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Chapter

Atherosclerosis in Rheumatology: Old and New Insights

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Abstract

Cardiovascular diseases are the leading cause of morbidity and mortality in general population worldwide. There is an increasing significance of cardiovascular risk in the field of rheumatology, and accordingly, the evidence on the relation between immune system disorders and atherosclerosis has been substantially growing especially in last decades. Since novel immune and metabolic factors are considered to participate in pathogenesis of atherosclerosis and increased cardiovascular risk in rheumatic patients, they are getting to the forefront of the research. Since novel therapeutic approaches have improved survival of rheumatic patients, and decreased morbidity caused by rheumatic disease activity and damage, the significance of other comorbidities leading to premature mortality has arisen. Nevertheless, appropriate recommendations for the management of cardiovascular risk are still lacking. Recently, European League Against Rheumatism (EULAR) recommendations for management of the cardiovascular risk and comorbidities in patients with inflammatory arthropathies have been published. However, the cardiovascular management of these patients is still suboptimal. In addition, the situation in other orphan diseases such as idiopathic inflammatory myopathies, systemic sclerosis and others is even more uncertain and strongly requires further research. This chapter provides an overview of epidemiology, pathogenesis, clinical manifestations, screening and management of atherosclerosis in patients with rheumatic diseases.

Keywords: atherosclerosis, rheumatic diseases, metabolic risk factors, management, therapy

1. Introduction

Cardiovascular diseases (CVDs) are estimated to be the leading cause of mortality and morbidity worldwide and are responsible for one-third of world's population mortality [1]. Atherosclerosis (ATS), as the main cause of CVD, starts to develop early in the life and presents later with clinical manifestations depending on other circumstances. ATS is a multifactorial disease, in which the immune system and impairment of vascular system play a significant role. Inflammation, which can be triggered by infectious agents or by autoimmune reaction, worsens and promotes atherogenesis by several mechanisms [2]. In addition to the immune system, other factors significantly participate in atherogenesis by facilitating the vascular damage, initiating the formation, progression and the rupture of atherosclerotic plaques leading to consequent clinical manifestation of ATS. So-called traditional risk factors include dysregulation of lipid and glucose

metabolism, arterial hypertension, and degeneration of vascular tissue caused by aging, smoking and hormonal factors [3].

It is well known that autoimmune diseases are accompanied by increased CV morbidity and mortality, caused by exacerbation of atherogenesis [2]. Traditional risk factors of ATS in general population such as dyslipidemia, glucose intolerance, arterial hypertension, etc. can explain only about 75% of CV manifestations in rheumatic patients [4]. In these patients, non-traditional risk factors associated with the systemic inflammatory disease apply [5].

Despite the significant improvement of the therapy of rheumatic diseases, the incidence of CVD in rheumatic patients remains increased compared to that in general population [6]. Both the CV risk and CVD manifestations differ among rheumatic diseases according to the characteristic pathogenetic mechanism, inflammation activity and other specific features of the rheumatic diseases [7]. CV risk in the more prevalent rheumatic diseases such as rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE) is relatively best described. On the other hand, the situation is less clear in orphan connective tissue diseases such as systemic sclerosis (SSc), idiopathic inflammatory myopathies (IIM), primary Sjögren's syndrome (pSS) and others.

The aim of this review chapter is to provide an overview and sum up the current knowledge on CV risk factors and the treatment options of ATS-related comorbidities in rheumatic diseases.

2. Cardiovascular risks in rheumatic diseases

Traditional CV risk factors play two roles in rheumatic patients: the first one as a trigger, the second as a consequence of the rheumatic disease activity [3]. Non-traditional risk factors are given by genetic and epigenetic factors, concurrent autoimmune inflammatory disorder and the specific features of each particular rheumatic disease (age of onset, duration, activity and the type of the disease) and other comorbidities, among others depression [8–10].

2.1 Metabolic syndrome and its association with immune disorders

Metabolic syndrome (MetS) is defined as a cluster of comorbidities and risk factors leading to CVDs and increasing the CV mortality and morbidity. MetS includes obesity and visceral adiposity, diabetes and insulin resistance (IR), arterial hypertension (AH) and dyslipidemia [11]. The matter of mutual interactions and cross-talk of immune and metabolic system has become the object of many studies in recent years. Immune-metabolic interactions are regulated by genetic factors, nutritional status and by intestinal microbiome. The imbalance of the immune and metabolic interactions contributes to the occurrence and manifestation of rheumatic diseases [12].

The prevalence of MetS in general population is estimated to be 24–44% depending on the exact definition of the MetS and the studied population [11, 13], and increases in rheumatic patients and gout to as much as 36–42%, as was reported in studies comparing rheumatic patients to the healthy control population [13].

Different immune mechanisms have been reported to be implemented in the pathogenesis of MetS, including pro-inflammatory cytokines, namely interleukin (IL)-1 and IL-12 family. These cytokines are included in the regulation of immune response and atherogenic damage, and in the differentiation of T helper cells (Th), which participate in the pathogenesis of both autoimmune disorders and CVDs [14, 15]. Cytokines of IL-23/IL-17 signaling pathway are increased in rheumatic diseases, and significantly participate in atherogenesis [16]. MetS is associated with increased oxidative stress,

which, among others, leads to the formation of oxidized phospholipids (oxPL) and contributes to pathogenesis of autoimmune disorders [13].

