Particularities of cardiovascular patterns related to rheumatic disease from biological findings to clinical aspects

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Abstract

The prevalence of cardiovascular disease (CVD) in chronic inflammatory rheumatic diseases (CIRD) is higher than in the general population. This results from the compound effect of traditional cardiovascular (CV) risk factors (CVRF) along with chronic inflammation and genetic components. But, most patients with increased prevalence of CV events had a moderate CV risk. Despite recent advances in the management of chronic inflammatory rheumatic diseases, the prevalence of CVD remains high in subjects with CIRD who are followed up periodically at outpatient rheumatology clinics. Classic CVRF and CIRD duration are associated with an increased risk of CVD.

Key words: chronic inflammatory disease, cardiovascular disease, risk factors

Increased rates of subclinical atherosclerosis have been described in systemic autoimmune diseases, particularly in systemic lupus erythematosous (SLE), rheumatoid arthritis (RA) and systemic sclerosis (SSc). These patients with autoimmune disease present a higher mortality risk mainly for CV events. Acceleration of subclinical ATS damage is the main mechanism leading to this increased risk. The relationship between traditional CVRF and inflammatory and autoimmune markers may contribute to both induction and progression of atherosclerosis (ATS) (1-4). Traditional CVRF such as smoking, dyslipidemia, diabetes mellitus (DM), hypertension (HT) and increased body mass index (BMI), do not fully explain the high rates of subclinical ATS in these patients. Almost 2/3 of patients with primary Sjogren's syndrome (Ss) have evidence of subclinical ATS (defined by carotid intima media thickness (cIMT)>0,9 mm and/or carotid plaque).(5)

Rheumatoid arthritis (RA) is the prototype of CIRD associated with accelerated ATS and increased risk of CV death. Different studies have shown a higher incidence of CV events and CV mortality in RA patients compared to people of the same age and sex, similarly to what occurs in type 2 diabetes (T2D). Overall, patients with RA have a 2–3-fold higher risk of myocardial infarction (MI), even in the absence of traditional CVRF, as well as a higher rate of CV mortality (up to 50%). Consistent with data described in RA, patients with spondyloarthropathies (SA) also have a higher risk of CVD than the general population. CVD and CV mortality are more common in patients with psoriatic arthritis (PsA) compared to the general population. Besides traditional CVRF, the presence of severe psoriasis is an important predictor of CVD in these patients. Although the role of

classic CVRF cannot be ruled out, the disease by itself appears to be a predictor of CV events, since patients with PsA exhibit increased subclinical ATS regardless of the presence of classic CVRF. Ankylosing spondylitis (AS) has also been associated with 1.5–2.0-fold higher mortality rate compared to the general population, which is in great part due to CV complications. (6)

Evidence indicates that inflammation contributes to the onset and pathogenesis of ATS and CVD in the general population. Epidemiological studies suggest that a number of pro-inflammatory molecules, such as CRP, fibrinogen and cytokines, are involved in mediating this process. Levels of these pro-inflammatory molecules and cytokines are increased in RA patients; they not only promote endothelial dysfunction and structural vessel abnormalities, but also induce other CVRF, such as changes in lipid levels, insulin resistance and oxidative stress. (7-10) In RA, many studies have demonstrated a significant association between inflammatory measures, particularly ESR, and the risk of CVD. Inflammation contributes to all stages of ATS, from plaque formation to instability and eventual plaque rupture. ATS and RA share many common inflammatory pathways, and the mechanisms leading to synovial inflammation are similar to those found in unstable atherosclerotic plaque (11). The high levels of TNF, IL-6 and IL-1 associated with RA are also central to the development of ATS. IL-6 has been shown to be significantly associated with atherosclerosis in RA patients, independent of known CVRF (12). Some inflammatory markers are well known indicating the RA activity (CRP, fibrinogen, and soluble intercellular adhesion molecule-1) and are linked also with the inflammatory mechanism of CVD. These inflammatory cytokines, along with prothrombotic and adhesion molecules, may mediate a predisposition to vascular damage in RA. In inflammatory state, endothelial cell activation, vascular dysfunction, and subsequent atherosclerosis can develop (13). Between them, high serum amyloid A (SAA) concentration is strongly connected with the activity of the disease and the risk of CV and renal involvement in RA patients. SAA is not only an acute-phase protein but also an apolipoprotein, relevant in cholesterol metabolism. Normally, SAA circulates in low levels bound to high-density lipoprotein (HDL), but during inflammation SAA can contribute up to 80% of HDL apolipoprotein (apo) composition, exceeding apo-A1 in quantity and impairing the protective function of HDL. SAA may also increase the oxidation of low-density lipoprotein (LDL) and thus may be associated with CVD and atherogenesis. (14) Furthermore, acute phase reactants (APRs), typically elevated in RA, have been shown to be associated with subclinical ATS, indicated by increased cIMT and CV morbidity and mortality in patients with RA (15). In the general population, CRP level is an independent predictor of CVR, particularly MI, while in both RA patients and healthy subjects, CRP is associated with the number of atherosclerotic plaques and cIMT. Higher IL-6 levels are also associated with increased mortality in patients with ACS and with increased risk of future MI in healthy men, suggesting that IL-6R blockade could be considered a potential therapeutic approach for the prevention of CHD (16,17). In RA, inflammation is associated with a paradoxical inversion of the usual relationship between CVR and lipid levels (18). These observations imply that the traditional interpretation of lipid profiles for predicting CVR in the general population may be confounded by disease activity in RA patients but may include suppression of the reticuloendothelial system and reduced LDL particle synthesis. CRP mediates the uptake of LDL and oxidized LDL by macrophages, induces LDL deposition and increases LDL uptake by hepatocytes (19-22). The incidence of

