Original Article

Primary Sjögren's syndrome as independent risk factor for subclinical atherosclerosis

Marta Novella-Navarro[1] , José Luis Cabrera-Alarcón[2] , José Luis Rosales-Alexander[3] ,
Jorge Juan González-Martín[1] , Ofelia Carrión[4] , Paloma García de la Peña[1]

Abstract

Objective: To assess the prevalence of subclinical atherosclerosis in patients with primary Sjögren's syndrome (pSS) and its possible association with clinical and analytical parameters of the disease.
Methods: In this cross-sectional study, 38 consecutive patients with pSS were compared with 38 age and sex healthy controls. Demographic variables and classic cardiovascular risk factors (CVRFs): Hypertension, dyslipidemia, diabetes mellitus, obesity, and smoking habit were assessed in both groups, and also disease-related features were collected in pSS group. The presence of subclinical atherosclerosis was assessed by carotid ultrasound, with carotid intima-media thickness (CIMT) measurement and determination of the presence of atheromatous plaques.
Results: Subclinical atherosclerosis presence was remarkably greater in patients with pSS than in healthy controls (OR = 4.17, 95%CI [1.27-16.54]), as well as CIMT values (0.79 ± 0.43 mm vs. 0.66 ± 0.27 mm; P = .02). No differences for classic CVRFs were found between both groups. An association of subclinical atherosclerosis with erythrocyte sedimentation rate (ESR) and rheumatoid factor (RF) was observed in patients with pSS.
Conclusion: This cohort showed a greater prevalence of subclinical atherosclerosis in patients with pSS, indicating this disease as an independent risk factor for presence of early vascular damage.
Keywords: Primary Sjögren's syndrome, cardiovascular disease, carotid ultrasound, inflammation

ORCID iDs of the authors:
M.N.N. 0000-0002-2200-0859;
J.L.C.A. 0000-0003-2880-509X;
J.L.R.A. 0000-0002-1643-8088;
J.J.G.M. 0000-0002-3169-0206;
O.C. 0000-0002-7344-824X;
P.G.P. 0000-0001-6586-6903.

[1] Department of Rheumatology, Hospital Universitario Sanchinarro, Madrid, Spain
[2] Bioinformatic Unit, GENOXPHOS-group Centro Nacional de Investigaciones Cardiovasculares (CNIC), Madrid, Spain
[3] Department of Rheumatology, Hospiten Rambla, Santa Cruz de Tenerife, Spain
[4] Department of Vascular Surgery, Hospital Universitario Sanchinarro, Madrid, Spain

Address for correspondence:
Marta Novella-Navarro; Department of Rheumatology, Hospital Universitario Sanchinarro, Madrid, Spain

E-mail: mnovellanavarro@gmail.com

Introduction

Primary Sjögren's syndrome (pSS) is a chronic systemic disease mainly involving the exocrine glands. Studies investigating incidence and prevalence of pSS show heterogeneous results, so epidemiology of this syndrome remains poorly defined.[1] Although pSS mainly involves exocrine glands, 30-40% of cases present extraglandular manifestations that will determine the prognosis of the disease.[2,3] Available data on some comorbidities associated with this disease are still scarce,[1] although in recent years interest has increased in the study of interstitial lung disease, infections, tumors and cardiovascular (CV) pathologies in pSS patients.[4,5]

Atherosclerosis identification and cardiovascular risk (CVR) characterization in autoimmune diseases have been marked by increase in evidence in the literature, due to both a greater knowledge about the involved pathophysiological mechanisms and greater accessibility to noninvasive techniques, i.e., carotid ultrasound. Therefore, these patients show a greater prevalence of subclinical vascular damage and a higher incidence of CV events, and for this reason, numerous studies define autoimmune diseases as independent risk factor for CV morbidity and mortality. In particular, this fact has been analyzed concerning rheumatoid arthritis (RA) and other inflammatory arthropathies in which cardiovascular morbidity and mortality are clearly increased compared to the general population[6,7] due mostly to chronically sustained inflammation, greater prevalence of classic cardiovascular risk factors (CVRFs), and the potential effect of some drugs like glucocorticoids.[8]

For other connective tissue diseases (CTDs) like systemic lupus erythematosus (SLE) generally affecting young women (a population that is not usually at high risk for developing CVR), an increase in CVR has been observed when compared to the general population.[9,10] Other studies performed in systemic sclerosis (SSc) have also found an increase in CVR in these patients, evidencing the coexistence of macrovascular damage.[11-13] Nevertheless, there are fewer available studies on pSS than in other clinical entities. For this reason, the aim of this study was to assess presence of subclinical atherosclerosis by means of carotid

ultrasound in patients with pSS and to analyze clinical, analytical, and CVRFs along with their potential association with the presence of subclinical cardiovascular involvement.

