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Understanding Cardiovascular Risk in Primary Sjögren's Syndrome: Essential Insights for Patient Care

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ABSTRACT

Sjogren's syndrome (SS) is an autoimmune rheumatic disease that primarily affects women aged 40 to 60. It manifests as either Primary Sjogren's Syndrome (pSS) or Secondary Sjogren's Syndrome (sSS), the latter associated with other connective tissue diseases like Rheumatoid Arthritis (RA) and Systemic Lupus Erythematosus (SLE). pSS is characterized by lymphocytic infiltration leading to symptoms such as dry eyes and mouth, but can also have extra-glandular manifestations affecting various organ systems, including the cardiovascular system. This review highlights the interplay between cardiovascular disease (CVD) risk and pSS, focusing on both traditional and disease-specific risk factors.

Recent studies indicate that pSS patients have an elevated risk of major adverse cardiovascular events (MACEs), influenced by traditional risk factors like hypertension and dyslipidemia, alongside immunological factors unique to pSS. Notably, patients with pSS exhibit higher levels of subclinical atherosclerosis despite similar Framingham Risk Scores compared to the general population. The role of inflammation and immune dysregulation in the pathogenesis of CVD in pSS is explored, emphasizing biomarkers such as calprotectin and DKK1 that link inflammatory processes to atherosclerotic progression.

Therapeutic interventions, including hydroxychloroquine (HCQ), show potential in mitigating cardiovascular risks, while the effects of glucocorticoids and NSAIDs remain contentious. This review underscores the need for a tailored approach to cardiovascular risk assessment in pSS, considering both traditional and unique immunological determinants. The findings call for further research into the mechanisms linking CVD and pSS and the efficacy of targeted therapies in improving cardiovascular outcomes for affected patients.

Keywords: *Sjögren's Syndrome; rheumatic diseases; autoimmune diseases; autoimmunity; cardiovascular disease; CVD risk.*

1. INTRODUCTION

Sjogren's syndrome is categorized as an autoimmune rheumatic disorder, manifesting either as Primary Sjogren's Syndrome (pSS) or secondary (sSS) to other connective tissue diseases such as Rheumatoid Arthritis (RA) or Systemic Lupus Erythematosus (SLE). This syndrome typically affects individuals between the ages of 40 and 60 and is significantly more prevalent in women compared to men [1-3]. The hallmark symptoms of this condition include keratoconjunctivitis sicca (dry eyes) and xerostomia (dry mouth), which result from lymphocytic infiltration of the lacrimal and salivary glands, respectively. Importantly, lymphocytic infiltration can also impact extra-glandular organs, including the lungs and thyroid, and may involve the gastrointestinal tract, vasculature, kidneys, as well as central or peripheral nervous systems, with hematological implications [4,5]. Cardiovascular complications are infrequently associated with Primary SS, with acute pericarditis and myocarditis being rare occurrences. A unique complication related to neonatal lupus in adult patients is congenital heart block linked to anti-SSA antibodies, which can also present as a cardiovascular manifestation of PSS [6-9].

Cardiovascular disease (CVD) is frequently a major contributor to morbidity and mortality in patients with RA and SLE. Research shows a correlation between endothelial dysfunction and systemic inflammation, leading to chronic systemic vasculitis, which may result in the formation of atherosclerotic plaques and consequently CVD. However, the pathophysiology of atherosclerosis in pSS remains unclear. Patients with SS may experience necrotizing vasculitis affecting

medium-sized vessels that bears resemblance to polyarteritis nodosa (PAN), although it is uncertain if this is a direct cause of atherosclerosis [10,11].

Evaluating the risk of CVD can be achieved through measuring pulse wave velocity (PWV) or assessing artery intima-media thickness (IMT). Several studies suggest a possible link between subclinical atherosclerosis and arterial stiffness in pSS, indicating a potential progression towards CVDs [12,13].