IR is not only closely related to MetS, but is also considered to act as a key pathogenic factor in MetS [13]. The definition describes IR as a decreased sensitivity and responsiveness of target organs to the action of insulin resulting in hyperinsulinemia [17]. As consequence, this metabolic disorder leads to glucotoxicity, lipotoxicity and inflammation, all of which participate in endothelial damage and dysfunction [18]. The visceral fat tissue is considered to be the major locus of these unfavorable changes. Of note, CVDs, MetS and autoimmune disorders share common pathogenic mechanisms and mediators of inflammation and activity [13].

In recent years, study of microbiome has come to the forefront of interest. An imbalance of intestinal microbiota (dysbiosis) is characterized by a decrease of the number of beneficial intestinal bacteria and the overgrowth of potentially pathogenic bacteria. This phenomenon accompanies metabolic disorders and contributes to the emergence of MetS, obesity and type 2 diabetes mellitus (T2DM) [19]. Impaired balance of the intestinal flora may also contribute to the development of autoimmune disorders. Several studies have demonstrated onset of inflammation induced by alterations in the gut microbiome. This could explain the relationship between the microbiome and systemic inflammatory response [20].

2.2 Obesity as an active contributor to inflammation

The definition of obesity is mostly based on the body mass index (BMI—values higher than 30 kg/m^2). Obesity, as well as MetS, is a global health problem especially in developed countries. The prevalence has been constantly growing over the years and to date, it is estimated to be almost 40% in the general population [21, 22]. Nevertheless, the association of obesity and CVDs in the general population is not clear [23]. Some evidence even suggests better prognosis for people with higher value of BMI [24]. However, there is a well-known correlation of obesity and increased risk of T2DM and coronary arterial disease (CAD), as well as a negative impact of obesity on other comorbidities including rheumatic diseases [23]. The immunomodulatory potential of adipose tissue and its ability to create an inflammatory environment of moderate activity could explain the effect of obesity as a risk factor for the development of some autoimmune diseases [22, 25].

Adipose tissue not only consists of adipocytes and connective tissue cells, but also contains immune cells as well (T cells, eosinophils, B regulatory cells and macrophages) [26–28]. In individuals with normal BMI, the immune cells interact with adipocytes and maintain a non-inflammatory environment by production of anti-inflammatory cytokines (IL-10, IL-4, IL-13) [27]. On the contrary, predominance of pro-inflammatory T helper (Th) type 1 and 17 cells and pro-inflammatory type of macrophages has been found in increased adipose tissue mass of obese individuals [27, 29, 30]. These changes result in the production of pro-inflammatory molecules such as tumor necrosis factor (TNF) and IL-6, which are one of the crucial cytokines involved in the pathogenesis of several rheumatic diseases. Moreover, obesity leads to an altered expression of adipokines, multifunctional molecules produced by white adipose tissue cells and involved in the regulation of inflammatory and autoimmune processes [31, 32]. The MetS and secretion of pro-inflammatory adipokines can be associated with CVDs and autoimmune disorders [13].

Thus, obesity is not only a passive comorbidity, but can actively participate in the inflammatory process. According to the current evidence, obesity can negatively

affect the course of most rheumatic diseases, functional disability, quality of life and the overall prognosis [21, 22].

2.3 Dyslipidemia in autoimmune disorders

Dyslipidemia is one of the most common forms of metabolic disease in the general population and also a significant risk factor for atherogenic CVD. In the general population, dyslipidemia is characterized by an increased level of total cholesterol (TC), low-density lipoproteins (LDLs), triglycerides (TGs) and a decreased level of high-density lipoproteins (HDLs) [33]. Under normal circumstances, HDL (in normal serum levels) exerts an anti-atherogenic effect: it removes cholesterol particles from cells (especially macrophages in the artery wall) and from circulation; inhibits the migration of macrophages and the binding of monocytes to the endothelium, oxidation of LDL; promotes endothelial repair and improves endothelial function, and also exerts anti-inflammatory and anti-apoptotic effects [34–36]. In systemic inflammation, HDL is converted into a dysfunctional form due to loss of anti-inflammatory and anti-oxidative proteins. The modification of apolipoprotein A1 (apo-A1) results in the inability of HDL to uptake LDL from macrophages and in the activation of pro-inflammatory pathways leading to increased risk of coronary artery involvement [35, 37].

Moreover, quantitative changes of lipidogram related to disease activity are often seen in rheumatic diseases. In RA patients, the levels of TC and LDL are lower than in general population. This so-called lipid paradox, best described in RA, is associated with an increased CV risk [37]. Decrease in levels of TC and LDL has been found to precede clinical manifestation of RA. Later, TC and LDL levels tend to increase after the initiation of immunosuppressive therapy and on the contrary, decline during the relapse of RA [38]. Therefore, the low levels of TC and LDL can be misinterpreted as a low CV risk factor when evaluated according to the scoring tools (e.g., Framingham risk score, Reynolds risk score, Systemic Coronary Risk Evaluation—SCORE) [39–41].