Methods

This is a cross-sectional study including 38 pSS patients according to American–European Consensus classification criteria 2016,[14] and 38 age- and sex-matched healthy controls, recruited from the outpatient consults. The study was carried out in accordance with the Helsinki's declaration principles, and informed consent was obtained from all participants. All subjects were ≥18 years old. Patients with sicca syndrome not having pSS and those with Sjögren's syndrome secondary to any other chronic inflammatory disease were excluded. For both groups, history of CV events (stroke, myocardial infarction, and angina) was exclusion criteria.

Variables related to classic CVRFs were collected in both groups: smoking habit (as dicotomic variable), hypertension (HT), diabetes mellitus (DM), dyslipidemia (DL), and body mass index (BMI). Total cholesterol (TC), HDL-cholesterol (HDLc), LDL-cholesterol (LDLc), triglycerides, homocysteine, vitamin D, complete blood count, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) were measured. For pSS patients, antinuclear antibodies (ANA), anti-Ro, anti-La, complement C3 and C4, β2-microglobulin, rheumatoid factor (RF), and immunoglobulins (IgA, IgM, and IgG) were collected. Data of disease activity indexes such as ESSDAI (EULAR Sjögren's syndrome disease activity index)[15] glandular vs. extraglandular affection and treatments (systemic and symptomatic) were also collected.

Carotid intima-media thickness (CIMT) and carotid atheromatous plaque were assessed, and a qualitative variable was created for the presence of pathological CIMT and/or carotid atheromatous plaque, defined as subclinical atherosclerosis.
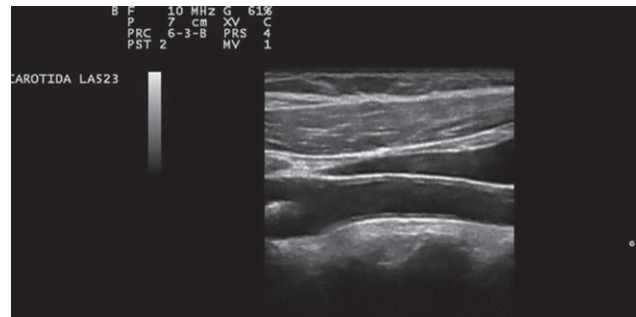
Figure 1. Ultrasound image of carotid intima-media thickness.

A study protocol was established with the vascular surgery department to determine the CIMT measurement and assessment of atheromatous plaques, according to which the physician in charge of the vascular examination was blinded to patients' clinical data.

For ultrasound exploration, Samsung Medison SonoAce R7® (Samsung Electronics Iberia, Madrid, Spain) with a linear transducer of 10 to 15 MHz was used. According to Mannheim consensus,[13] CIMT measurement and atheromatous plaque presence were obtained in: (i) distal portion of the common carotid artery, 1 cm from the carotid bulb, (ii) carotid bulb, and (iii) first portion of the internal carotid artery, 1 cm behind the bulb. Three measurements were manually taken in both carotid axes, and the mean was calculated considering CIMT >0.9 mm as pathological. Still in accordance with Mannheim consensus,[16] atheromatous plaque is a focal structure encroaching into the arterial lumen of at least 0.5 mm or 50% of the surrounding CIMT value, or demonstrating a CIMT thicker than 1.5 mm between arterial lumen and media adventitia (Figure 1).

Statistical analysis

Descriptive analysis was carried out by calculating the frequency for qualitative variables and for quantitative variables such as mean, standard deviation (SD), median, and interquartile range (IQR).

Normality of quantitative variables was assessed by Shapiro–Wilk test. To evaluate differences between patients and controls, t-test, or Wilcoxon test were used for quantitative features and Fisher test for categorical variables.

