Review

Atherosclerosis in Sjögren's syndrome: evidence, possible mechanisms and knowledge gaps

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ABSTRACT

Inflammation has been associated with higher cardiovascular risk in rheumatic autoimmune diseases like rheumatoid arthritis (RA) and systemic lupus erythematosus. More recently, primary Sjögren's syndrome (pSS) was also demonstrated as an independent risk factor for cardiovascular disease, emerging as a new interesting model to study atherosclerosis in autoimmune diseases. Patients with pSS have a higher prevalence of developing traditional cardiovascular risk factors like hypertension and dyslipidaemia predisposing for endothelial dysfunction and premature atherosclerosis. However, the disease-specific mechanisms for premature atherosclerosis in pSS are not fully understood. The aim of this review was to critically analyse the current literature on cardiovascular risks in pSS and to discuss the traditional and disease-associated risk factors. We also suggest possible new mechanisms that should be explored in future research to close the current knowledge gaps on the association of pSS, premature atherosclerosis, and clinical cardiovascular disease.

Introduction

Atherosclerosis remains an important cause of death and morbidity worldwide, accounting for 15.6 million or 29.6% of global deaths in 2010. This number is twice the number of cancer deaths, and atherosclerosis is more common as cause of death than all other communicable, maternal, neonatal, and nutritional disorders taken together (1). Among Europeans, cardiovascular disease (CVD) continues to cause a particularly higher mortality burden in women, attributable to stroke and other cardiovascular diseases, while in men, coronary artery disease (2) is the main cause of death (3). Beyond mortality, morbidity has an important social-economic impact. The total direct and indirect cost of CVD and stroke in the USA is estimated to be $315.4 billion, according to published data in 2014 (4). Atherosclerosis is characterised by the presence of atherosclerotic plaques in the systemic arteries, which are formed by lipid deposits together with infiltration of monocytes, neutrophils, and T cells covered by fibrous cap composed mostly of collagen produced by the vascular smooth muscle cells. The recruitment of inflammatory cells, in all stages of the disease, is directed by chemokines, adhesion molecules, and their receptors (5, 6). Chemokines are expressed by activated endothelial cells, smooth muscle cells, and emigrated leukocytes. They not only control emigration but also exert non-chemotactic function that controls activation and cell homeostasis (7).

CVD is a frequent and potentially severe complication of autoimmune rheumatic disease and it is well known in systemic lupus erythematosus (8) and rheumatoid arthritis (RA) (9-11), and now primary Sjögren's syndrome (pSS) emerges as an independent risk factor for cardiovascular disease (12, 13). pSS occurs in 0.01%–0.5% of the general population (14-16), and it is more common in females, especially those in their fifties (17). It is a chronic autoimmune inflammatory rheumatic disease, with slow and progressive evolution, characterised by a lymphocytic infiltrate that affects the epithelium of the exocrine glands, primarily the salivary and lacrimal glands, which leads to a decrease in tear and saliva production. In addition to the glandular manifestations, there are systemic manifestations in the lungs, nervous system, and kidneys and a higher risk of lymphoma (18, 19).

The aim of this review was to critically analyse the current literature on cardiovascular risks in pSS and to discuss the known traditional and disease-associated risk factors. We also suggest new mechanisms for accelerated atherosclerosis that should be explored in future research in pSS. Improved understanding of atherosclerosis mechanisms in pSS can give insights about the interaction between inflammatory autoimmune disease and the development of premature CVD.

Review of the literature on cardiovascular risk in primary Sjögren's syndrome

New evidence of cardiovascular event in Sjögren's syndrome

Recent studies from different countries had evaluated cardiovascular events as outcomes in pSS (13, 20-23). The prevalence of stroke and myocardial infarction was higher in large cohort, including 788 pSS and 4774 age-matched healthy controls, from Italy (13). Similar to RA and SLE (9), the risk found for myocardial infarction (21) and ischaemic (20) and haemorrhagic stroke (20, 22) was 2-fold higher in pSS compared with the general population, among patients from Sweden hospitalised for immune-mediated disease between 1987 and 2008 (20, 21), and from England between 1999 and 2011 (22). Data from the national cohort from Taiwan did not confirm a higher risk for stroke in pSS (23). This study was very well designed and investigated whether pSS increased the risk of ischaemic stroke in a large, nationwide cohort with adjustment for age, gender, and comorbid disorders. In another hand, other studies were not controlled or retrospective. Currently, some registries of pSS in different countries are being conducted. Some effort should be spent to bring more information about cardiovascular event in pSS.