A small study in early RA patients reported non-significant, beneficial effect of methotrexate similar to that of tumor necrosis factor inhibitors (anti-TNF) on lipidogram [42]. On the other hand, higher levels of TC, LDL and TG were described in patients with ankylosing spondylitis (AS) treated by anti-TNF compared to AS patients on nonsteroidal anti-inflammatory drug (NSAID) therapy. Nevertheless, results reported in a cross-sectional study do not allow for a generalized assessment of the influence of long-term anti-TNF therapy on lipidogram in AS [43].

Dyslipidemia is found in almost half of SLE patients, characterized by elevated levels of very-low density lipoprotein (VLDL) and TG. Increased levels of TC and TG are associated with two times increased risk of CVD [44]. In SSc, dyslipidemia is characterized by increased levels of lipoprotein A (LpA) and LDL and decreased levels of HDL and TC [45].

2.4 Role of immune system and autoantibodies in atherogenesis

The presence of immune cells in atherosclerotic plaques proves the participation of immune system in atherogenesis [46, 47]. These infiltrating immune cells are responsible for the promotion and exacerbation of ATS [48]. All the components of immune system are included in atherogenesis, while TNF and IL-1β are the most significant pro-inflammatory cytokines and mediators [1].

Damage of endothelium is the first step in atherogenesis. Particles circulating in the blood penetrate the damaged endothelial barrier into subendothelial layer via the interaction with adhesion molecules on the surface of endothelium. These

reactions lead to activation of endothelium and attraction of immune cells [1]. Penetrating particles consist mainly of LDL, which are one of the targets of oxidation and form oxLDL (oxidized LDL). oxLDLs are taken up by macrophages, which subsequently transform into the foam cells. Specific autoantibodies against oxLDL (anti-oxLDL) were detected in the sera of individuals from the general population as well as in rheumatic patients [49]. Furthermore, in rheumatic patients, the levels of anti-oxLDL are increased compared to those in the general population [49, 50]. The presence of these antibodies can predict the peripheral vascular involvement and even the severity of ATS [51]. On the other hand, increased levels of anti-oxLDL antibodies in patients with pSS were paradoxically associated with decreased occurrence of plaques (unlike in RA or SLE), which suggests a possible protective role of anti-oxLDL antibodies in pSS [52].

Many autoantibodies have been described to have a relation to higher risk of ATS and its clinical manifestations [2]. These include the antibodies against heat shock proteins (HSPs), which are expressed on the surface of endothelial cells exposed to stress, and to β-2-glycoprotein I (β2GPI), which are abundantly expressed within the subendothelial layer and intima-media borders of plaques [46, 53]. Furthermore, antinuclear antibodies (ANAs) are more frequently detected in patients with symptomatic angina pectoris and the three-vessel disease compared to individuals without coronary artery involvement [54]. Moreover, ANA positivity is associated with an increased risk of myocardial infarction (MI) in non-rheumatic individuals [55]. Specific anti-endothelial cell antibodies (AECAs) are associated with subclinical or manifested ATS in non-rheumatic population, as well [56].

2.5 Immunosuppressive therapy and its effect on CV risk

Immunosuppressive therapy of rheumatic diseases has a potential effect on CV morbidity and mortality in two ways: on the one hand, it suppresses the inflammatory activity and thus decreases the CV risk; on the other hand, the adverse effect of some drugs can worsen the CV risk [9, 57]. NSAIDs and coxibs (selective blockers of cyclooxygenase-2) mostly used in inflammatory arthropathies exert pro-thrombotic effect and have a negative impact on the CV risk. Due to this fact, benefit-risk ratio should be evaluated individually in every case. Naproxen is considered as the relatively safest drug from this group [58].

Corticosteroids (CSs) suppress the inflammatory activity, hence dampen the CV risk [59, 60]. On the other hand, CSs cause or worsen the traditional CV risk factors [61]. Meta-analysis evaluating CS therapy in RA reported that a long-term therapy with prednisone or prednisone-equivalents in high doses (above 7.5 mg per day) is associated with an increased risk of CV mortality [62]. The effect of lower doses (7.5–10 mg a day) is uncertain [63]. Duration and the cumulative dose of CS are considered as CV risk factors in SLE. Nevertheless, current evidence regarding the CS therapy in SLE is not conclusive [44]. European League Against Rheumatism (EULAR) recommends, especially in inflammatory arthropathies, to keep the glucocorticoid dosage to a minimum and to taper glucocorticoids in case of remission or low disease activity and to regularly check the reasons to continue glucocorticoid therapy [59].

The group of disease-modifying anti-rheumatic drugs (DMARDs) is a heterogeneous entity of medicaments with immunosuppressive effects of various specificity: less specific conventional synthetic DMARDs (csDMARD), or more specific biologic (bDMARDs), biosimilar (bsDMARDs) or targeted synthetic molecules (tsDMARDs). The side effects differ within the whole group. csDMARDs have a potential to reduce atherogenesis and progression of ATS [64]. Thus, the early initiation of therapy with scDMARDs can prevent development of CVDs [65].