To test the presence of pSS as an independent risk factor for subclinical atherosclerosis from other features as classic CVRFs or analytical data (CRP, ESR, vitamin D, homocysteine), first we adjusted logistic binomial regression in a bivariate analysis, to select possible predictors to be included in a multivariate analysis. The same analyses were performed to assess disease-related features as risk factors for subclinical atherosclerosis in pSS group.

A multicollinearity study among the variables selected for the multiple regression was performed using Wilcoxon, chi-square, or Fisher test to check pair-wise association between predictors and variance inflation factor for complex association between them. From this point, a stepwise strategy was adopted to decide which variables were to be discarded by comparing the different nested models with an F-test in analysis of variance (ANOVA).

$P < .05$ were considered statistically significant, and for all adjusted models (bivariate and multivariate), the odds ratio (OR) and 95% confidence intervals (CI) were calculated.

All analysis were performed with R-statistics (R version 3.5.0 and R car v3.0-3).

Results

All subjects were women, aged between 32 and 73 (mean ± SD: 53.7 ± 11.7). Table 1 shows demographic characteristics, classic CVRFs, and analytical parameters collected from patients and controls. Significant differences regarding classic CVRFs were not found between both groups, with the exception of ESR values significantly higher ($P < .001$) in pSS patients.

Considered separately, neither the presence of pathological CIMT (>0.9 mm) ($P = .11$) nor the presence of atheromatous plaque ($P = .26$) differed significantly between both groups. Nevertheless, when assessing subclinical atherosclerosis defined by the presence of pathological CIMT and/or carotid atheromatous plaques, it was statistically significant. Subclinical atherosclerosis presence was remarkably greater in pSS patients than in controls (OR = 4.18, CI95% [1.27-16.54]). On the other hand, it was found that CIMT was substantially higher in patients than in controls (0.79 ± 0.43 mm vs. 0.66 ± 0.27 mm; $P = .02$).

Regarding pSS-associated features, disease duration ranged between 4 and 15 years with a mean of 7.23 ± 4.34 years. Approximately 40%

Main Points

- pSS may predispose to early subclinical atherosclerosis.

- Autoimmune conditions including pSS may contribute to develop cardiovascular diseases.

- An early CVR stratification in pSS patients would be advisable to avoid the progression of the atherosclerotic diseases.

Novella-Navarro et al. Primary Sjögren's syndrome

Eur J Rheumatol 2022;9(1):20-25

Table 1. Demographic variables: Patients vs. controls.

	Patients (n = 38)	Controls (n = 38)	P
Age (mean, SD)	53.74 (11.86)	53.66 (11.75)	.97[§]
Gender F:M (n, %)	38:0 (100:0)	38:0 (100:0)	1[‡]
BMI kg/m² (mean, SD)	25.82 (3.99)	24.54 (3.19)	.12[§]
Classic CVRF (n, %)			
HT	7 (18.4)	4 (10.5)	.51[‡]
DL	5 (13.1)	5 (13.1)	1[‡]
DM	1 (2.6)	0 (0)	1[‡]
Smoking habit			.28[‡]
Smoker/ex-smoker	8 (21.1)	5 (13.1)	
Never smoker	30 (78.9)	33 (86.84)	
Cholesterol (median, IQR)			
Total	194 (184-200)	191 (186-210)	.89[¶]
HDL-C	47 (41-55)	55 (45-69)	.20[¶]
LDL-C	122 (107-130)	116 (103-127)	.28[¶]
Triglycerides	133 (91-178)	121 (89-161)	.22[¶]
25-hydroxi-vitamin D (median, IQR)	22 (17-28)	27 (23-32)	.06[¶]
ESR mm/1st h (mean, SD)	22.74 (15.63)	7.34 (5.65)	<.001[¶]
CRP mg/L (mean, SD)	0.67 (1.66)	0.55 (1.12)	.22[¶]
Hyperhomocysteinemia (n, %)	3 (7.89)	2 (5.26)	1[‡]