2. CARDIOVASCULAR RISK IN SJOGREN'S SYNDROME

Patients with primary Sjogren's Syndrome (pSS) can experience both conventional and specific risk factors for cardiovascular (CV) issues. A recent study has revealed two distinct patterns in how CV events are distributed among individuals with SS. One pattern indicates that traditional risk factors substantially coincide with glandular involvement, while the other pattern associates longer disease duration and extra-glandular disease manifestations (such as purpura, leukopenia, cryoglobulinemia, and hypocomplementemia) with CV events [14]. Numerous studies suggest that the likelihood of major adverse cardiovascular events (MACEs) and cardiovascular disease (CVD) is increased in patients with pSS. One in-vestigation identified an elevated risk for cerebrovascular events (RR = 1.46 [95% CI 1.43-1.49]; P < 0.00001) as well as coronary events (RR = 1.34 [95% CI 1.06-1.38]; P = 0.001), noting that both clinical and immunological factors, in addition to traditional CV risk factors, play a role in CV events [15,16]. Another study confirmed the link to CVD (OR = 1.30 [95% CI 1.09-1.55]; P = 0.03) but did not find a substantial difference in the risk of cerebrovascular events (OR = 1.31 [95% CI 0.96-1.79]; P = 0.09). Interestingly, the risk of cardiovascular mortality among pSS patients does not seem to be elevated when compared to the general population, which contrasts with findings in RA or SLE. This positions pSS as a unique case among autoimmune disorders regarding its CV risk factors, MACEs, and cardiovascular mortality [17].

2.1 TRADITIONAL CARDIOVASCULAR RISK FACTORS

The diversity among pSS patients regarding age and comorbidities complicates the assessment of traditional risk factors. Various studies present mixed results; some cohorts indicate that certain traditional risk factors are more common in pSS patients, while others suggest that these factors are equally common with those not specifically identified [18,19]. For instance, some studies report that hypertension, hy-pertriglyceridemia, and metabolic syndrome have a twofold higher prevalence, while conditions like smoking, obesity, and diabetes are reported as less common. Conversely, other research suggests a twofold increased prevalence of diabetes mellitus in pSS patients. Notably, diabetes mellitus appears to be more prevalent in cohorts of Spanish patients, highlighting the importance of genetic and metabolic factors; the shared autoimmune characteristics between pSS and diabetes mellitus have also been established in prior research [20,21]. Increased levels of extraglandular manifestations (EGM) and elevated CRP levels are linked with CV risk factors, while there is a lower frequency of hypergammaglobulinemia and anti-Ro antibodies. The reasons for these risk factors in patients with pSS remain uncertain, especially regarding hypertension and dyslipidemia, with potential contributors including disease duration, activity, and treatment [22-24]. For example, corticosteroid treatment in pSS patients is associated with a higher prevalence of CV risk factors, notably diabetes mellitus, hypertension, and hypertriglyceridemia. As a result, the evaluation and management of traditional and modifiable CV risk factors are still inadequate, similar to other rheumatological conditions. Another possible explanation involves the underrepresenta-tion of women (who represent the majority of pSS patients) in cardiovascular studies; CVDs in women are often underdiagnosed and undertreated, leading to an underrecognition of CV risk factors, which hampers effective management [25,26]. Patients with autoimmune diseases, particularly those with rheumatoid arthritis (RA), exhibit a heightened risk for cardiovascular issues. In the general population, the risk of CVD, MACEs, and cardiovascular mortality is assessed using various validated risk scores. For RA patients, the Systemic Coronary Risk Estimation (SCORE) should be multiplied by 1.5 for a more precise as-sessment. However, pSS does not appear to require a separate risk reassessment in existing risk scores [27,28]. Data indicate that individuals with pSS have a significantly increased level of subclinical ath-erosclerosis, evidenced by greater arterial wall thickening and higher pulse wave velocities (PWVs) compared to a control group. Nonetheless, their Framingham Risk Scores are comparable to those of the general population, meaning that the application of CV prediction tools for pSS patients remains the same as for the general population [29,30]. The accuracy of CV risk estimates for pSS patients is still being questioned. If these estimates reflect the true CV risk, the relevance of how accurately various risk scores predict MACEs and cardiovascular mortality in individuals with pSS continues to be a pertinent topic [31].

2.2 SPECIFIC RISK FACTORS AND POSSIBLE MECHANISMS

The importance of immune and non-traditional risk factors in cardiovascular diseases (CVDs) is increasingly being recognized. Recently, a new subset of patients, identified as SMuRF-less (those lacking standard modifiable cardiovascular risk factors) but exhibiting elevated CV risk, has emerged [32-34]. Although this group is growing, it often goes unnoticed. Notably, individuals in this category who ex-perience acute coronary syndrome exhibit higher in-hospital mortality rates compared to those with at least one SMuRF. This trend is particularly evident among women and is critical for accurately assessing the real CV risk of patients with pSS, given that non-traditional, overlooked risk factors are linked to both patient groups [35,36].

