyperuricemia is firmly related to endothelial dysfunction an initial marker of atherosclerosis (136,137). Increased serum urate concentrations have been associated with greater smooth muscle cell proliferation, LDL oxidation, and platelet activation suggesting a reason for hyperuricemia in atherosclerotic disease with a potential role in the pathogenesis of hypertension (138). Studies on the CV impact of uric acid-lowering therapy (ULT) have shown disagreement results; a useful effect on surrogate endpoints has been suggested although the improvement in clinical outcomes is unknown.

Studies have shown that CV morbidity and mortality are increased in gout, vasculitis, SSc, myositis, mixed connective tissue disease (MCTD), SS, SSc, SLE, and APS, which led to recommendations by EULAR in 2022 (83). A comprehensive evaluation of conventional CVD risk factors and the use of CV prediction tools for the general population are suggested. As the Framingham risk score for antineutrophilic cytoplasmic antibody (ANCA)-related vasculitis may underestimate CVR information from the European Vasculitis Society (EUVAS) model may complement the modifiable Framingham risk factors should be considered, blood pressure, lipid management and treatment with platelet inhibitors should follow suggestions for the general population. Diuretics shouldn't be used in gout patients and beta-blockers in SSc patients. For gout patients a serum uric acid level below 0.36 mmol/L (6 mg/dL) is suggested to reduce the risk of CV cases and CV mortality potentially. From a CV perspective, there is no specific predilection for urate-lowering therapy in patients with gout. Remission induction and maintenance of remission in patients with ANCA-associated vasculitis will also reduce CVR. An appropriate glucocorticoid regimen that reduces the relapse rate in giant cell arteritis patients may also reduce CVR despite CV side effects.

## CONCLUSION

Awareness of the risk of CVD in patients with chronic rheumatism is still not exactly established. The main principles of CVR management are the pharmacologic and nonpharmacologic treatment of risk factors, good control of inflammation and thus, disease activity, smoking cessation, a balanced diet, and regular physical activity. All patients should be regularly screened for conventional risk factors and any increased risk should be treated accordingly. The goal is to recognize and treat diseases early. Although some DMARDs reduce CVR by reducing inflammation, attention should also be paid to possible cardioprotective or harmful properties of the drugs.

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CHAPTER **54**

# CARDIOVASCULAR EFFECTS OF OSTEOPOROSIS TREATMENT

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## INTRODUCTION

Osteoporosis is a progressive systemic metabolic disease characterized by microarchitectural deterioration of bone structure, followed by a consequent increase in susceptibility to fracture. Clinical diagnosis is based on the measurement of bone mineral density (BMD), as microarchitectural changes can not be measured. The BMD-based definition of osteoporosis is a T score of ≤ -2.5 with or without a history of fracture and the decision to initiate treatment is made according to the associated risk factors (1). Considering the age group, osteoporosis often presents concomitantly with other comorbidities such as cardiovascular diseases (CVD). The association between osteoporosis and CVD has been suggested by animal and human studies that elaborate a common biological pathway (2) (3).

All current treatment modalities including vitamin D replacement, bisphosphonates, denosumab, romosozumab, and menopausal hormonal therapies have cardiovascular safety studies (4). Interaction between treatment agents used in osteoporosis and cardiovascular diseases is summarized in this chapter.

## VITAMIN D

Vitamin D (cholecalciferol ($D_3$) supplementation plays a pivotal role in the treatment of osteoporosis. Current guidelines suggest a minimum of 800 international units (IU) daily for people in high-risk groups for vitamin D deficiency such as those with fragility fractures, as well as for symptomatic vitamin D deficiency (5). Vitamin D receptors are found widespread around human tissues and, therefore, have effects on vasculature, the renin-angiotensin system, and cardiac muscle. Low levels of vitamin D could contribute to loss of bone density via increased parathormon levels as well.

Although most of the intervention studies reported a positive effect of supplementation with calcium and vitamin D on bone in patients with osteoporosis, this therapeutic approach has been a matter of debate regarding potential side effects on the cardiovascular (CV) system.Studies regarding the relationship between vitamin D supplementation and cardiometabolic outcomes had different conclusions. The suggested benefits of supplementation have failed to be confirmed by prospective randomized controlled studies (RCTs) (6) (7). The largest RCT stated that vitamin D supplementation did not reduce major adverse cardiovascular events (MACE) in older adults (6). Studies with smaller sample sizes have speculated that supplementation may lead to improvements in risk factors such as insulin resistance, but have not produced consistent results. Another RCT evaluated

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efit assessment should be carried out in people with a high cardiovascular risk profile. Further studies with larger populations are needed to assess and decide the cardiovascular risk of treatment with romosozumab.