BMI, body mass index, CVRF, cardiovascular risk factors, HT, hypertension, DL, dyslipidemia, DM, diabetes mellitus, ESR, erythrocyte sedimentation rate, CRP, C-reactive protein.
HDL-c, high-density lipoprotein- cholesterol; LDL-c, low-density lipoprotein- cholesterol.
[‡]Fisher test.
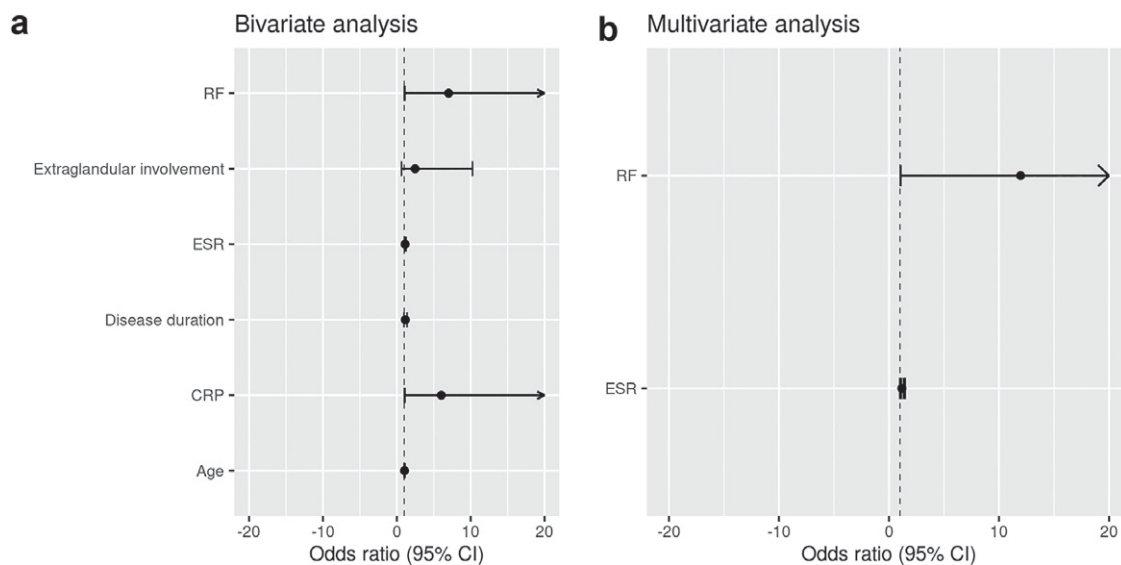[¶]Wilcoxon test with continuity correction.
[§]*T*-test.

Figure 2. a, b. Odds ratio (OR) and 95% Confidence Interval (CI) significant associated risk factors for subclinical atherosclerosis in pSS, with a *P* < .05 in bivariate analysis (a) and in the multivariate model (b). Dashed line represents OR = 1.

of patients had extraglandular involvement, and 75% of patients had low disease activity measured with ESSDAI.

Analyzing all the individuals included in this study in the bivariate analysis, the presence of pSS, HT, age, and ESR were selected as predictors for multivariate model (Table 2), and both predictors presented a VIF > 2. Multivariate model revealed pSS as independent risk factor for subclinical atherosclerosis (OR = 4.18 CI95% [1.27-16.54]).

Subclinical atherosclerosis-associated factors in pSS patients

In the bivariate analysis, subclinical atherosclerosis (atheromatous plaque and/or pathological CIMT) was associated with ESR, CRP and RF, extraglandular affectation, disease duration,

Eur J Rheumatol 2022;9(1):20-25

Novella-Navarro et al. Primary Sjögren's syndrome

Table 2. Results of bivariate and multivariate analyses for the association of subclinical atherosclerosis in all individuals and in pSS patients.