Endothelial dysfunction and higher subclinical cardiovascular organ-damage in primary Sjögren's syndrome

It is well known that cardiovascular events are preceded by subclinical organ-damage in the arteries and heart, including structural and functional changes related to atherosclerosis. In pSS, higher subclinical cardiovascular organ-damage or subclinical atherosclerosis has been described by different methods (Table I) (12, 24-36). It indicates a higher risk for cardiovascular event among patients with pSS, and that the atherosclerotic process is accelerated in this disease.

Vaudo *et al*. (25), were the first to propose and to observe subclinical cardiovascular organ-damage in pSS. They studied 37 patients *versus* 35 age-matched controls and had observed higher intima-media thickness (IMT) in the patients than in the controls in both the carotid and femoral arteries, and almost half of the patients showed carotid intima-media thickening (25). This result could not be reproduced by 2 other smaller studies (31, 35). However, among 64 Greek pSS patients, increased arterial wall thickening (IMT>0.9mm) was detected in approximately two-thirds of primary pSS patients, and the presence of pSS was as an independent risk factor for arterial wall thickening (12). The protocol to evaluate IMT used by this group was similar and of high quality as Vaudo *et al*.

In a pilot study using the ankle-brachial index (ABI) to detect subclinical cardiovascular end-organ damage in patients with pSS, the 20% of pSS patients *versus* only 4% of controls had an abnormal ABI (ABI <1), but the study was underpowered to show a statistical difference. The authors also pointed out that the subgroup of patients with longstanding disease was more likely to have an abnormal ABI than those newly diagnosed, suggesting that the duration of the disease as well as more modern disease-modifying treatment may influence incident atherosclerosis in pSS (29).

Aortic stiffness reflects the mechanical tension and elasticity of the aorta, and it is an independent risk factor for CVD and mortality (37). Increased aortic stiffness has been reported in pSS and was associated with presence of left ventricular diastolic dysfunction (32). Another echocardiographic study showed higher left ventricular mass among patients with pSS (38).

Flow-mediated dilation (FMD) is endothelial-dependent and nitrate-mediated vasodilatation (NMV) is endothelial-independent. Pirildar *et al*. (24) have demonstrated that FMD, but not NMV, was impaired in pSS (n=25) compared with controls (n=29), indicating endothelial dysfunction in pSS. Similar results were confirmed in a study by Akyel *et al*. (2012). They found that FMD of the brachial artery was impaired in 35 pSS patients compared with 20 age- and sex-matched healthy controls despite similar cIMT in the groups, suggesting endothelial dysfunction to precede subclinical cardiovascular organ-damage (31). On the contrary, Gerli *et al*. found no FMD differences between pSS patients (n=45) and controls (n=59), while NMV was impaired in pSS patients. They proposed that involvement of the muscle component in the media layer of the arterial wall is more important than the primary breakdown in nitric oxide (NO) release (26). The authors discussed that the discrepancy between FMD and NMV could be a result of the possible hyperactivation of endothelial NO production. Activation of neuronal and endothelial NO synthase was described in pSS as a consequence of increased production of antibodies against muscarinic acethylcholine receptors (39). Endothelial dysfunction is the primary event in the natural history of atherosclerosis and the disease duration difference between studies of Gerli *et al*. (>8 years) (26) and Pirildar *et al*. (<4 years) (24) could explain why only Pirildar *et al*. found FMD impairment. Higher VCAM-1 and intercellular adhesion molecule-1 (ICAM-1) levels and the correlation with NMV as demonstrated by Gerli *et al*. indicated that both endothelial and smooth cells are involved in pSS atherosclerosis (26).

Recently, a large number of methods to detect subclinical atherosclerosis, such as asymmetric dymethil arginine (ADMA), arterial stiffness by pulse-wave velocity (PWV), coronary flow reserve (CFR), carotid IMT (c-IMT), and echocardiography, were evaluated in a small (n=22) case control-study. Higher ADMA levels and higher PWV indicating higher arterial stiffness, and

lower CFR were found in pSS (33). Another recent study confirmed higher PWV, especially under 50 years (36).
Taking all results together, it seems that pSS has a higher risk for impaired endothelial function, coronary flow reserve, arterial stiffness, and carotid intima-media thickening, all indicating subclinical cardiovascular organ-damage explaining the higher cardiovascular risk.