Antimalarial drugs have been reported to act favorably on lipid and glucose metabolism, and in SLE patients, they have been described to reduce hypercholesterolemia, ATS and the risk of thrombosis [44, 66, 67]. In addition, hydroxychloroquine (HCQ) influences the production of cytokines, activation of T cells and monocytes via interaction with Toll-like receptor (TLR) signaling pathway, and attenuates the oxidative stress and endothelial dysfunction [68].

The effects of methotrexate (MTX) on the CV risk have been best studied in RA, in which the potential to reduce the risk of heart failure by half was demonstrated [69]. Moreover, MTX can decrease the mortality of RA patients caused by CVDs by 30% [70]. The data suggest that MTX should be considered cardioprotective in rheumatic diseases, although the exact mechanism of this effect is not known yet [71]. A possible link with anti-inflammatory effect has been proposed [72]. On the other hand, according to the results of a recent randomized controlled trial in patients with carotid artery disease or history of MI and concurrent T2DM or MetS, no protective effect of MTX in low doses (15–20 mg weekly) on future risk of CVD was described [73]. Data in other DMARDs are insufficient and, therefore, the effect on CV risk is not clear.

bDMARDs are targeting selectively specific pro-inflammatory molecules, which significantly participate in both pathogenesis of inflammatory diseases and atherogenesis (e.g., TNF, IL-1r, IL-6 and others) [74]. In this group, TNF inhibitors (anti-TNFs) are the best-studied drugs regarding the possible effect on the CV risk. On the one hand, they exert anti-inflammatory and anti-atherogenic effect; on the other hand, they have been demonstrated to worsen the cardiac insufficiency in a couple of first published studies [3, 8]. Their benefit was proven in several randomized controlled trials (RCTs) with more or less significantly beneficial effect when compared to MTX [72, 75–77]. Anti-TNFa influences particularly the level of HDL and restores its anti-atherogenic potential [78]. The results of RCTs in RA, PsA and psoriasis show a beneficial effect of anti-TNF therapy on glucose metabolism and MetS [79]. Anti-TNFs also reduce the risk of T2DM manifestation and prevent endothelial damage due to specific inhibition of TNF [74, 80]. Overall, current data support the beneficial effect of anti-TNF therapy on CV risk and CVD incidence that is probably related to the attenuation of inflammation and thus also of atherogenesis rather than to the effect on lipidogram (which can change as a consequence of changes in disease activity as well). Published studies have reported the potential of anti-TNF to reduce intima-media thickness and the number of unstable plaques [81]. Nevertheless, anti-TNF therapy is not recommended in patients with congestive heart failure [82]. Not only no positive effect, but even a negative effect of anti-TNF on chronic heart failure has been described. Experts therefore suggest performing a baseline echocardiography examination in patients at risk before the commencement of anti-TNF therapy [81].

Higher IL-6 levels are associated with an increased CV risk, therefore therapeutic blockade of tocilizumab (inhibitor of IL-6 receptor) has a protective potential [83]. Recently published RCT with tocilizumab and etanercept (anti-TNF) reported very similar effect of both drugs on CV risk [84]. Inhibition of the IL-6 receptor by tocilizumab is assumed to influence lipid metabolism in a favorable manner due to blockade of the mobilization of fatty acids to peripheral tissues mediated by IL-6 [84]. On the contrary, anti-IL-6r therapy is known to cause a significant increase in the levels of HDL, TC, LDL and TG [85].

Rituximab (RTX, anti-CD20) is supposed to have a beneficial effect on CV risk due to inhibition of B cells and release of (auto)antibodies, which participate in the vasoconstriction, activation of thrombocytes and promote rupture of atherosclerotic plaques [74]. In SLE patients, the RTX therapy was associated with improvement of lipidogram [86]. The overall effect of RTX on CV risk is not clear, due to limited data

and lack of SLE patients treated by RTX [44]. To date, studies with RTX have not shown any long-term adverse cardiovascular effects or cardiotoxicity [74, 87].

The recent study CANTOS (Canacinumab Antiinflammatory Thrombosis Outcome Study) has proven the ability of anti-IL-1b (canacinumab) to reduce the CV events and stroke in non-rheumatic patients with history of MI [88]. The effect of bDMARDs, including the latest bsDMARDs and tsDMARDs, on the CV risk needs to be closely monitored and evaluated in long-term studies with sufficiently large cohorts of rheumatic patients.

3. Atherosclerosis and its manifestation in rheumatic diseases

3.1 Rheumatoid arthritis

RA is relatively the most common autoimmune disease with prevalence of 1%, which primarily affects joints and can also manifest by extra-articular involvement. The most frequent occurrence of RA is in middle-aged women. It can shorten the life expectancy by up to 2.5 years [89, 90]. In addition, there is up to three times higher mortality in RA patients compared to the general population [91]. CV involvement and complications, including asymptomatic heart failure or silent MI and sudden death, are the leading death causes in RA patients and occur in RA patients 1.5 times more often than in the general population [2, 92]. CV risk in RA is comparable to the risk in diabetes [93].

The underlying mechanism of increased CV mortality in RA is not completely understood [94]. The main cause of death in RA is ischemic heart disease (IHD), often asymptomatic and underdiagnosed [91, 95, 96]. Up to three times increased risk of IHD in RA patients with positivity of anti-cyclic citrullinated peptide (aCCP) antibodies and rheumatoid factor (RF) has been reported [69, 97].