While the specific contribution of these factors to CV risk remains unclear and is often underesti-mated, particular mechanisms have been identified in pSS patients. These include immunological, thrombotic, and pro-atherogenic processes, as well as antibody-mediated endothelial dysfunction, neu-trophil activation, and elevated pro-inflammatory cytokines. Additionally, the lipid paradox observed in other autoimmune conditions is relevant here [37-39]. This phenomenon describes the inverse relationship between an increased CVD risk and decreased levels of low-density lipoprotein (LDL) amidst active in-flammation. Conversely, biological therapies that reduce inflammation can positively influence vascular risk markers, despite potentially raising LDL levels, possibly due to changes in the composition of high-density lipoprotein (HDL) particles [40,41].

Neutrophil extracellular traps (NETs), formed during a controlled process known as NETosis, have been implicated in the progression of conditions such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), pSS, and potentially atherosclerosis [42,43]. While not exclusive to pSS, NETosis is rec-ognized as a pathogenic factor in heart failure and represents a common pathway for the development of CVDs in the context of pSS. Investigating NETosis could enhance our understanding of the cardiovascular profiles of patients with autoimmune diseases, including pSS [44,45].

Patients with pSS frequently face hematological abnormalities, particularly leukopenia and lym-phopenia, which serve as markers for disease activity. Leukopenia specifically indicates vascular damage in pSS, correlating with macrovascular endothelial-independent dysfunction and intima-media thickening [46-50]. Even in the absence of traditional cardiovascular risk factors, leukopenic patients have been shown to be at significantly higher risk for developing angina [51,52].

Oxidative stress is another non-traditional risk factor for CVDs. Recent studies have revealed lower levels of paraoxonase-1 (PON) in patients with Sjogren's Syndrome, a protein that protects LDL particles from oxidation. Notably, PON levels in SS patients appear unaffected by steroid use, which typically influences LDL particle levels [53-56].

Elevated production of cytokines, including interleukin (IL)–1β and IL–6, sustains the inflammatory response. In pSS, this persistent inflammation is driven by dysregulated B and T lymphocyte activation. Increased levels of these cytokines (IL-1β, IL-6) and C-reactive protein (CRP) contribute to the progression of atherosclerosis independent of LDL particle levels. Interestingly, pSS patients with metabolic syndrome exhibit heightened IL-1β levels, underscoring the significance of this marker in CV risk evaluation for pSS patients [57-59].

2.3 TREATMENT AND THE CARDIOVASCULAR RISK

As a chronic systemic condition, primary Sjogren's Syndrome (pSS) necessitates various treatment modalities over both the short and long term, influencing comorbidities and cardiovascular (CV) risk. In pSS, traditional and specific CV risk factors often overlap. Hydroxychloroquine (HCQ) has been found to offer a protective effect on cardiovascular health, leading to a reduced prevalence of CV risk factors among pSS patients [60-63]. The administration of HCQ is associated not only with lower mortality rates and a reduced likelihood of coronary artery disease (CAD) but also with beneficial effects on endothelial function and pro-inflammatory cytokine modulation [64-66].

Non-steroidal anti-inflammatory drugs (NSAIDs) are typically linked with a heightened risk of major adverse cardiovascular events (MACEs) within the general population. Nevertheless, their usage does not appear to significantly elevate the risk of MACEs for patients with pSS [67-69]. Likewise, although glucocorticoids (GC) are known to be connected with dyslipidemia, diabetes, and CAD, they do not significantly impact the risk of CV events in pSS patients, likely due to lower dosing and shorter treatment durations. Immunosuppressive treatments have been observed to potentially increase CV event risks, but their specific effects on patients with SS remain inadequately explored [70,71].

Multiple studies have indicated that biological therapies may provide benefits independent of lipid-lowering effects. Reports have shown lower CV risk and MACEs in both the general population and among individuals with autoimmune

diseases. Although biological therapies have exhibited positive effects on subclinical atherosclerosis in rheumatoid arthritis, their impact on pSS remains to be conclusively determined. To date, no disease-modifying drugs have received approval for pSS, and previous trials involving biological therapies have not yielded definitive results [72-75].

3. ATHEROSCLEROSIS IN SS: THE CONTRIBUTION OF INFLAMMATION

Recent research has demonstrated that patients with Sjogren's Syndrome (SS) experience approximately a 1.5-fold elevated risk of cardiovascular disease (CVD) and cerebrovascular incidents compared to the general population, similarly to the risks associated with rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) [76-78].