cardiovascular and cerebrovascular disease is higher in patients with RA than in general population and increased cIMT has been recommended for the CVR stratification in these patients. Chronic inflammation, the basic feature of RA, plays a major role in accelerated ATS in patients with RA through its influence on insulin resistance, lipid status, atherothrombogenic factors an endothelial damage. (23).Systemic inflammation and CVRF are associated with rapid cIMT progression, the mean rate of increase reported is 0.016-0,0018 mm/year in RA patients comparative with 0,0014 in non-RA subjects and the rate of IMT progression is correlated with the number of CVRF (mostly HT) and with the inflammatory activity of the disease. Carotid artery plaque also identified by ultrasound (US) represents a very high CVD risk and strongly predicts incident CV event rates in RA patients. (24-28) Despite the fact that the risk of heart failure (HF) in RA is almost twice that of the general population and it has been associated with worse outcomes, the treatment of HF in RA remains less aggressive. Patients with RA are less likely to have angina pectoris (AP) as a manifestation of (coronary artery disease (CAD), more likely to have silent MI compared with the general population and less likely to have typical electrocardiogram findings at presentation. The difference in clinical presentation may contribute to delays in the recognition and treatment of patients with RA and emphasizes the importance of a high index of suspicion in these patients. Clinical features of HF typically seen in the general population are less likely to be evident at presentation in patients with RA. Population studies of incident HF in patients with RA showed that they are less likely to have dyspnea on exertion, orthopnea, or paroxysmal nocturnal dyspnea at presentation. Patients with RA in this study were also more likely to have rales compared with non-RA subjects and less likely to have elevated blood pressure (BP) at presentation. The risk of diastolic dysfunction in patients with RA may be associated with the duration of RA disease. Patients with RA are more likely to have abnormal left ventricular (LV) geometry (higher LV mass, LV hypertrophy, LV concentric remodeling) than healthy people without RA and these abnormalities are associated with an increased risk of CVD developing to HF. LV dysfunction could be present before the clinical evidence of CV in RA patients with active disease (with high titers of CRP and anti-CCP). (29).The disease characteristics of RA seems to influence the risk of development of CVD and CV mortality, the rheumatoid factor (RF) positivity and disease severity conferring the greatest risk. RF positivity is a significant predictor of CV events including HF all-cause and CV mortality among the general population, suggesting a role for antibodies in the pathogenesis of CVD. The increased risk of HF is significant with a 2.5-fold increased risk among RF-positive subject. Severe extra-articular manifestations of disease are associated with a higher likelihood of developing even after adjustment for CVRF. The presence of rheumatoid lung disease and RA vasculitis, which are markers of disease severity, has also been associated with a greater incidence of CV death (30). Among patients without clinical CVD, those with RA are more likely to have elevated brain natriuretic peptide (BNP) than non-RA subjects (16% vs 9%). Patients with RA with abnormal BNP are more likely to have LV diastolic dysfunction with those with normal BNP, but the specificity compared with non-RA patients and the positive predictive value (25%) of elevated BNP in patients with RA is low (25%) and is not a good screening tool. The duration of RA and CRP levels is independently associated with BNP. Patients with RA demonstrated a significantly higher long-term systolic BP and pulse pressure variabilities than the non-RA subjects.