	Global participant's analysis (n = 76)		pSS patients' analysis (n = 38)	
	Bivariate (OR 95% CI)	Multivariate (OR 95% CI)	Bivariate (OR 95% CI)	Multivariate (OR 95% CI)
pSS	4.42 (1.38-17.19)	4.18 (1.27-16.54)	–	–
Age	1.05 (0.99-1.11)	–	1.04 (0.99-1.10)	–
Smoking (yes vs. no)	–	–	–	–
BMI	–	–	–	–
HT	3.68 (0.93-11.33)	–	–	–
DL	–	–	–	-
DM	–	–	–	-
TC	–	–	–	–
LDLc	–	–	–	–
HDLc	–	–	–	–
Triglycerides	–	–	–	–
ESR	1.12 (1.06-1.20)	–	1.12 (1.04-1.25)	1.17 (1-05-1.40)
CRP	–	–	6.02 (1.45-48.58)	–
Hyperhomocis-teinemia	–	–	–	–
Vitamin-D	–	–	–	–
B2-microglobulin	–	–	–	–
Corticosteroids	–	–	–	–
Extraglandular involvement	–	–	2.47 (0.63-10.24)	1.26 (0.14-1.77)
Disease duration	–	–	1.15 (0.98-1.38)	1.26 (0.99-1.77)
ESSDAI	–	–	–	–
RF	–	–	7.01 (1.48-51.7)	11.96 (1.05-239.18)
Anti-SSA/Ro	–	–	–	–
Anti-SSB/La	–	–	–	–
HCQ	–	–	–	–

TC, total cholesterol; LDL-c, low-density lipoprotein-cholesterol; HDL-c, high-density lipoprotein-cholesterol; BMI, body mass index; HT, hypertension; DL, dyslipidemia; DM, diabetes mellitus; TC, total cholesterol; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; ESSDAI, Eular
Sjögren's Syndrome Disease Activity Index; RF, rheumatoid factor; HCQ, hydroxichloroquine.

and corticosteroid treatment (Table 2). There was not association with any of classic CVRFs, age, antibodies, immunomodulating treatment, or ESSDAI. Multivariate model confirmed ESR (OR = 1.17, CI95% [1.05-1.40]), RF (OR = 1.28, CI95% [1.63-2.26]), and disease duration as independent predictors for subclinical atherosclerosis (Table 2, Figure 2).

None of considered predictors in this model presented a VIF > 2. However, in the final multivariate model, ESR (OR = 1.12 CI 95% [1.06-1.20]) and RF (OR = 11.9 CI 95% [1.50-239.19]) were found as independent risk factors for subclinical atherosclerosis in pSS patients (Table 2, Figure 2).

Discussion
Atherosclerosis has been considered as a degenerative process in which age and classic CVRFs play an important role in its development. Nevertheless, the identification of infiltrates of macrophages and lymphocytes in atherosclerotic lesions[17] (suggesting an immune-mediated process), together with the activation of inflammatory mediators that perpetuate vascular damage and antibody formation, has led to the understanding that atherosclerosis might be increased in patients with autoimmune diseases.[18]

The most relevant finding in our study was that pSS is significantly and independently associated with the presence of subclinical atherosclerosis. To date, the study of Gravani et al[19] with 64 pSS patients, 77 RA patients, and 60 healthy controls, is the only study that considered the presence of pSS as an independent risk factor for CIMT increase. In addition, both Gravani et al[19] and our study observed significant differences in pathological CIMT and plaque presence as a determinant of subclinical atherosclerosis between pSS and healthy controls (OR = 2.2, CI 95% [1.02-4.55]). Vaudo et al[20] observed significant differences regarding the mean CIMT between participants in their study (37 pSS patients and 35 healthy controls), although the presence or absence of pathological CIMT was not analyzed. Azteni et al[21] with a smaller sample (22 subjects in each group), also found a greater mean CIMT in pSS patients, but without statistical significance. Ozisler et al,[22] Zardi et al[23] and García et al[24] did not show differences between CIMT and subclinical atherosclerosis in pSS with regard to healthy subjects.

Thus, studies assessing subclinical atherosclerosis in pSS patients are scarce and present varied conclusions. Regarding establishment of a potential relationship between thickening of artery walls and typical serological markers of the disease, Vaudo et

Novella-Navarro et al. Primary Sjögren's syndrome

Eur J Rheumatol 2022;9(1):20-25

al,[20] and Gerli et al[26] found an association between anti-SSA antibody and a higher CIMT in pSS patients. However, our study did not observe any association with these specific antibodies, but it did observe an association with RF that was also described by García et al.[24] The clinical relevance of this finding may be controversial since, on the one hand, it would be expected that the presence of RF in pSS patients might be associated with a greater vascular affectation, due to the physiopathological mechanisms that pSS shares with RA.