In fact, RA itself can act as an independent risk factor for development of CVD [98]. The relation between an increase in the CV risk and the disease duration of RA patients is partly attributable to a higher prevalence of hypertension and smoking [99]. In RA, CV risk is also significantly related to traditional risk factors [100]. Smoking has a negative impact on the course of RA and stimulates the production of RF and aCCP nevertheless, the direct role in the increase of CV risk was not proved [98, 101].

Systemic inflammation accompanying the activity of RA significantly contributes to the atherogenesis and CV mortality [102]. The reduction of CV risk was observed during the DMARD therapy (namely HCQ, MTX, anti-TNFs). According to available studies and their meta-analysis, CV risk is most increased by CS therapy (up to 47%) and NSAIDs, in particular by coxibs (by 36%), and, on the contrary, is decreased by MTX (by 28%) or anti-TNF therapy (by about 30%) [72].

3.2 Ankylosing spondylitis

AS is a chronic inflammatory disease, which primarily affects the joints in the site of enthesis. It belongs to the group of diagnostic entity called spondyloarthropathies, which typically manifest in HLA-B27 positive patients. Similar to RA, AS can also manifest with extra-articular manifestations, such as gastrointestinal, ocular and cardiac involvement. The prevalence of AS in the population is about 0.1% (the overall prevalence of spondyloarthritis is around 1%) and, unlike most rheumatic diseases, occurs more frequently in men (up to three times) [103].

Similar to RA, an increased CV risk has been reported in AS patients [104, 105]. However, views on the close association of ATS and AS are divergent, in particular, due to the small evidence and conflicting results of studies [106]. Regarding the evidence

on CV events in AS, the situation is similarly unsatisfactory and inconclusive [107–109]. Recently published meta-analysis has reported an increased risk of MI (RR = 1.6) and cerebrovascular events (RR = 1.5) compared to the general population [110].

There are several risk factors in AS, which participate in CV comorbidities. Since laboratory markers of inflammation are not elevated in many patients, CV risk is likely related to the risk profile of a typical patient with AS: a smoker with arterial hypertension and dyslipidemia, in whom low levels of HDL and TC accompany the disease activity [105, 110]. In addition, extra-articular cardiac manifestations of AS (e.g., conduction disorders, aortic valve insufficiency, left ventricular dysfunction) contribute to CV morbidity and mortality [105]. Levels of C-reactive protein (CRP), therapy with NSAIDs and work disability are considered significant predictive factors of CV mortality in AS [111, 112]. NSAIDs as the first-line therapy with the highest safety profile should be prescribed for the shortest time period possible [110]. On the other hand, anti-TNFs have a favorable effect on the endothelial function and a decrease of the CV risk [105, 113].

3.3 Psoriatic arthritis

PsA is a systemic inflammatory disease from the spondyloarthritis spectrum, associated with psoriasis [114]. The prevalence is 0.05–0.25% in the general population, but rises to 15–30% in patients with psoriasis [115]. The relative risk of CV involvement in psoriasis is reported to be 1.4, but the relative risk in PsA is less studied and the data are conflicting [116–119]. Meta-analysis demonstrated a 1.43 fold higher CV risk in PsA patients compared to the general population. The incidence of MI, cerebrovascular events and heart failure has been reported to be increased (1.68, 1.22 and 1.31, respectively) [120].

According to the current evidence, various manifestations of ATS in PsA have been described, from subclinical involvement to symptomatic manifestations [121–125]. PsA is considered to be an additional independent CV risk factor, as proved by findings of more severe subclinical ATS compared to the general population and the association of plaque development with the inflammatory activity of PsA [120].

PsA is typically associated with high prevalence of MetS, which is two or three times more common than in other rheumatic diseases and the general population [126]. During the active inflammatory phase, there are characteristic alterations of lipidogram with a decrease of HDL and LDL, which consequently rises in remission of the disease [9]. The suggested mechanism, which causes changes of HDL levels, is the uptake of apoA-1 in the tissue affected by inflammation: particles of HDL penetrate from the circulation due to increased endothelial permeability. The consequent decline of serum HDL concentrations increases the CV risk in PsA in a similar manner as in RA [127].

The presence of subclinical ATS and its correlation with inflammatory markers and the effect of immunosuppressive therapy are questionable [9, 128]. Anti-TFN therapy seems to have a beneficial effect on CV risk in PsA, as well as in AS [129].

3.4 Systemic lupus erythematosus

SLE is characterized by a wide spectrum of clinical manifestations and involvement of different organs. The prevalence is 0.03% in Caucasian population, while SLE affects predominantly women in reproductive years, in whom the clinically significant ATS is not usually found under normal circumstances [130]. Although the survival of SLE has significantly improved, thanks to new therapeutic options, it still remains 5–10 years shorter compared to the general population [131]. The rate of SLE-associated mortality has declined, but the rate

of CV complications, which are considered to be the leading cause of mortality in SLE nowadays and are responsible for 30% of deaths, has risen [131]. The bimodal mortality pattern describes two peaks of mortality in SLE population: the first peak represents death early in the course of the disease related to the disease activity and infectious complications, and the second peak refers to late death from the CV manifestations [132].