Increased BP variability was associated with adverse CV outcomes and all-cause mortality in RA, adjusting for systolic and diastolic BP, BMI, smoking, DM, dyslipidemia and use of antihypertensives drugs. (31). There is a strong association between individual CVRF (HT, T2D, smoking, hypercholesterolaemia, obesity, and physical inactivity) and rate of either MI, combined CV morbidity (MI, AP, HF, stroke, and peripheral arterial disease (PAD)) or CV mortality in RA patients (32,33). In Japanese study population, stroke morbidity was 3.6 per 1000 person-years and acute coronary syndrome (ACS) morbidity was 2.5 per 1000 person-years, although RA patients had few traditional CVRF. This CVR in patients with RA was higher than the estimated risk according with the Japanese Atherosclerosis Society (JAS) Guidelines for Prevention of Atherosclerosis Cardiovascular Disease, in which the 10-year risk of CHD death in Japanese subjects who have equivalent RF shown in this RA population is less than 0.5. Long RA duration correlated with the risk of CVD, including coronary artery calcification and cIMT. (34,35). The CVR in RA is increased to a similar magnitude to that seen in T2D and is related to the systemic inflammatory burden associated with RA as well as an increased prevalence of traditional RF. Anti-rheumatic therapies which are highly effective at reducing inflammation appear to increase total cholesterol and low density lipoproteins (LDL) levels, in the light of the lipid paradox in RA, the benefits of suppression of inflammation are likely to outweigh lipid changes that might otherwise be considered to be adverse.The suppression of inflammation through tight and sustained disease control is important for lowering CVR, but also to permit accurate screening of patients at high CVR. Current assessment tools and recommendations may underestimate CVR in some RA patients.

There is an increased frequency of comorbidities in patients with **early rheumatoid arthritis (ERA) and early axial spondyloarthritis (ESpA)** with increased prevalence of HT compared with the general population. In addition is an increased 10-year risk in patients with ERA for developing CVD and increased heart age in patients with both ERA and ESpA. (36).Patients with ankylosing spondylitis (AS) have higher cIMT than the subjects of the general population and that index is correlated with disease chronicity. (37)

A major cause of morbidity and mortality in the context of **the antiphospholipid syndrome (APs)** is the occurrence of thrombotic events due to its trombocytopenia and procoagulant state. APs frequently occurs as a primary autoimmune disease or as secondary association in other autoimmune or CVD and is correlated with a worse clinical outcome. The common manifestations in these patients are: deep vein thrombosis, pulmonary, thromboembolism, stroke, transient ischemic attack, and CAD with acute MI. The possible roles of antiphospholipid (aPL) in the pathogenesis of thrombosis in APs are well established and includes changes in the coagulation cascade, inhibition of protein molecules C, antithrombin and annexin, platelet activation and complement and increased expression of endothelial adhesion molecules. Other risk factors and/or medical conditions, which are conditions for traditional risk of an individual without the APS, can coexist in this patient, raising their risk of developing thrombosis. Between traditional CVRF, others risk elements (hyperhomocysteinemia, increased lipoprotein a, oxidized low density lipoproteins), could be involve in the pathogenesis of CV events. Approximately 30% of APs patients have silent CAD and 11.1% of them show typical patterns of MI by cardiac magnetic resonance imaging and/or contrast echocardiography. The evaluation of patients with primary APS from the use of positron emission tomography (PET) revealed the presence of endothelial

dysfunction that may contribute to the acceleration of ATS. The use of transcranial ultrasound also demonstrated possible association with subclinical ischemic transient attack by enhancing cerebral blood low abnormalities in patients with APs without neurological symptoms. In APs there is an increase arterial stiffness, carotid and femoral IMT and plaque formation including aorta. (38). APs might occur in AAA (abdominal aortic aneurysm) patients and is associated with increased serological markers of inflammation and predicted progressive disease (the presence of an intra-aneurysmal thrombus). These findings further support the concept of possibly underlying immune-mechanisms in AAA development and the need for imagistic screening in polyvascular patients with APs. (39).