In multivariate analyses, pSS has been identified as a predictor of a higher likelihood of subclinical atherosclerosis, independent of traditional cardiovascular risk factors. Certain traditional risk factors, including hypertension, dyslipidemia, and metabolic syndrome, are found to be more common in individuals with SS than in the general population [79,80]. Consequently, these factors may contribute to a greater incidence of subclinical atherosclerotic damage and an increased risk of cardiovascular events. However, the interplay between conventional cardiovascular risk factors and the immune and inflammatory characteristics specific to the disease requires further investigation [81-83].

3.1 ROLE OF IMMUNITY

The development of early atherosclerosis in patients with Sjogren's Syndrome (SS) is largely influenced by dysregulation of immune responses. Two specific markers associated with systemic manifestations of pSS are anti-SSA and anti-SSB antibodies, which contribute to the disruption of the endothelial layer and an increase in arterial intima-media thickness [84]. It has been proposed that the damage to smooth muscle cells in the media layer of blood vessels may result from cellular infiltration in the subendothelial space, alongside elevated serum levels of adhesion molecules such as ICAM-1 and VCAM-1. The heightened expression of these molecules on the endothelial surface is believed to facilitate the infiltration of leukocytes into the arterial wall, ultimately leading to atherosclerotic damage. Additionally, patients with circulating anti-SSB antibodies have shown a greater prevalence of normal aortic stiffness, indicating early dysfunction of large arteries [85,86]. This condition is typically reversible and can be influenced by increased inflammatory response intensity, rather than solely by immune dysregulation, as seen in polymyalgia rheumatica. Interestingly, patients with systemic sclerosis (SSc) have not exhibited any significant changes in aortic stiffness or stiffness of the upper limb arteries, likely due to the markedly reduced inflammation observed in SSc. This further underscores the critical role of inflammation and immune regulation in the progression and manifestations of atherosclerotic damage to arterial walls [87,88].

3.2 ROLE OF INFLAMMATION

The role of inflammation in atherosclerotic damage among patients with Sjogren's Syndrome (SS) remains uncertain. Certain inflammatory biomarkers and markers of endothelial damage have been linked to an increased risk of subclinical atherosclerosis and overt cardiovascular disease (CVD) in SS. Multiple studies have found elevated levels of C-reactive protein (CRP) in SS patients; however, this increase has not been directly correlated with a heightened risk of atherosclerosis or cardiovascular events. For instance, a Spanish study reported elevated CRP levels associated with traditional cardiovascular risk factors [89-91]. Additionally, one study found a relationship between CRP levels and carotid to femoral pulse wave velocity (PWV), indicating inflammation's potential relevance in arterial stiffness. Nevertheless, levels of CRP or high-sensitivity CRP (hsCRP) in most patients did not differ significantly from the general population and were not linked to subclinical atherosclerosis or cardiovascular events, suggesting that systemic inflammation is typically low in SS cases [92,93].

Calprotectin, a complex of S100A8 and S100A9, is considered a potential marker for atherosclerosis in SS. This pro-inflammatory factor of innate immunity is abundantly found in neutrophil cytoplasm and has a pro-inflammatory effect on endothelial cells. Calprotectin acts as an endogenous damage-associated molecular pattern molecule, activating TLR-4 cells with released cellular debris [94-96]. In the context of SS, this mechanism links atherosclerosis to inflammatory processes that contribute to the disease's progression. Increased levels of S100A8/A9 have been noted in both the glands and bloodstream of SS patients, correlating with focus scores and with higher expressions of IL-1β, IL-6, TNFα, IFNγ, IL-10, IL-17A, and IL-22 [97,98]. The involvement of self-antigens has been identified in the induction of type I interferon release by TLR9 activation, particularly in cases of hepatosteatosis and various components of metabolic syndrome. Additionally, CRP levels have been shown to correlate with levels of Calprotectin, indicating its importance in CVD assessment beyond traditional risk factors, especially concerning coronary heart disease (CHD), where it may influence disease pathogenesis via inflammatory processes [99-101].

The WNT signaling pathway is a crucial regulator of inflammatory processes, including cardiac and vascular development. The soluble Dickkopf WNT signaling pathway inhibitor 1 (DKK1) has been linked to atherosclerosis, as it is overexpressed on endothelial cells and in atherosclerotic plaques, thereby enhancing the interaction between platelets and the endothelial layer [102,103]. Consequently, DKK1 contributes to local inflammation, plaque destabilization, and rupture. Furthermore, plasma DKK-1 levels are known to correlate with hs-CRP, serving as an independent predictor of cardiovascular events. An inverse relationship has been observed between DKK1 levels and plaque formation in patients with pSS, paralleling findings in diabetic and predialysis patients with chronic kidney disease [104,105]. This could further contribute to atherogenesis and plaque instability by promoting direct expression within symptomatic plaques through a DKK-1-driven inflammatory loop that may operate within atherosclerotic lesions. The purinergic P2X7 receptor (P2X7R)-NLRP3 inflammasome complex, particularly in its role in caspase-1-mediated IL-18 release, is associated with the pathogenesis of focal lymphocytic sialadenitis in SS. This suggests that the mechanisms linking the inflammatory pathogenesis of glandular infiltration in SS to the inflammatory components of arterial wall atherosclerotic damage require further investigation [106-108].