Higher traditional risk factors could partially explain higher cardiovascular risk in primary Sjögren's syndrome

As in SLE, traditional risk factors are increased in pSS as found in three cohorts from Spain, United Kingdom, and Italy (13, 30, 34), and could explain, at least partially, a higher cardiovascular risk in pSS.
In a transversal study including 624 patients from Spain, higher frequencies of diabetes (27% *vs*. 13%, $p<0.001$) and hypertriglyceridaemia (22% *vs*. 15%, $p<0.023$) in patients with pSS were observed. Interestingly, lower frequencies of hypertension (30% *vs*. 46%, $p<0.001$) and smoking (19% *vs*. 31%, $p<0.001$) were found. Higher hypertension in control group could be explained by a selection bias. Control group included patients from primary care in follow-up to prevalent diseases such as hypertension. Interestingly, pSS patients who received treatment with corticosteroids had higher prevalence of hypertension, dyslipidaemia, and hypertriglyceridaemia (30). Higher prevalence of hypertriglyceridaemia was also confirmed in a large cohort from the United Kingdom Primary Sjögren's Syndrome Registry, including 543 well-characterised patients and 478 healthy controls (34). High triglycerides can reflect higher abdominal adiposity and metabolic syndrome; it is also associated with reduced fibrinolysis, which may explain the higher prevalence of thrombotic cardiovascular events like acute myocardial infarction and ischaemic stroke.
In the same registry, it was also observed that pSS patients have a 2-fold higher prevalence of hypertension, and that it is underdiagnosed and suboptimally treated in pSS (34). Research in hypertension has revealed gender differences in cardiac adaptation to chronic pressure overload. Women with hypertension more often have left ventricular hypertrophy than their male counterparts, and women also have more residual hypertrophy even after systematic antihypertensive treatment (40). Atherosclerosis and arterial stiffness can affect cardiac load and the success of antihypertensive treatment (41). In pSS, little is known on cardiac structural and functional changes including the cardiac effect of antihypertensive treatment and the effect of disease-modulating treatment on blood pressure.
The prevalence of smokers was low in previous studies in pSS (30, 34). This may be related to aggravation of xerostomia by smoking, or reflecting patient education about the health risks of tobacco use. Additionally, considering that pSS affects more women and that tobacco is more common among men, smoking seems to be a less relevant risk factor in pSS.
In the same line, an Italian population-based cohort including 1343 pSS and 4774 age-matched healthy controls, found that patients had more cardiovascular event, hypertension and hypercholesterolaemia, and low frequencies of smoking, diabetes, and obesity (13). In particular, the central nervous system involvement and the use of immunomodulating therapy were identified as risk factors for future cardiovascular events (13).
Previous studies have demonstrated dyslipidaemia including lower HDL (27, 28, 42) and hypertriglyceridaemia (30, 34), rather than hypercholesterolaemia (13) to be associated with pSS. Metabolic syndrome (MetS), reflecting a clustering of cardiovascular risk factors including obesity, hypertension, low HDL cholesterol, hypertriglyceridaemia and impaired glucose metabolism, is emerging as an important risk factor in pSS. Sabio *et al*. (36) reported that MetS in pSS patients was associated with increased arterial stiffness measured by pulse wave velocity. The association of MetS with arterial stiffness was recently reported also in young patients with ischaemic stroke (41). The association of clustering of cardiovascular risk factors with arterial stiffness in pSS should be further investigated exploring the association of pro-inflammatory cytokine profile with subclinical cardiovascular structural and functional alterations.
Even not fully understanding why inflammatory diseases can potentiate and interact with traditional cardiovascular risk factors, these are modifiable factors with potential impact in decreasing cardiovascular risks in pSS. From this point of view, the aggressive diagnosis and treatment of traditional risk factor should probably be included in the management strategies of pSS on an empirical basis.

Gaps in knowledge about cardiovascular risk factors associated with the disease itself

New evidences have shown that cardiovascular risk is also higher in pSS even after controlling the traditional factors indicating that disease itself is an independent risk factor for cardiovascular disease (12, 36). In SLE, higher disease activity, disease duration, neuropsychiatric and/or renal manifestation, and glucocorticosteroid therapy, are also associated with cardiovascular events (9-11, 43). In pSS, there are scarce studies demonstrating that patients with more severe, systemic and with longstanding disease could be under higher risk. A large Italian cohort showed that higher prevalence to MI and stroke was associated with the central nervous system or lung involvement, and longstanding disease (13). In this cohort, patients with leucopenia had higher risk for angina (13). Subclinical cardiovascular organ-damage and endothelial dysfunction were related to CRP, leukopenia, anti-SSA-Ro (25, 36, 42), Raynaud phenomenon (24), joint involvement and parotid enlargement (42).
The higher frequency of traditional risk factors seems to be linked to disease features. In a Spanish cohort, patients with at least 3 cardiovascular traditional risk factors were older, had more liver and central nervous system involvement, and higher levels of CRP. Interestingly, these patients had a lower

Table I. Studies of endothelial dysfunction, subclinical atherosclerosis and cardiovascular risk factors in primary Sjögren's syndrome.