Systemic Lupus Erythematosus (SLE) patients suffer a high prevalence of premature CVD. The overall prevalence of CV events in SLE patients was7.4% in RELESSER Registry and was similar in the LUMINA cohorts (7%). Other European and American studies reported a higher prevalence of CV events ranged from 9.8% to 19.0.The frequency of cerebrovascular events is higher compared with coronary or peripheral artery diseases. Lupus patients have a higher burden of traditional risk factors compared with the general population. However, after controlling for traditional risk factors, individuals with SLE are at increased risk for CVD. There is a risk of CAD that is 2 to 10 times that of the general population, with a greater increase in relative risk generally observed in younger patient groups. This reflects the fact that lupus patients have a higher risk of accelerated ATS, comparable to that of diabetes patients. The estimated 10-year mortality rate is 26% for SLE subjects versus 19% for comparisons reported US population-based. Women with lupus between the ages 35–44 years old had a hazard for cardiac events that was elevated 50-fold compared to age-matched peers (40). On the other side the SLE patients have a higher prevalence of diabetes. The overall CV risk is increased by the presence of low complement, antiphospholipid antibodies (APLA), valvular dysfunction, serositis (pericardial effusion). Valvulopathy in SLE can be caused by activity or damage and is a known source of cerebral emboli causing transient ischemic attacks and strokes. SLE patients who are positive for APL had a 57% greater risk of suffering a CV event. APLA syndrome is characterized by recurrent arterial thrombosis, including ictus and MI and might play a role in the development of ATS via several mechanisms, such as the proinflammatory activity they directly or indirectly exert on endothelial cells or by enhancing the lipid peroxidation of lipoproteins or reducing paraoxonase activity. (41). cIMT seems to be increase in SLE patients and this finding appears to be more significantly (57% of patients and a twofold increase risk) when is present lupus nephritis (42). ATS is common in SLE patients and is associated with a 2-5 fold increased risk of future cardiac, cerebral or peripheral arterial ischemic events and mortality. Patients with SLE as compared to age and sex matched controls and after controlling for traditional ATS risk factors, have a higher prevalence of subclinical carotid and aortic atherosclerosis (AoA) manifested as intima-media thickening or plaques, aortic stiffness(AoS) defined as decreased vessel distensibility (higher pulse pressure to achieve similar degree of vessel distension) and a higher prevalence of subclinical CAD. cIMT measurement could be used as one of the clinical predictors of risk of accelerated atherosclerosis in lupus patients. (43). Unlike for carotid and CAD, the prevalence, characteristics, risk factors or predictors, clinical manifestations, prognosis, and therapy of AoA in SLE patients have not been well defined. This is important because AoA may have different clinical and prognostic implications than those of carotid and

coronary ATS .Premature AoS is common in patients with SLE. In SLE it is unclear if AoS is a precursor of AoA, is a condition that occurs simultaneously but independently of AoA, or is a consequence of AoA. Immune-mediated inflammation, thrombogenesis, traditional ATS factors, and therapy-related metabolic abnormalities are the main pathogenic factors of AoA and AoS. Pathology of AoA and AoS suggests an initial subclinical endothelial lesion or vasculitis, which is exacerbated by thrombogenesis and atherogenic factors and ultimately resulting in AoA and AoS. Although imaging techniques demonstrate highly variable prevalence rates, on average about 1/3 of adult SLE patients may have AoA or AoS. Age at SLE diagnosis; SLE duration, activity and damage, corticosteroid therapy, metabolic syndrome, chronic kidney disease and mitral annular calcification are common independent predictors of AoA and AoS. Also, AoA and AoS are highly associated with carotid and coronary ATS. Earlier stages of AoA and AoS are usually subclinical. (44). AoS and LV diastolic dysfunction are common and associated with increased morbidity and mortality in SLE patients and compared to controls they have higher degree of AoS independently of ATS risk factors including HT and AoA. In SLE patients, aortic stiffness is correlated with increased LV mass, LA volume and LV diastolic dysfunction(45). Earlier stages of disease may be causally related or contribute to peripheral or cerebral embolism, pre-hypertension and hypertension, and increased left ventricular afterload resulting in left ventricular hypertrophy and diastolic dysfunction. Later stages of disease predisposes to visceral ischemia, aortic aneurysms and aortic dissection (46).