## CONCLUSION

Vitamin D supplementation appears to be cardiovascular safe. The association of bisphosphonates with arrhythmias and atrial fibrillation is inconclusive, and they should not be prominently prescribed for their additional CV benefit in relation to atherosclerotic CVD. HRT may cause thromboembolic events and should be used in selected cases. Teriparatide and denosumab have no significant data on adverse cardiac events. Romosozumab needs more post-marketing data to address cardiovascular safety concerns. Treatment of osteoporosis should be individualized based on the patient's comorbidities and CV risk profile.

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CHAPTER **55**

# PREOPERATIVE ASSESSMENT BEFORE CARDIOVASCULAR SURGERY

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## INTRODUCTION

Rheumatic diseases are multisystemic, complicated,and occasionally challenging conditions to manage. Involvement of the cardiovascular system is a frequent extra-articular manifestation of rheumatic disorders (1). Individuals diagnosed with rheumatic illness are at a heightened risk of developing severe and premature cardiovascular disease as a result of chronic systemic inflammation, as well as experiencing cardiac involvement unique to their condition (2). Therefore, the necessity for cardiovascular surgery might result from both cardiovascular involvement and accelerated atherosclerosis. If surgery is required, a detailed preoperative examination and multidisciplinary approach are necessary due to the long-term use of immunosuppressants and the multi-organ involvement. This section will discuss the preoperative assessment for cardiovascular surgery in rheumatic diseases.

## PREOPERATIVE ASSESSMENT

Purposes of preoperative assessment: evaluating comorbidities that may impact the perioperative process, optimizing the treatment of all current medical problems, determining the severity and type of anesthesia and surgery-related risks, and predicting the risk of postoperative complications (3).

Perioperative assessment should involve an extensive medical history and physical examination, laboratory analyses, evaluation of surgical risk (patient-specific risk and surgery-related risks), and decision of the anesthetic technique (4).

The important points are as follows: (5)

1. Identifying the disease activity
2. Management of the medications
3. Cervical spine evaluation
4. Determination of cardiovascular risk
5. Deep vein thrombosis prevention
6. Prophylaxis for bacterial infection

## MANAGEMENT OF THE MEDICATIONS

**Anti-rheumatic drugs:** The main challenge in patients receiving anti-rheumatic/immunosuppressive therapy scheduled for cardiovascular surgery is to achieve the optimal balance between maintaining rheumatic disease control while minimizing the risk of postoperative wound infection risk and preventing wound healing impairment (4).

Currently, there is no specific guideline for preoperative assessment for cardiovascular surgery in rheumatic diseases. In 2022, the American College of Rheumatology (ACR) published a guideline for the perioperative management of hip or knee arthroplasty (6). This guideline includes perioperative

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## ANTIPHOSPHOLIPID SYNDROME

Antiphospholipid syndrome is a condition caused by antiphospholipid antibodies and linked to vascular thrombosis, pregnancy loss, and mortality (14). It may be primary without underlying connective tissue diseases, or it may be secondary and frequently accompanied by connective tissue diseases such as systemic lupus erythematosus (SLE). Lupus anticoagulant and anticardiolipin antibodies are linked to an increased thromboembolic risk (15). Due to hypercoagulability and the need for temporary cessation of anticoagulant agents used during surgery, the risk of postoperative thrombosis is increased. These agents should be resumed as soon as possible postoperatively (4).

Anticoagulant drugs should be resumed 4-5 days before surgery, and bridge therapy with therapeutic dosages of low molecular weight heparin (1 mg/kg every 12 hours) should be maintained until the night before surgery (16).

Intermittent venous compression may be used both before and after surgery (4).

## POSTOPERATIVE INFECTIONS

Efforts to detect and prevent any infectious process before and after surgery are extremely important. Especially in patients under chronic immunosuppressive therapy, dental, skin, and urinary tract infections must be excluded with a careful physical examination and appropriate laboratory evaluation and cultures. (4).

## CONCLUSION

Patients with chronic rheumatic disease should be regarded as high-risk surgical individuals. The perioperative process can becomplicated by specific problems of rheumatic disease. Careful preoperative evaluation and postoperative treatment with the participation of the surgery team and rheumatologists are essential for optimal surgical outcomes.

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