The prevalence of traditional risk factors is higher in SLE compared to the general population [133]. In addition, SLE-related risk factors, including renal involvement, apply in CV morbidity. The presence of SLE itself increases the risk of heart failure up to three times [134]. The clinical manifestation of ATS in SLE is predicted particularly by higher age at the onset of SLE, presence of arterial hypertension and hypercholesterolemia. Among others, the cumulative dose and the duration of CS therapy, long duration of SLE, and activity of immune system including autoantibodies play significant role in ATS [2].

Due to their pathophysiologic mechanism both SLE and vasculitis predispose to the atherosclerotic involvement of coronary circulation [135]. Coronary artery disease affects 6–10% of SLE patients and the incidence is four to eight times higher than in the general population [136, 137].

Risk of heart failure in SLE significantly rises immediately after the first manifestation of the autoimmune disorder, mostly at a young age. The relative risk of heart failure is therefore most increased in young patients in the age between 20 and 30 years, and decreases with a higher age. However, the incidence of CV diseases and heart failure is continually increasing in positive correlation with the increasing age of patients [134]. SLE patients are at 5–10 times higher risk, and young SLE women at age around 40 years are even at 50 times higher risk of MI compared to the general population [138].

Concerning the risk of a stroke in SLE, the ischemic stroke is estimated to be two times, hemorrhagic stroke three times and subarachnoid hemorrhage four times more common in SLE than in the general population [139]. In case of a stroke, young patients are more threatened due to accelerated ATS during the high activity of inflammation. The relation between disease activity and the risk of a stroke was described also in other diseases. Immunosuppressive therapy and other comorbidities (e.g., vasculitis, antiphospholipid syndrome, arterial hypertension) take part in this increased risk, as well [139]. Accompanying factors such as antiphospholipid syndrome, Liebman-Sacks endocarditis and formation of immune complexes of antibodies with antigens predispose patients to thrombotic complications and ischemic stroke, while endothelial dysfunction and interrupted endothelial layer integrity can lead to hemorrhagic stroke. Subarachnoid hemorrhage in SLE probably results from intracerebral vasculitis and concurrent arterial hypertension [139].

Atherosclerotic plaques have been detected in 17–65% of SLE patients using ultrasound examination. The age seems to play a major role in prediction of atherosclerosis and its manifestations in SLE. Some experts suggest a role of consequences of the disease activity and side effects of therapy in older patients with SLE [2].

3.5 Systemic sclerosis

SSc belongs to orphan connective tissue diseases with the prevalence of 0.003–0.06%, and is less understood, concerning the CV risk. The key pathologies leading to CV involvement are vasculopathy, inflammation and tissue fibrosis, which can also affect the heart. In addition to pathognomic microvasculopathy, macrovascular involvement is getting more attention in the last years [45].

To date, the relative risk of CV diseases in SSc in not known. Survival of SSc patients is about 16–34 years shorter compared to the general population with about

3.5 times higher mortality [140]. Due to advances in therapy of scleroderma renal crisis (SRC) and pulmonary arterial hypertension (PAH), new causes of death have got to the front, and the prevalence of ATS in SSc has risen [141]. Cardiac causes account for a quarter of the overall mortality in SSc patients [142]. The prevalence of traditional CV risk does not seem to differ from the general population. SSc-associated factors, which participate in endothelial damage, include inflammation and ischemia-reperfusion injury caused by impaired vasodilation [45]. The level of inflammation in SSc is lower than in RA or SLE, which indicates lower rate of acceleration of ATS. Impaired vasodilation characteristic for both SSc and ATS precedes the clinical manifestation of SSc. It is accompanied by the mechanisms typical for both of these pathologies: imbalance between vasodilators (e.g., nitric oxide, NO) and vasoconstrictors (e.g., endothelin), defective angiogenesis caused by the increased expression of VEGF, the presence of AECA and others. The main clinical manifestations of microvascular impairment, Raynaud's phenomenon, PAH and SRC, probably predict macrovascular impairment in SSc [45].

Reports on the prevalence of ATS and its clinical manifestations in SSc differ in various studies. Among others, the reason is asymptomatic subclinical cardiac involvement. Increased risk of CV events is attributed both to ATS and the pathogenesis of SSc and its consequences (impaired microcirculation, myocardial fibrosis, arrhythmia, etc.), and last but not least, secondary deterioration of cardiac function due to renal vasculopathy, interstitial lung disease (ILD) and PAH [143].

The risk of MI is almost 2.5 times higher compared to the general population, while the impact of SSc itself outweighs the effect of hypertension or diabetes on the risk of MI. Ischemic injury of myocardium can be caused by occlusive vasculopathy and intermittent vasospasm (so-called myocardial Raynaud's phenomenon) [144].

It is not clear whether the prevalence of subclinical ATS in SSc is higher compared to the general population. Nussinovitch and Shoenfeld reported carotid involvement in more than 60% of SSc patients, where the findings were described to be more frequent and more severe than in a control group from the general population [143].