Psoriatic arthritis (PsA) is a chronic auto-immune inflammatory arthritis associated with an increased risk of sub clinical, clinical CVD and early CV mortality. Chronic inflammation plays a pivotal role in the pathogenesis of ATS and in subclinical CVD in PsA patients. Inflammation is involved in foam cell formation, endothelial dysfunction and cytokine production, which leads to the development of arterial dysfunction and ATS plaque. PsA patients have increased arterial stiffness compared with healthy control subjects. Cumulative inflammatory burden contributes to the increased arterial stiffness independent of traditional CVRF, suggesting that increasing arterial stiffness may be one of the mechanisms linking inflammation and CVD in PsA. (47)). More than a 1/3 of PsA patients deaths are caused by CVRF.A recent meta-analyses found that compared to normal individuals, PsA patients have a higher prevalence of CAD), HT, AP, MI, HF and vascular disease, obesity, metabolic syndrome, T2D, dyslipidemia and inflammation. It has been established that PsA is equivalent to RA and T2Dregarding its CV risk (48). Applying the mSCORE to PsA patients the mean value is 2,3% (1,7-2,9%) risk of CV mortality (49).

In comparison to SLE and RA, accelerated ATS appears to have a different prevalence in **systemic sclerosis (SSc).** Moreover, the inflammatory component seems to be less prominent and ATS less aggressive in SSc, making more difficult to demonstrated subclinical ATS in these patients (50). Prevalence of CV and macrovascular disease has been demonstrated to be increased in SSc patients in comparison to healthy individuals and correlated with a poorer prognosis, 20-30% of deaths in SSc patients are related to CV causes. The 2010 survey from the European League Against Reumatism Scleroderma Trials and Research (EUSTAR) database estimated that 26% of SSc-related causes of death were due to cardiac causes (mainly HF and arrhytmias) (51-53.). It still remains unclear if a premature ATS occurs even in SSc. Although microvascular disease is a hallmark of SSc, in the last few years a number of studies highlighted a higher prevalence of macrovascular disease in SSc

patients in comparison to healthy individuals and these data have been correlated with a poorer prognosis. The mechanisms promoting ATS in SSc are not fully understood, but it is believed to be secondary to multi-system organ inflammation, endothelial wall damage and vasculopathy. Both traditional CVRF and endothelial dysfunction have been proposed to participate to the onset and progression of ATS in such patients. The prevalence of traditional CVRF in SSc has not been assessed in large studies. Traditional CVRF alone do not seem be able to explain CV disease because the majority of these studies showed a similar distribution between patients and controls, suggesting that other factors may contribute to the increased prevalence of CV disease in SSc (54-56). SSc patients may have increased levels of LDL, homocysteine, CRP and lipoprotein a, all associated with an increased risk of ATS and CV events. In addition, hypercholesterolaemia, DM and obesity were significantly less prevalent in SSc compared with the general population Primary cardiac involvement in SSc may manifest with different features, including myocardial damage, fibrosis of the conduction system, pericardial and, less frequently, valvular disease. In addition, cardiac complications in SSc may develop as a secondary phenomenon due to pulmonary arterial hypertension (PAH) and kidney pathology. Microvascular disease, characterized by both vasospasm and structural alterations, is a pathognomonic feature of SSc and Raynaud's phenomenon,PAH and scleroderma renal crisis represent the main clinical manifestations. Microvascular involvement predicts macrovascular ATS over time (57,58). Endothelial dysfunction contributes to the pathogenesis of ATS risk in SSc. An impairment of endothelium-dependent vasodilation seems to occur before the onset of clinical ATS in SSc, the role of endothelial damage is one of the most important mechanisms involved in the pathogenesis of ATS. The main clinical features of ATS disease in SSc patients are represented by an involvement of peripheral, cerebrovascular, carotid and coronary arteries with consequent high risk of peripheral vascular disease, stroke and coronary heart disease. (54). Earliest endothelial changes occur in smaller arterioles and microvascular beds, but not in medium or macrovascular beds, in which vascular alterations could occurs later in early diffuse SSc(59). Microvasculopathy related to disease pathogenesis more than ATS damage may be considered the leading mechanism of peripheral vascular abnormalities in SSc and beside the lower limbs might affect also the upper limbs. (60) The vascular lesions are associated with endothelial dysfunction (assess by impaired vasodilatation mediated flow on brachial artery meaning an endothelial defective nitric oxide release). Other vascular implication is the increase of AoS (evaluated by pulse wave velocity PWV) (61). Circulating anti-centromere antibodies have been demonstrated to be more frequent in patients with symptomatic ischemic events (62). Patients with SSc showed a 6-times increased prevalence of peripheral macrovascular disease, detected by angiography, doppler ultrasound or physical examination. In a SSc is 22% prevalence of symptomatic PAD with intermittent lower limb claudication sometime can developed critical limb ischemia. Angiographic findings the lower and upper limb in SSc patients showed a correlation between CV risk factors and proximal, but not distal, PAD.