Author (9)	Sample size	Mean age (years)	Disease duration	Cardiovascular risk factors and subclinical atherosclerosis	Biomarkers	Results
Pirildar, 2005 (21)	25 SS (European criteria, 1996)	47.1 ± 9.7	35 (6-120) months	FMD NMV	---	Patients with pSS had endothelial dysfunction and it was associated with Raynaud phenomenon.
Vaudo, 2005 (22)	37 SS (AECG) *vs*. 35 HC	48 ± 14	>3 years	IMT (carotid and femoral) Traditional risk factors	Homocysteine CD4/CD8 Anti-oxLDL IgM/IgG Anti-Hsp60 IgM/IgG Anti-Hsp65 IgM/IgG AECA s-Thrombomodulin hs CRP	Carotid atherosclerosis is associated with pSS and presence of anti-SSA-Ro AECAs and sTM were higher in pSS
Gerli, 2006 (25)	37 SS (AECG) *vs*. 35 HC	53.5 ± 12.3	12 ± 8.4	Total cholesterol, LDL. HDL, triglycerides	---	HDL is lower in SS Anti-SSA-Ro/SSB-La patient subgroup has lower HDL
Lodde, 2006 (24)	46 SS (AECG) *vs*. 12 Sicca Syndrome	53.5 ± 12.3	12 ± 8.4	Cholesterol (total, LDL, HDL)	---	Total and HDL cholesterol in lower in pSS
Rachapalli, 2009 (26)	25 SS (AECG) *vs*. 25 HC	61.8 ± 9.1	8.7 ± 3.2	ABI Traditional risk factors	---	No difference between groups. Longstanding disease subgroup had lower ABI, not related to aging.
Gerli, 2010 (23)	45 SS (AECG) *vs*. 59 HC	44 ± 8	9.1 ± 6.2	FMD NMV Traditional risk factors	s-VCAM-1 s-ICAM-1 nitrotyrosine hsCRP homocysteine	Endothelial dysfunction was associated with parotid enlargment, joint involvement or positive RF No difference compare to controls. ESR, sVCAM-1, sICAM-1 and nitrotyrosine were higher in pSS.
Perez-De-Lis, 2010 (27)	312 SS (AECG) *vs*. 312 HC	49.5 ± 1.52	-----	Traditional risk factors	CRP	Higher frequency of diabetes hypertriglyceridaemia and lower hypertension and smoking Cardiovascular risk factors was associated with aging, liver and central nervous system involvement, CRP and hypogammaglobulinaemia Corticosteroid associated with cardiovascular risk factors
Akyel, 2012 (28)	35 SS (AECG) *vs*. 20 HC			cIMT FMD	---	Carotid atherosclerosis was similar between groups. Patients had endothelial dysfunction.
Çiçek, 2013 (29)	50 SS *vs*. 47 HC	42.8 ± 8.3	---	2D echocardiography Aortic stiffness	---	Patients had left ventricular diastolic dysfunction and it was correlated with aortic stiffness measurements
Juarez, 2014 (31)	543 SS (AECG) *vs*. 473 HC	59 ± 12.4	---	Traditional risk factors	CRP	Patients had higher CRP, hypertrygliceridemia, hypertension, lower smoking.
Atzeni, 2014 (30)	22 SS (ACR 2012) *vs*. 22 HC	60.14 ± 7.81	3.8 ± 0.6 years	Dypiridamole transthoracic stress echocardiogram (wall motion and CRF) Arterial stiffness PWV cIMT	Plasma ADMA CRP	Patients showed endothelial dysfunction (higher ADMA) and subclinical atherosclerosis (higher PWV) No difference in c-IMT, CRF.

Author (9)	Sample size	Mean age (years)	Disease duration	Cardiovascular risk factors and subclinical atherosclerosis	Biomarkers	Results
Zardi, 2014 (32)	18 pSS *vs*. 18 OA (older patients)	65 ± 5.93	6.5 years	IMT	---	No difference between groups
Sabio, 2015 (33)	44 pSS *vs*. 78 HC	52 (44-56)	7 (3-9) years	PWV	25 (OH) vitamin D homocystein fibrinogen	pSS has higher subclinical atherosclerosis measured by aortic stifness (PWV). Disease Damage index and traditional risk factors were independent risk to PWV. Homocystein was higher in pSS
Gravani, 2015 (10)	64 pSS *vs*. 77 RA *vs*. 60 HC	57.2 ± 12.4	8.4 ± 7.0	IMT Carotid plaque	Wnt signalling mediators BMD	pSS emerged as an independent risk factor for arterial wall thickening after adjusting for age, sex, hypertension, smoking (pack/years), LDL and HDL levels [adjusted OR 95% (CI): 2.8 (1.04-7.54] Wnt signalling mediators are potentially involved in the pathogenesis of atherosclerosis and low BMD