Cerebrovascular involvement in SSc patients is 1.3 times more common than in the general population. SSc as an independent risk factor increases the risk of ischemic stroke by up to 43%. There are several pathologic mechanisms in SSc playing a role in the manifestation of a stroke, including vasospasm of cerebral arteries corresponding to the Raynaud's phenomenon, which can manifest as a transient ischemic attack or a focal neurologic deficit [145].

3.6 Idiopathic inflammatory myopathies

IIM is a heterogeneous group of diseases, which primary affect the skeletal muscles as the common pathologic mechanism. The most prevalent subtypes are dermatomyositis (DM) and polymyositis (PM) [146, 147]. IIM belongs to orphan rheumatologic diseases and occurs in approximately 0.02% of population [148]. The mortality in IIM is almost four times higher than in the general population, with CV involvement as the leading cause [149]. The main pathology responsible for the cardiac involvement in IIM is myocarditis and accelerated ATS in coronary arteries [150]. Other mechanisms have not been sufficiently studied. Resulting structural alterations in myocardium can lead to disturbed function, arrhythmia and other, mostly asymptomatic, rarely fatal manifestations [151].

Data on cardiovascular disability in IIM are insufficient. Meta-analysis of studies in IIM reported 2.24 times higher CV risk compared to the general population [152]. With regard to the prevalence of MI in IIM, there are only limited data. A retrospective study by Rai et al. in more than 700 IIM patients described

an increased risk of MI, but not of a stroke. The risk of MI has been increased in PM almost four times and in DM three times compared to the general population. Patients were most threatened by these complications during the first years after the onset of IIM [153].

Traditional risk factors in IIM are specifically related to the specific features of the disease, particularly muscle involvement resulting in impaired physical activity and CS therapy. The prevailing effect of CS in IIM, whether anti-inflammatory or pro-atherogenic, is not clear and has yet to be elucidated [152].

3.7 Primary Sjögren's syndrome

Primary Sjögren's syndrome is another relatively rare rheumatic disease with a prevalence of 0.06%. It is characterized by lymphocytic infiltration of exocrine glands (especially lacrimal and salivary) leading to dryness of the mucous membranes (sicca syndrome) and hyperactivity of B lymphocytes. pSS affects preferentially females at the age of 40–60 years [154].

The situation in terms of the CV risk in pSS is similarly unclear as in the above-mentioned rare systemic connective tissue diseases [155]. There is a lack of studies concerning the CV risk in pSS, moreover, the results are conflicting. CVD-associated mortality accounts for 30% of deaths. According to the recent meta-analysis including 14 studies in pSS, the CV risk is significantly increased compared to the general population: the relative risk of coronary artery disease is 1.34, cerebrovascular events 1.46, heart failure 2.54 and thromboembolism 1.78. This meta-analysis has not demonstrated a significantly increased risk of mortality due to CV causes (RR = 1.48) [155].

Similar results have been reported in a population study that also described higher prevalence of arterial hypertension and hypercholesterolemia in pSS patients, and, in addition, suggested pSS as an independent CV risk factor [156]. On the other hand, some studies did not confirm the increased CV risk in pSS [157, 158]. One study has reported subclinical atherosclerotic involvement in pSS patients detected by coronary flow reserve (CFR) and pulse wave velocity (PWV), while the echocardiography showed no pathology [159]. Impaired PWV is thus suggested as a marker of endothelial dysfunction even in patients with normal CFR [160].

Available data rather suggest higher CV risk in pSS patients compared to the general population, and the need of preventive screening and appropriate management, eventually including consultation and monitoring by a cardiologist [155].

4. Examination and estimation of the CV risk

Chronic inflammatory condition can skew the results of the examination, which have otherwise good reliability in the general population [3]. For example, ultrasound imaging of clinically insignificant atherosclerotic lesions or plaques cannot reveal the higher susceptibility to the progression and rupture of plaques in the inflammatory environment [5]. Several scoring systems were developed to facilitate the estimation of the CV risk in the general population. These scoring systems include particularly the traditional risk factors. The most used and widespread systems are Framingham Risk Score (FRS), Systemic Coronary Risk Evaluation (SCORE), QResearch Risk Score (QRISK2, or rather its updated version QRISK 3), Reynolds Risk Score and many others [161, 162]. FRS was the first developed scoring system and served as a default model for creating newer scoring systems. Nowadays, SCORE is probably the most used and widespread scoring system,

especially in Europe [163]. Above-mentioned classic scoring systems underestimate the CV risk in rheumatic patients and therefore are not suitable for estimating the CV risk in these patients. A certain compromise was made by developing the Reynolds Risk Score by inclusion of CRP value as a marker of inflammation, and QRISK2 by inclusion the presence of RA as an independent risk factor [161]. Based on the recent EULAR recommendations for management of the CV risk in inflammatory arthropathies published in 2016, a modified SCORE system (mSCORE) should be used for evaluation of the CV risk in RA patients, which is calculated by multiplying the standard calculated value by a coefficient of 1.5 in all RA patients [58]. Despite this modification, mSCORE is not completely reliable in estimation of the CV risk, as was shown in studies describing findings of subclinical ATS in rheumatic patients classified in the low-risk category according to the mSCORE, and the evidence of higher tendency to formation of ATS plaques and instability of these plaques in RA. Due to these reasons, EULAR proposed simultaneous regular non-invasive examination by ultrasound of carotids and/or measuring the ankle-brachial index (ABI) for detection of subclinical ATS in asymptomatic patients in a low-risk category (SCORE 1–4%) [58, 82].