Central nervous system may be affect by a microvascular damage as complication of systemic involvement. Patients with circulating anti-U1 RNP and anti-Scl70 antibodies have a higher risk of developing neurological complications. Intracerebral vascular calcifications, an independent risk factor of ischaemic stroke in the general population, were found by CT scan in 32% of

asymptomatic SSc patients but in only 9% of controls. White matter hyperintensities on brain MRI, a known risk factor for future symtomatic stroke (76), were more common in asymptomatic SSc patients than in healthy controls (77,78). A single photon emission computed tomography (SPECT) investigation showed focal or diffuse hypoperfusion in mainly neurologically asymptomatic SSc patients, for microangiopatic damage of brain vessels. Patients with circulating anti-U1 RNP and anti-Scl70 antibodies have a higher risk of developing neurological complications. SSc is independently associated with a 43% increase in ischaemic stroke risk and the medications commonly employed in these patients, including calcium channel blockers, angiotensin-converting enzyme inhibitors, oral corticosteroids or immunosuppressants, did not modify the risk. (63). Patients with SSc have a significant increased prevalence of carotid artery stenosis, evaluated by B mode and color Doppler ultrasound, in 64% of cases. Since carotid artery stenosis is a predictive factor of stroke, these findings suggest that SSc patients may have an increased risk of stroke. The increased ischemic stroke risk in SSc may be due to different pathogenic mechanisms such as vascular injury, chronic inflammation and vasospasm. (64). Significantly higher cIMT values are founded in SSc patients compared to controls in 43% of them, demonstrating increased risk of ATS. cIMT values, directly correlated with disease duration, were similar to those observed in patients with RA, DM or familial hypercolesterolemia and in relation with increased levels of circulating anti-Scl70 antibodies. Increase cIMT in SSc patients is associated with a relative risk of 1.15 for MI and 1.18 for stroke (50). In SSc patients is a significant higher prevalence of carotid plaque (45.6% vs.19.5%) with similar cIMT in comparison to matched controls and these patients are characterized by increased concentration of serum proteins implicated in both vasculopathy and fibrosis in comparison to patients without plaque. (65.)

Primary cardiac involvement in SSc may depend on myocardial damage secondary to microvascular alterations (vasospastic events which result in areas of focal ischemia and recurrent ischemia-reperfusion injury), myocardial fibrosis with a ‘mosaic’ distribution (due to collagen accumulation), involvement of the conduction system with consequent arrhythmias and conduction defect, but also pericardial and valvular disease. Secondary heart disease due to renal vasculopathy, interstitial lung disease and PAH, could adversely influence cardiac function. Hpertension, obesity, diabetes and other comorbidities may contribute to adversely influence cardiac function, mainly in older SSc patients. MI has been described in SSc patients with unaffected coronary arteries. Microvascular disease leading to ischemic events and contraction band necrosis, resulting from both occlusive vascular disease and intermittent vasospasm (the so called ‘myocardial Raynaud’s phenomenon’), has been demonstrated to be the main mechanism associated with myocardial ischemic events in these patients. Prevalence of CAD (MI, percutaneous coronary intervention, coronary artery bypass grafting, and CVRF in a wide cohort of SSc patients is about 3 times higher in SSc patients in comparison with control, even after controlling for diabetes mellitus, obesity and hypercholesterolemia. (54, 66) The risk of acute MI is independently associated with SSc with a 2.45-fold greater in SSc patients than in general population while immunosuppressants did not reduce this risk. Only 1/3 of acute episodes of MI had CAD, confirming that MI may be caused by microvascular ischemia and not only by coronary artery stenosis. (67). Patients with anti-centromere antibodies (ACA) had more ischemic arterial events compared to the other SSc patients, while anti-topoisomerase I-positive patients were