SS: Sjögren's syndrome patient; HC: healthy controls; AECG: American-European Consensus Group; IMT: intima-media thickness; cIMT: carotid intima-media-thickness; ESR: erythrocyte sedimentation rate; hsCRP: high-sensitivity C-reactive protein; VCAM-1: vascular cell adhesion molecule 1; ICAM-1: intercellular adhesion molecule 1; FMD: flow-mediated dilation; NMV: nitrate-mediated vasodilation; sTM: soluble thrombomodulin; oxLDL: oxidised low-density lipoprotein; Anti-Hsp60: anti-heat shock protein 60 antibody; Anti-Hsp65: anti-heat shock protein 65 antibody; AECA: anti-endothelial cell antibody; CRF: coronary reserve flow; PWV: pulse-wave velocity; ADMA: asymmetric dimethylarginine; SSDI: Sjögren's syndrome disease index; ESSDAI: Eular Sjögren's syndrome disease activity index; OA: osteoarthritis; BMD: bone mineral density.

frequency of hypogamma-globulins. Gamma-globulins are markers of disease activity, but a decrease in their levels may indicate transformation to lymphoma (30) or a more severe disease. Also, the leukopenia and anti-SSA-Ro subset of patients have shown lower HDL (25, 27, 28).

Autoantibodies anti-Ro-SSA and anti-La-SSB are markers of the disease, and are associated with systemic manifestation. Surprisingly, 2 studies did not find any association between subclinical atherosclerosis and cardiovascular event with the presence of anti-Ro-SSA and anti-Ro-SSB (13, 36). Actually, patients with positive anti-La-SSB had higher frequency of normal PWV (36), and patients with anti-Ro-SSA showed lower level of hypertension and hypertriglyceridaemia (13). Further and larger studies are necessary to understand why anti-Ro-SSA or anti-La-SSB patients have less traditional cardiovascular risk factors, even having more systemic and severe disease.

Together with anti-Ro-SSA and anti-La-SSB, focal lymphocytic inflammatory infiltration, are the 2 more specific characteristics of the disease. A higher focus score (1 foci is more the 50 aggregated lymphocytes per 4 mm^2 of glandular tissue) and the presence of germinal-like centre (GC) pSS in labial salivary glands are associated with a more severe subset of patients characterised by different cytokines (44, 45) and genetic (46-48) profiles. It is associated with more lymphomas, more systemic manifestations (49) and probably more cardiovascular risks. Only one study investigated focus score and found association with IMT (12). Future studies should investigate if the GC subset of pSS patients also carries a higher cardiovascular risk.

Among RA patients, a higher disease activity was independently associated with greater left ventricular relative wall thickness pointing the importance of disease activity control to prevent progression to clinical heart disease (50). On the other hand, currently, anti-inflammatory and immune-modulation therapies against atherosclerosis are being tested and discussed (51). In pSS, only 2 studies evaluated disease activity measured by EULAR Sjögren's syndrome disease activity index (ESSDAI) and did not find a correlation with subclinical cardiovascular organ-damage (12, 36). Actually, chronic damage (evaluated by Sjögren's syndrome damage index - SSDI) but not disease activity (evaluated by ESSDAI) was associated with higher PWV after adjusting for Framingham score (36). A single evaluation of disease activity, measured by disease activity index does not directly reflect previous inflammation, but damage index identifies patients with more severe diseases in the past and that most likely have used more glucocorticoid or immunosupressant therapy. Further studies should evaluate disease activity measured by ESSDAI or immunological parameters, and if higher ESSDAI at the time of pSS diagnosis can predict risk for atherosclerosis development.

The metabolic side effects of glucocorticoids are well known, contributing to the pathogenesis of atherosclerosis. In pSS, glucocorticoid therapy was independently associated with higher cardiovascular event risk in a Italian cohort (13). Otherwise, hydroxychloroquine in patients with systemic autoimmune diseases, including SS, has been demonstrated to be associated with a beneficial effect on lipid profile and insulin sensitivity(52-54). Hydroxychloroquine potentially can be a protective

factor in the cardiovascular risk in pSS as it is known in SLE (36).