On the other hand, it has been postulated that chronic inflammation could play a greater role in inducing an accelerated atherosclerosis compared to the antibodies production. In fact, persistent increase in CRP levels seems to be closely linked to CVR development in both the general population and in AR and SLE patients.[25] Nevertheless, serum CRP levels are similar in pSS patients and in general population, and do not seem associated with arterial wall thickening. Our study confirms these data; differences in CRP and ESR levels were observed between patients and controls in bivariate analysis but when adjusting in multivariate, only ESR showed significant differences between both groups, and it was statistically associated with subclinical atherosclerosis; therefore, we might consider that there is an association between this inflammatory marker and subclinical atherosclerosis in pSS patients although CRP lost the significance, maybe due to the small sample size. Hence, further studies would be necessary to confirm this relation.

As for classic CVRFs, in this study, as well as in other studies analyzing subclinical atherosclerosis,[19-24,26] no significant differences between the patient and control groups nor an association of these factors with CIMT increase or the presence of atheromatous plaque were observed. This result contrasts with data provided by Bartoloni et al[27] in a recent revision, in which observed a significantly higher incidence and prevalence of CVRFs in pSS patients compared to the general population.[27] In our study, there was no evidence of an increase frequency of classic CVRF in pSS patients vs. controls, but it is worth emphasizing that data corresponding to lipid profile could be modified, since both patients and controls with DL were under hypolipemiant treatment at the time of their inclusion in the study. The major limitation of this study is the number of patients in the sample. Additionally, due to the cross-sectional design, the incidence of CV events

could not be analyzed, which probably could have been an objective of interest to determine in these patients.

The presence of subclinical atherosclerosis was significantly higher in pSS patients than in controls, being pSS an independent risk factor for the presence of early vascular affection. These findings led us to consider that early CVR stratification in these patients would be advisable in order to control CVRFs and to avoid the progression of the atherosclerotic disease. However, further studies with a higher number of patients are needed to verify these findings, as well as to assess disease features that might be associated with vascular damage in these patients.

References

1. Qin B, Wang J, Yang Z, et al. Epidemiology of primary Sjögren's syndrome: a systematic review and Meta-analysis. *Ann Rheum Dis*. 2015;74:1983-1989. **[Crossref]**
2. Mariette X, Criswell LA. Primary Sjogren's syndrome. *N Engl J Med*. 2018;378:931-939. **[Crossref]**
3. Fox RI. Sjögren's syndrome. *Lancet*. 2005;366: 321-331. **[Crossref]**
4. Reina D, Roig Vilaseca D, Torrente-Segarra V, et al. Sjögren's syndrome-associated interstitial lung disease: A multicenter study. *Reumatol Clin*. 2016;12(4):201-205. **[Crossref]**
5. Pego-Reigosa JM, Restrepo-Vélez J, Baldini C. Rúa-Figueroa Fernández de Larrinoa Í. Comorbidities (excluding lymphoma) in Sjögren's