characterized by fewer ischemic events (68). These suggest that antibody profile and different disease subsets may contribute to macrovascular involvement. Epicardial coronary arteries in SSc patients have been reported to be free of significant lesions (34% compared to patients from general population) even in the setting of MI, congestive HF and sudden cardiac death, which mean that vasospasm, rather than ATS, is a major pathogenic mechanism of SSc-related heart disease. The evaluation of coronary flow reserve (CFR), a diagnostic marker of CAD (by transthoracic echocardiography), confirmed coronary vessels involvement. (61). Patients with SSc were found to have higher levels of coronary calcium in SSc (56.2%) and homocysteine than control subjects (18.8%) (evaluated through multidetector CT, a noninvasive procedure that provides a surrogate marker for coronary ATS by generating a coronary calcium score).

SSc is associated with increased risk of developing MI (4,4% vs.2,5%), stroke(4,8% vs.2,5%) and peripheral vascular disease (7,6% vs.1,9%). These associations persisted after adjustment for CV risk factors, including BMI, smoking, HT, DM and hyperlipidaemia, suggesting that the increased risk of CV events in SSc may depend on both ATS and non-atherosclerotic factors, like vasospasm, SSc specific vasculopathy, vasculitis and thrombosis. (69.) ATS mechanisms underlying CV events, such as MI, stroke and PAD, may be different. CVD prevention and surveillance represent an opportunity to further reduce morbidity and mortality in SSc and modification of traditional CV risk factors should be part of standard care for these patients. (62).

PAH is a frequent complication of SSc with 10% prevalence and its presence represent an impairment condition leading to an important cause of death in this disease. An estimated systolic pulmonary arterial pressure>36 mmHg at baseline echocardiography was significantly and independently associated with reduced survival, regardless of the presence of pulmonary hypertension based on right heart catheterization (70)

In about 50% of patients with systemic sclerosis (SSc) are described ECG changes. These are represented by arrhythmias, conduction delay and/or STT variations. Arrhythmias could be supraventricular beats, tachycardia and atrial fibrillation in 66% of patients and ventricular beats in 90% of patients systematized in pairs (28%) , multiform (40%) and/or repetitive premature (13%) or tachycardia like unsustain ventricular tachycardia (21%). Conduction trouble are sinus node dysfunction and atrioventricular conduction delay founded in 57% of the patients (left bundle branch block (16%), followed by first-degree atrioventricular block (8%), while second and third-degree atrioventricular block were infrequent <2%). Abnormal ventricular arrhythmias were more likely in patients with echocardiographic abnormalities (46% of patients and consist in Doppler echocardiography findings, PAH, a decreased LV ejection fraction, an increased right ventricular (RV) diameter and a greater number of enhancing myocardial segments especially (antero-)septal at delayed enhanced cardiac MRI study) and ECG (at rest but especially 24 hour Holter monitoring validation) changes like ST/T variations (in 14% of patients). In the patients underwent coronary angiography, there was normal results. The prevalence and severity of ventricular arrhythmias did not correlate with clinical variants or with other clinical symptoms and signs of the disease. Despite the very frequent occurrence of ventricular arrhythmias, sudden cardiac death is not very common in SSc (5% of patients). Severe cardiac arrhythmias with a poor prognosis are significantly more frequent in patients with concomitant skeletal and cardiac muscle