Few studies have evaluated atherosclerosis biomarkers in pSS. Of potential importance to the pathogenesis of atherosclerosis were higher anti-endothelial cell antibody (AECA), soluble trombomodulin (sTM) (25), VCAM-1, nytrosine (26), ADMA (33) in recent smaller studies, while normal levels of heat-shock protein (anti-Hsp60 and anti-Hsp65) (25), antibodies anti-oxidised lipids (anti-oxi-LDL) were found, conflicting results regarding elevated or normal levels of homocysteine were reported (25, 36, 42). These were all tested in small study samples, and the results need further verification in larger studies.

High-sensitivity C-reactive protein (CRP) is the main known biomarker of inflammation and cardiovascular risk (34). Some authors found a higher risk of hypertension and diabetes and high levels of CRP in patients with pSS (30, 34). However, other authors found no correlation between CRP and intimal thickening (25) or PWV (36). CRP is not usually increased in pSS and most patients have mild and slow progressive disease, pointing that CRP is probably not the best biomarker for inflammation in pSS. New biomarkers for inflammation and cardiovascular disease should be explored.

Possible mechanisms for atherosclerosis in primary Sjögren's syndrome

The mechanisms of atherosclerosis in SLE as well as other inflammatory autoimmune diseases are higher traditional risk factors, side effects of medication, production of atherogenic pro-inflammatory cytokines, and imbalance between the damage and repair of the endothelium (55). pSS is an autoimmune inflammatory chronic disease sharing some clinical and immune characteristics with SLE. Based on similarities with lupus and on some characteristics of the disease, we present possible new mechanisms involved in cardiovascular risk in pSS (Fig. 1).

pSS is more common in women in their fifties concomitant to the menopausal period when the female hormonal protective cardiovascular effect is fainting. Also, because of the pSS symptoms of fatigue, depression, and associated low quality of life, pSS patients probably have a sedentary lifestyle that could worsen their metabolic profile. The role of symptoms and lifestyle in atherosclerosis of pSS and other autoimmune diseases should be better studied.

Castejon *et al*. showed that SLE patients with reduced circulating endothelial progenitor cells have pathological arterial stiffness and a higher frequency of cardiovascular risk factors (56, 57). Endothelial damage is also a possible mechanism for atherosclerosis in pSS. Recently, it was demonstrated that pSS patients display higher endothelial microparticle (58), endothelial progenitor cells (EPC), and mature EPC cell numbers, but EMP is directly related to disease duration and ECP is inversely related to disease duration, indicating that the reparative capacity of the endothelial layer appears to be preserved in the earliest stages of the disease. However, during the course of the disease, progressive exhaustion of the precursor endothelial pool leads to defective vascular layer restoration and endothelial dysfunction (59). Some biomarkers to endothelial cell damage were higher in pSS, such as AECAs (60), sTM (25), adhesion molecules (VCAM-1 and ICAM-1) (26) and ADMA (33). It would be interesting to know if the very precocious biomarker of endothelial lesion, the endothelial progenitor cells, is related to endothelial dysfunction measures in pSS like it seems to be in SLE (56).

Autonomic symptoms are common among patients with pSS and may contribute to the overall burden of symptoms and link with systemic disease activity (61, 62). In pathological conditions such as atherosclerosis, hyperactivation of sympathetic neural activity has pro-atherogenic effects on the vascular function by increasing vasoconstriction, accumulation of modified lipoproteins in the vascular wall, induction of endothelial dysfunction, and stimulation of oxidative stress and vascular remodelling (63).

Some genetic susceptibility to atherosclerosis in pSS could be assigned by interferon-I (INF-I) signature and disadvantageous paraoxonase 1 (PON1) phenotype distribution. pSS is associated with INF-I signature (64) and serum activity of IFN-I is increased in the atherosclerotic plaque. It also impairs EPC, promotes angiogenesis and is associated with subclinical atherosclerosis and endothelial dysfunction in SLE (65).

Decreased PON-1 activity was observed in pSS patients and it was described in several systemic autoimmune diseases, including SLE (66). PON-1 is a calcium-dependent ester hydrolase that can prevent LDL oxidation by hydrolysing lipid peroxides in the lipoprotein, thus having an important anti-atherogenic function. Lower LDL and Apo-A1 were found in pSS patients, and it was proposed that there was more a reduction of anti-atherogen than an increase of pro-atherogen process (67).

Atherosclerosis and autoimmune diseases like pSS are both inflammatory conditions that share the same pro-inflammatory cytokines. It is interesting to observe that some cytokines such as IL-1β, INF-α, macrophage inflammatory protein-1 (MIP-1), monokine induced by interferon-γ (68) and monocyte chemoattractant protein-1 (MCP-1) associated with GC in pSS are also very important in the atherosclerotic process (5, 45). Those cytokines and other risks, rheumatoid arthritis (69) and lupus (70, 71), and periodontal diseases (72) such as TNF-α and IL-6, associated with atherosclerosis in the general population (73-75) should be investigated (76).