3.3 ENDOTHELIAL CELL DAMAGE

The gathered data do not clarify the direct role of inflammatory biomarkers in the development of atherosclerosis within the context of Sjogren's Syndrome (SS), as elevated levels of endothelial activation markers may suggest additional mechanisms contributing to the heightened cardiovascular risk in these patients [109,110]. An increase in circulating endothelial microparticles has been noted in SS patients, particularly in those with a longer duration of the disease. This observation indicates a progressive depletion of the endothelial precursor pool, which leads to impaired vascular healing and, subsequently, chronic endothelial damage and fragmentation.

Several markers of endothelial activation, including soluble thrombomodulin (sTM), nitrotyrosine, and plasma asymmetric dimethylarginine (ADMA), have been found at elevated levels in SS patients compared to controls [111-113]. sTM is a soluble fragment of thrombomodulin, a membrane glycoprotein involved in regulating fibrinolysis and coagulation, serving as an indicator of endothelial injury. Increased serum sTM levels have been associated with coronary artery disease (CAD), stroke, and peripheral occlusive arterial disease. Moreover, sTM is considered particularly relevant to atherosclerotic lesions due to its mitogenic effects on vascular smooth muscle cells, which may promote atherosclerosis [114,115].

The presence of nitrotyrosine-modified proteins in both plasma and atherosclerotic lesions of CAD patients highlights oxidative stress as a potential contributing factor to atherosclerosis in SS. This conclusion is supported by animal studies that indicated the occurrence of 3-nitrotyrosine modifications in mice predisposed to atherosclerosis. The infiltration of inflammatory cells into the subendothelial space correlates with the generation of reactive oxygen species (ROS) and nitrogen species (RNS), which can modify proteins and lipids. Nitric oxide (•NO)-derived oxidants often change the activity of target molecules during post-translational modifications [116-118]. Such protein nitration fosters interactions between oxidative stress and inflammation, thereby facilitating plaque development and rupture.

Oxidative stress also contributes to the generation of oxidized low-density lipoprotein (ox-LDL), which is significantly linked to various stages of atherosclerosis. Higher levels of ADMA indicate endothelial dysfunction and suggest increased oxidative stress, as ADMA acts as a nitric oxide synthase inhibitor. In the context of SS, both ADMA and nitrotyrosine may serve as potential markers for atherosclerosis and cardiovascular risk. Likewise, elevated levels of ICAM-1 and VCAM-1 could result from chronic endothelial damage caused by the infiltration of inflammatory cells into the arterial wall [119-120].

4. CONCLUSION

In summary, Sjogren's syndrome (SS) presents a complex interplay between autoimmune dysfunction and cardiovascular risk. Patients with Primary Sjogren's Syndrome (pSS) experience a significantly elevated risk of cardiovascular disease (CVD) and major adverse cardiovascular events (MACEs), influenced by both traditional and disease-specific risk factors. The insights gained from this review highlight the importance of recognizing the multifaceted nature of cardiovascular risk in pSS, moving beyond conventional as-sessment methods to include unique immunological markers and mechanisms.

Key factors such as inflammation, immune dysregulation, and associated biomarkers (e.g., calpro-tectin, DKK1) play a critical role in the pathogenesis of atherosclerosis in pSS patients. While traditional cardiovascular risk factors are prevalent, the distinct characteristics of pSS necessitate a tailored approach to monitoring and managing cardiovascular health.

Future research should focus on elucidating the specific pathways linking SS to increased cardio-vascular risk and evaluating the long-term effects of current and emerging therapies on cardiovascular outcomes. By integrating comprehensive cardiovascular risk assessments with targeted therapeutic strategies, we can improve care for patients with pSS, aiming to reduce both morbidity and mortality related to cardiovascular diseases. Continuous efforts in research and clinical practice are essential to enhance our understanding and management of cardiovascular risks in this unique patient population.

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