syndrome. *Rheumatology* (*Oxford*). 2021 May 14;60(5):2075-2084. **[Crossref]**
6. Castañeda S, Martín-Martínez MA, González-Juanatey C, et al. Cardiovascular morbidity and associated risk factors in spanish patients with chronic inflammatory rheumatic diseases attending rheumatology clinics: Baseline data of the CARMA project. *Semi Arthritis Rheum*. 2015;44:618-626. **[Crossref]**
7. Rosales-Alexander JL, Salvatierra J, Llorca J, et al. Cardiovascular risk assessment in rheumatoid arthritis: Impact of the EULAR recommendations on a national calibrated score risk index. *Clin Exp Rheumatol*. 2014;32:237-242.
8. Meek IL, Picavet HS, Vonkeman HE, et al. Increased cardiovascular risk factors in different rheumatic diseases compared with the general population. *Rheumatology*. 2013;52:210-216. **[Crossref]**
9. Croca S, Rahman A. Atherosclerosis in systemic lupus erythematosus. *Best Pract Res Clin Rheumatol*. 2017;31:364-372. **[Crossref]**
10. Fieri M, Stampf H. Systemic lupus erythematosus and atherosclerosis: Review of the literature. *Autoimmun Rev*. 2016;15:16-21.
11. Dave AJ, Fiorentino D, Lingala B, et al. Atherosclerotic cardiovascular disease in hospitalized patients with systemic sclerosis: Higher mortality than patients with lupus and rheumatoid arthritis. *Arthritis Care Res*. 2014;66:323-327. **[Crossref]**
12. Man A, Zhu Y, Zhang Y, et al. The risk of cardiovascular disease in systemic sclerosis: A population-based cohort study. *Ann Rheum Dis*. 2013;72:1188-1193. **[Crossref]**
13. Gonzalez-Martin JJ, Novella-Navarro M, Calvo-Aranda E, et al. Endothelial dysfunction and subclincal atheromatosis in patients with systemic sclerosis. *Clin Exp Rheumatol*. 2020;125(3):48-52.
14. Shiboski CH, Shiboski SC, Seror R, International Sjögren's Syndrome Criteria Working Group, et al. 2016 American college of rheumatology/European league against rheumatism classification criteria for primary Sjögren's syndrome: A consensus and data-driven methodology involving three international patient cohorts. *Ann Rheum Dis*. 2017;76(1):9-16. **[Crossref]**
15. Seror R, Theander E, Brun JG, et al. Validation of EULAR primary Sjögren's syndrome disease activity (ESSDAI) and patient indexes (ESSPRI). *Ann Rheum Dis*. 2015;74:859-866. **[Crossref]**
16. Touboul PJ, Hennerici MG, Meairs S, et al. Mannheim carotid intima-media thickness and plaque consensus (2004-2006-2011). an update on behalf of the advisory board of the 3rd, 4th and 5th watching the risk symposia, at the 13th, 15th and 20th European stroke conferences, Mannheim, Germany, 2004, Brussels, Belgium, 2006, and Hamburg, Germany, 2011. *Cerebrovasc Dis*. 2012;34:290-296. **[Crossref]**
17. Sanjadi M, Rezvanie-Sichanie Z, Totonchi H, et al. Atherosclerosis and autoimmunity: A growing relationship. *Int J Rheum Dis*. 2018;21: 908-921. **[Crossref]**

18. Libby P. Inflammation in atherosclerosis. *Arterioscler Thromb Vasc Biol*. 2012;32:2045-2051. **[Crossref]**

19. Gravani F, Papadaki I, Antypa E, et al. Subclinical atherosclerosis and impaired bone health in patients with primary Sjogren's syndrome: Prevalence, clinical and laboratory associations. *Arthritis Res Ther*. 2015;17:99. **[Crossref]**

20. Vaudo G, Bocci EB, Shoenfeld Y, et al. Precocious intima-media thickening in patients with primary Sjögren's syndrome. *Arthritis Rheum*. 2005;52:3890-3897. **[Crossref]**

21. Azteni F, Sarzi-Puttini P, Signorello MC, et al. New parameters for identifying subclinical atherosclerosis in patients with primary Sjögren's syndrome: A pilot study. *Clin Exp Rheumatol*. 2014;32:361-368.

22. Ozisler C, Kaplanoglu H. Evaluation of subclinical atherosclerosis by ultrasound radiofrequency data technology in patients with primary Sjögren's syndrome. *Clin Rheumatol*. 2019;38:709-771. **[Crossref]**

23. Zardi EM, Sambataro G, Basta F, et al. Subclinical carotid atherosclerosis in elderly patients with primary Sjögren syndrome: A duplex Doppler sonographic study. *Int J Immunopathol Pharmacol*. 2014;27:645-651. **[Crossref]**

24. García AB, Dardin LP, Minali PA, et al. Asymptomatic atherosclerosis in primary Sjögren syndrome. Correlation between low ankle brachial index and autoantibodies positivity. *J Clin Rheumatol*. 2016;22:295-298. **[Crossref]**

25. Bartoloni E, Alunno A, Cafaro G, et al. Subclinical atherosclerosis in primary Sjögren's syndrome: Does inflammation matter? *Front Immunol*. 2019;10:817. **[Crossref]**

26. Gerli R, Vaudo G, Bocci EB, et al. Functional impairment of the arterial wall in primary Sjögren syndrome: Combined action of immunologic and inflammatory factors. *Arthritis Care Res*. 2010;62:712-718. **[Crossref]**

27. Bartoloni E, Alunno A, Valentini V, et al. The prevalence and relevance of traditional cardiovascular risk factors in primary Sjögren's syndrome. *Clin Exp Rheumatol*. 2018;36(Suppl. 112):113-120.