Calgranulins are expressed and secreted by neutrophils, granulocytes, and phagocytes, and they bind receptors of advanced glycation end products (RAGE) expressed on vascular smooth muscle cells, mononuclear phagocytes, and endothelial cells. Then, calgranulins modulate inflammatory reaction, through encoding of pro-inflammatory cytokines related to atherogenesis, such as IL-6, IL-1β, and TNF-α. Some calgranulins, such as S100A12 and S100A8/A9 (calprotectin) are predictors to cardiovascular event in healthy (77-79) and end-stage renal disease (79). They are increased and correlated with disease activity in both SLE (80) and pSS (81). In RA, calprotectin was reduced and associated with the improvement of aortic elasticity after 1

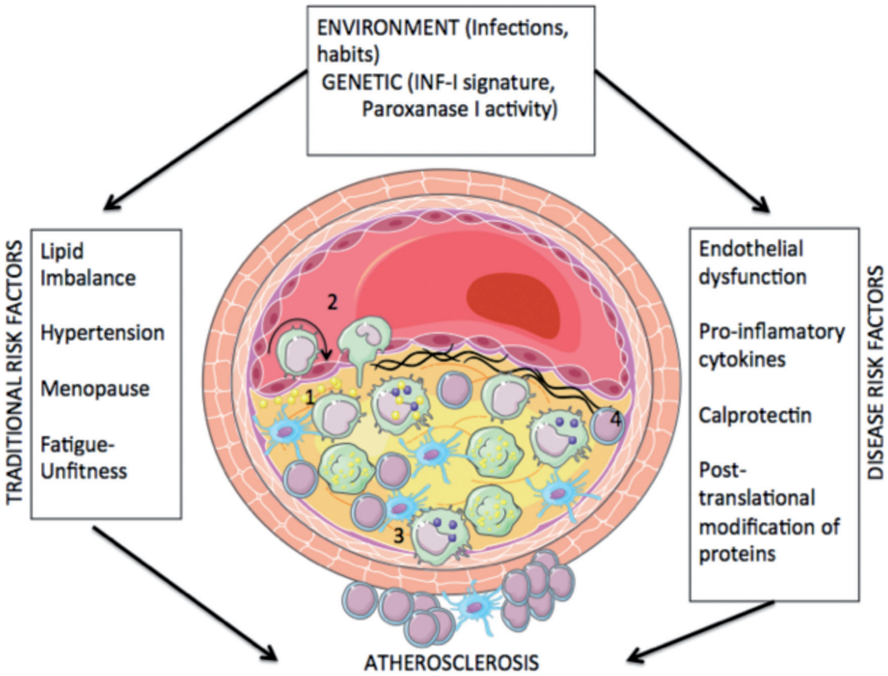

Fig. 1. Possible mechanisms of atherosclerosis in Sjögren's syndrome. Genetic and environmental factors increase traditional risk factors and activate the autoimune process. LDL in the subendothelial space is prone to oxidative stress. SS patients have low HDL not enough to prevent LDL oxidation (1). Higher traditional risk factors, such as hypertension, hypertrigliceridemia, and metabolic syndrome cause lipid imbalance. Fatigue and low quality of life contributes to a sedentary lifestyle. Menopause and unfitness worse lipid balance. Modified lipids activate endothelial cells and macrophages to produce adhesion molecules, like vascular cell adhesion molecule-1 (VCAM-1) and E-selectin, and also chemokines that are important to attract monocytes, dendritic cells (DCs), and T cells into the intima (103). Lipids can trigger pattern recognition receptors (PRRs) of innate immunity as well as serve as autoantigens for cellular and humoral immune reactions. Inflammation is amplified (3). Vascular smooth muscle cells infiltrate plaque and form fibrous cap (4). In SS, the production of atherogenic pro-inflammatory cytokines and endothelium dysfunction can accelerate atherosclerosis. Higher calprotectin and post-translational modified proteins can amplify inflammation. Both are atherogenic and can be implicated in SS. The image was produced using Servier Medical Art.

year of treatment with anti-tumoural necrosis factor-α (anti-TNF-α).