involvement and in the patients who died of more advanced disease and in whom an abnormal ECG was found in 95% of cases. These rhythm disorders may have several origins (related to primary heart involvement, pericardial disease, valvular regurgitation or PAH) and may negatively affect the overall prognosis of these patients. Cardiac involvement is the result of microvascular alterations, collagen overproduction by altered fibroblasts with extracellular matrix deposition and complex immune system dysregulation. A variable combination of the above mechanisms leads to ischemic, fibrotic and inflammatory lesions involving all cardiac structures, including the cardiac conduction system. The arrhythmias and conduction defects in SSc may be mild, but can also lead to a fatal outcome. It is demonstrated also the impairment heart rate variability (HRV), confirming that patients with SSc develop cardiac autonomic nervous system dysfunction. HRV seems to be a potential useful tool for the identification of patients at risk for ventricular arrhythmia and might be considered an independent risk factor for mortality in SSc. The underlying arrhythmogenic mechanisms are not well understood, but myocardial damage by focal fibrosis seem to be the most important factors, dynamic vasospasm and inflammation of the heart and small heart nerves are possible causal factors. Sympathetic autonomic nervous system activation resulting from even subclinical HF, and a subsequent recruitment of baroreceptors, may also be important causal factors and may contribute to the severity of SHD All these important cardiac alterations could be integrated in the concept of "sclerosis heart disease" (SHD). Early recognition of life-threatening ventricular arrhythmias and the treatment with anti-arrhythmic drugs, adapted to the individual patient may be crucial in improving the overall prognosis of SSc patients. (71)

According to the increase arguments for the prevalence of CVD in inflammatory arthritis (including RA), The EUropean League Against Rheumatism (EULAR) recently reported recommendations for CVD risk management (72). The CVD-RF model score represent an important step in the multitask management of RA disease and CVD complications (73). This comprised risk stratification based on the Systematic COronary Evaluation Score (SCORE), a multiple major traditional risk fact or equation, together with the use of a multiplier of 1.5 when two of three criteria were met the latter consisted of a disease duration>10 years, rheumatoid factor or/and anticyclic citrullinated peptide (ACP) positivity and the presence of severe extraarticular manifestations, providing a modified (m)SCORE in patients with RA. The mSCORE can underestimate the actual CVD risk in patients with RA. (74). Among patients, women with aged>49.5 years or/and a total cholesterol concentration of>5.4 mmol/l (CV risk factors included in low-risk CVD according to EUROSCORE), more than 1/3 had carotid plaque, which means the presence of an independent risk factor for develop CVD. The addition of activity inflammation marker for RA like rheumatic factor and ACP might increase twofold the risk for CVD. (75)

There is growing evidence that serum uric acid (sUA) may play a role in CVD in the general population. Epidemiologic studies have found that hyperuricemia appears to be an independent risk factor for HT, HF, CAD and stroke. Experimental studies have also shown that uric acid is a functionally active molecule that can contribute to proatherogenic processes including inflammation, endothelial dysfunction and oxidative stress. Hyperuricemia was associated with increased risk of peripheral arterial (PAD), but not for CVD events and also increase all-cause mortality. (76). Both hyperuricemia and gout

increase the risk of CV morbidity and mortality. (77). The role of aditional CVRF even in younger ages is supported also by the observation that is a significantly positive correlation between seric urat acid (sUA) concentration and the development of CVD outcomes among young to middle-aged adults during a 27-year follow-up. During young adulthood, sUA may be responsive to individual metabolic abnormalities, suggesting that monitoring sUA concentrations may be of clinical importance to CVD prevention and management (78).

Ankylosing spondylitis (AS) is an inflammatory disease with documented elevated CVR events due to systemic inflammation and a higher prevalence of CVRF. In AS patients is an increased rate of HT comparative with the basic population and most patient with AS die from complications of atherosclerosis. When adding 15 years to the age of the AS patients, the percentage of patients with high CV risk increases from 7% to 2 6%. Subsequently, undertreated, this CV risk increased from 28% to 44%. (79)

The pathogenesis of the increased CVD risk seen in CIRD remains incompletely understood, but the role of systemic inflammation in the pathogenesis of premature ATS, CAD and HF is stipulated (80). Innate and adaptive immune mechanisms shared by CVD and systemic CIRD have been identified and could represent potential novel treatment targets. It has been recognized that the increased risk of CVD in rheumatic diseases is not explained entirely by the traditional CVRF. Isolated treatment of CV risk factors in the absence of adequate control of disease activity is unlikely to effectively reduce the CVR, therefore, the current treatment strategies are focused on targeting both of these areas. Traditional CVRF identification and treatment is suboptimal among patients with RA. It remains unclear if the treatment targets used for the general population are applicable, especially in light of the paradoxical role of some risk factors. Treatment strategies for the context of CVD and RD involve cardiologic drugs and modulator therapy for a common purpose which is the control of the disease activity.

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