The CV risk should be assessed at least every 5 years in patients with low disease activity and should be reconsidered after major changes in therapy or progression of the disease [58, 59, 82]. In common practise, this assessment means regular examination of blood pressure and lipidogram during the outpatient control and in case of pathologic findings, early consultation by a preventive cardiologist and an adequate therapeutic intervention [62, 164].

5. Therapy

Preventive measures are the first-line therapy recommended in the general population to manage the CV risk. In rheumatic patients, these measures may be complicated due to a chronic disease. Therefore, the pharmacological treatment is needed [62, 82].

Metformin is recommended as the first line for the treatment of the MetS. It has a beneficial effect not only on improvement of insulin sensitivity, but also reduces the levels of LDL and TC and has a beneficial effect on the vascular function, as well as statins. Similar beneficial effect on glucose metabolism is related to administration of antimalarial drugs, which are often used in the treatment of SLE, pSS and also RA. HCQ exerts immunomodulatory and anti-inflammatory effect, and, in addition, induces an increase in insulin activity and serum levels of glucagon and improves the glucose tolerance. Moreover, HCQ reduces plasma glucose levels even in the general population and is therefore suitable as a part of MetS therapy [82]. Other drugs for glucose metabolism control include pioglitazone (a nuclear peroxisome proliferator-activated receptor-γ agonist), and liraglutide (glucagon-like peptide-1 analog), which has a beneficial effect in obese patients [13].

When managing and treating dyslipidemia, the recommended target levels of LDL (especially for RA) are lower than for the general population (LDL < 2.6 mmol/L; in individuals at higher risk, even <1.8 mmol/L). At the same time, preventive antiplatelet therapy should be considered [62]. Statins have been extensively discussed, especially in rheumatology. Via competitive inhibition of HMG-CoA (3-hydroxy-3-methyl-glutaryl-coenzym A) reductase, they inhibit the intermediate step in the synthesis of cholesterol. Despite the concerns of potential side effects as induction of immune-mediated necrotizing myopathy (IMNM), the use of statins in IIM patients does not seem to be more

risky than in the general population [165]. Several studies demonstrated a beneficial potential of statins to reduce the CV risk via attenuation of the oxidative stress and improvement of endothelial function. Due to their anti-inflammatory potential, statins are preferentially recommended in the therapy of rheumatic patients according to the EULAR recommendations [62]. For example, atorvastatin, when administrated to RA patients, not only reduces the levels of TC and LDL, but apparently also inhibits the inflammation activity [166]. This favorable effect was confirmed in TRACE-RA study [167]. Rosuvastatin exerts a similar beneficial effect in inflammatory joint diseases [168]. Another therapeutic option for dyslipidemia treatment is fenofibrate, which increases the HDL levels, and niacin [13].

Regarding the management of arterial hypertension, targeting the optimal blood pressure is more important than considering the type of drug used in therapy [58]. ACE inhibitors or blockers of AT1 receptor for angiotensin II exert a potential anti-inflammatory effect similar to statins, and therefore are preferentially recommended for treatment of arterial hypertension [62]. There is an exception in SSc patients. ACE inhibitors are recommended in the treatment of manifested SRC, but not as a prevention of SRC. Thus, other antihypertensive drugs should be prescribed (if SRC is not present), especially calcium channel blockers due to their beneficial effect on Raynaud's phenomenon [169].

Among other drugs with beneficial effect, vitamin D should not be forgotten. It was demonstrated that vitamin D acts as an immunomodulator and probably plays a protective role in the development of CV diseases, insulin resistance and obesity, and has anti-inflammatory effect and can potentially prevent from the development of MetS in RA patients. Also, probiotics are worth mentioning. Based on the results of studies showing that adverse changes of gut microbiome can induce autoimmune disorders, administration of probiotics may be profitable, as this could prevent the development of autoimmune disease or mitigate the consequences of already present pathological metabolic changes. However, further studies are needed to confirm these hypotheses [13].

Finally, the other side of this issue must not be forgotten, that is, adequate anti-inflammatory therapy of rheumatic diseases using DMARDs (especially MTX and TNF inhibitors in RA). Such therapy leads to mitigation of inflammatory activity and also improvement of quality of life and fitness of patients. Better fitness enables physical activity and thus facilitates the elimination of traditional risk factors and thereby reduces the CV risk [13].

6. Conclusion

Rheumatic patients are significantly more at risk of atherosclerosis and its complications than individuals from the general population. Traditional risk factors are in rheumatic patients more frequent. Moreover, these risk factors are often hard to manage by modification of life style. Nowadays, a wide range of therapeutic options is available for elimination of traditional risk factors and reduction of the cardiovascular risk. The appropriate anti-inflammatory therapy represents the golden standard. Despite the growing evidence on the cardiovascular risk in rheumatic patents, the adequate recommendations for management of these patients and early detection of a higher risk are still lacking. The task for the future is to create an examination algorithm to prevent underestimation and negligence of risk in rheumatic patients and also to extend the knowledge on the cardiovascular risk in rare rheumatic diseases.

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