Oxidative stress was not properly examined in pSS and should be examined in future studies. It is a very important mechanism of atherosclerosis because it modifies LDL. Lipids are an important trigger to initiate the atherosclerotic process. Oxidation not only leads to the release of bioactive lipids, but it also causes modification of the remaining LDL particles. These bioactive lipids activate endothelial cells and macrophages to produce adhesion molecules and chemokines that are important to attract monocytes, dendritic cells (DCs), and T cells into the intima. Uptake of modified LDL particles, such as oxidised-LDL (oxi-LDL), through scavenger receptors leads to the intracellular accumulation of cholesterol that can activate the inflammasome, leading to interleukin-1β (IL-1β) secretion (5). The presence of auto-antibodies to oxidised lipids (anti-oxLDL) indicates oxidative stress. It was demonstrated (82, 83) to be higher in SLE but similar to controls and not associated with subclinical atherosclerosis in pSS (25). However, a higher level of nytrosine was found, indicating involvement of oxidative stress (26).

Post-translational modifications of proteins and lipoproteins, such as carbamylation of LDL (84, 85) and carbonylation of fibrinogen (86), lead to alteration in their structure and function, being associated with higher cardiovascular risk in healthy (84, 87) and renal populations (88). Post-translational modifications of apoA-1 transform its anti-inflammatory molecule into a pro-inflammatory one (89, 90). In SLE, pro-inflammatory HDL is associated with the presence and progression of carotid atherosclerosis plaque (90). Carbamylation has been found to be associated with chronic inflammatory conditions and it could influence the atherogenic process in chronic inflammatory rheumatic diseases (91) like RA (92, 93), SLE, and pSS.

Infections, such as periodontal infection could also contribute to the pathogenesis of atheroma. Periodontal disease (PD) is among the most prevalent chronic infections in humans and the prevalence and incidence of CVD are significantly increased in this population (94). A recent meta-analysis, including 1,748 individuals and 18 trials, showed that PD treatment reduces serum hsCRP, IL-6, TNF-α, fibrinogen, and HDL (95), and also improved endothelial function (96). Some studies have shown an increase in the frequency and risk of PD in pSS. Olate et al., in a non-controlled cross-sectional study, observed a 90% prevalence of periodontal inflammation in 35 patients (97). In 212 Senegalese patients, the risk of periodontal disease in pSS was 5-fold compared with healthy controls (98). Interestingly, in a limited-sized case-control study, pSS patients showed higher plaque, gingival and clinical attachment indexes, ProBind depth, and bleeding upon probing (99). The large bias in these studies was to include patients with primary and secondary SS. They also had limited and poorly characterised samples. In spite of the controversial results from studies with methodological bias and a few number of individuals, the correlation between atherosclerosis and PD in pSS should be investigated. Several inflammatory biomarkers are elevated in PD, such as CRP, metalloproteinase (MMP-3 and MMP-8) (100), fibrinogen, and pro-inflammatory cytokines (IL-6, IL-1b, TNF-α) (101). Many of these cytokines are both associated with pSS and with cardiovascular disease.

It is interesting to consider all rationally proposed mechanisms, especially because they should be very similar in all autoimmune diseases, and pSS could be an interesting model to study cardiovascular disease, as most patients are out of medication. Arterial inflammation seems to be particularly important for heart failure in women, while fibrosis seems to be more important in men (102). Because the vast majority of

pSS patients are women, the model is of particular importance for closing the knowledge gap on the prevention and management of cardiovascular disease in women.

Take-home messages

Traditional risk factors like hypertension, hypertriglyceridaemia, dyslipidaemia, and metabolic syndrome are more prevalent in pSS than in the general population.

Preliminary studies show that pSS has impaired endothelial function and coronary flow reserve, and increases arterial stiffness and carotid intima-media thickness, all reflecting subclinical atherosclerosis. A 2-fold risk for cardiovascular events like myocardial infarction and stroke has been documented in pSS, suggesting that traditional cardiovascular risk factors in pSS patients should be meticulously diagnosed and empirically intervened on to prevent progression from subclinical atherosclerosis to cardiovascular events. Fatigue, sedentary lifestyle, endothelial dysfunction, interferon-I (INF-I) signature and disadvantageous paraoxonase 1 (PON1) phenotype distribution, higher levels of calprotectin, periodontal disease, and post-translational modifications of proteins are possible mechanisms involved in atherosclerosis in pSS that should be targeted in future research.

Future studies should aim to investigate if traditional cardiovascular risk factors and disease-associated risk factors are correlated with a cardiovascular event and precocious subclinical atherosclerosis. If there is a subtype of patients under higher risk, like disease activity, presence of germinal centre-like lesions, and positive serology, they should also be investigated.

pSS emerges as an interesting model to study inflammation in atherosclerosis in autoimmune disease, particularly in women.

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