Arch Rheumatol 2022;37(x):i-ix
doi: 10.46497/ArchRheumatol.2022.8838

ORIGINAL ARTICLE

Lipoprotein-associated phospholipase A2 and carotid intima-media thickness in primary Sjögren syndrome

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ABSTRACT

Objectives: This study aims to evaluate serum lipoprotein-associated phospholipase A2 (Lp-PLA2) level and carotid intima-media thickness in primary Sjögren syndrome (pSS) as an indicator of atherosclerosis.

Patients and methods: Between July 2019 and July 2020, a total of 33 female pSS patients (mean age: 44.5±11.2 years; range, 23 to 60 years) and 37 female age- and sex-matched healthy individuals (mean age: 40.9±7.2 years; range, 25 to 54 years) were included. Carotid intima-media thickness and serum Lp-PLA2 levels were measured in the patient and control groups.

Results: The patients had a higher median serum Lp-PLA2 of 560 (range, 108 to 1,222) ng/mL *vs.* 328 (range, 0 to 1,280) ng/mL in the controls (p=0.024) and a similar mean intima-media thickness of carotid artery (0.64±0.14 mm *vs.* 0.62±0.15 mm, respectively; p=0.595). Serum Lp-PLA2 was positively correlated with platelet count (r=0.411, p=0.018) and negatively correlated with erythrocyte sedimentation rate (r=-0.409, p=0.018). The mean value of carotid intima-media thickness was positively correlated with disease duration (r=0.316, p=0.074) and was negatively correlated with the level of leucocyte (r=-0.458, p=0.007).

Conclusion: Our study suggests that the patients of pSS have a potential risk of atherosclerotic cardiovascular disease, independent of traditional cardiovascular risk factors and disease severity.

Keywords: Atherosclerosis, cardiovascular disease, carotid intima-media thickness, lipoprotein associated phospholipase A2, primary Sjögren syndrome.

Atherosclerosis is a multifactorial process that inflammation has a promoter role in its pathogenesis, suggesting as an inflammatory disease.[1] The evidence of the contribution of inflammation to the course of atherosclerosis has led to investigate the association between atherosclerotic events and rheumatic disease. The increased risk of atherosclerosis and atherosclerotic cardiovascular disease (CVD) in rheumatic diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) has been identified.[2] In this regard, there is a great deal of interest in cardiovascular (CV) risk in primary Sjögren syndrome (pSS). It is due to that, besides some clinical and autoimmune similarities with SLE and RA, pSS has distinguishing features distinct from

Received: March 07, 2021 ***Accepted:*** May 04, 2021 ***Published online:*** October 16, 2021

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Citation:
Gültuna S, Can Sandıkçı S, Kaplanoğlu H, Aydın FN, Özalp Ateş FS. Lipoprotein-associated phospholipase A2 and carotid intima-media thickness in primary Sjögren syndrome. Arch Rheumatol 2022;37(x):i-ix.

other rheumatic diseases, such as characterized by low-grade inflammation, mostly benign nature and slow progression, female preponderance, and less necessity of immunosuppressive treatment.[3] However, the number of studies of CV risk of pSS patients is limited.[4]

Atherosclerotic CVD is still a significant cause of morbidity and mortality; therefore, detection of early stages of atherosclerosis in individuals who have a high risk for CVD is critical. For early detection, applicable and cost-effective methods have a great importance.[5] Lipoprotein-associated phospholipase A2 (Lp-PLA2), which is accepted as a novel inflammatory biomarker of CV risk prediction, is a member of the phospholipase A2 family of enzymes that hydrolyzes phospholipids. The Lp-PLA2 has been accepted as a pro-atherogenic enzyme with a link between lipid metabolism and inflammatory response. It is secreted by monocyte, macrophages, and T cells in the circulation and vascular intima. It binds to apolipoprotein B-100 containing lipoproteins, but primarily related to low-density lipoproteins (LDL). Oxidation of LDL, which occurs by subsequent mechanisms in the arterial wall, induces the progression of atherosclerotic plaque.[6] The Lp-PLA2 hydrolysis of oxidized LDL (oxLDL) to pro-atherogenic metabolites, including lysophosphatidylcholine (lyso-PC) and free fatty acids (FFAs), leads to upregulation of adhesion molecules expression, accumulation of lipid-rich macrophage to atherosclerotic plaque, and leucocyte activation.[7] It has been proven that elevated Lp-PLA2 is an independent marker of CVD.[8] Certain guidelines suggest as a diagnostic test to define patients at high risk who would benefit from lipid-lowering medications.[9] To the best of our knowledge, there are no studies regarding the association between Lp-PLA2 level and subclinical atherosclerosis in patients with pSS.

Accumulation of lipid-rich macrophage, lymphocytes, and smooth muscle cells in the intimal wall leads to the thickness of intima. This stage may proceed to atherosclerotic plaque. Carotid intima-media thickness (CIMT) is considered one of the surrogate markers of subclinical atherosclerosis and predictor of future CVD. In several studies, CIMT has been shown as an endpoint validation for the evaluation of new anti-atherosclerotic drugs.[10] There are few studies to evaluate subclinical atherosclerosis with CIMT in pSS, with contradictory results. In the present study, we aimed to evaluate the potential risk of atherosclerotic CVD in patients with pSS by measuring LP-PLA2 and CIMT, which are the biomarkers of atherosclerosis.

PATIENTS AND METHODS

Study design and study population

This cross-sectional study was conducted at Dışkapı Yıldırım Beyazıt Training and Research Hospital, Rheumatology outpatient clinic between July 2019 and July 2020. A total of 33 eligible patients with pSS (mean age: 44.5±11.2 years; range, 23 to 60 years) who met the 2016 American College of Rheumatology (ACR)/ European League Against Rheumatism (EULAR) classification criteria[11] were included in the study. The control group consisted of 37 female age- and sex-matched healthy individuals (mean age: 40.9±7.2 years; range, 25 to 54 years) without a history of any inflammatory, autoimmune disorder, and CVD. Inclusion criteria for both groups were as follows: age >18 years, having no secondary Sjögren syndrome or concomitant connective tissue disease, renal failure, diabetes mellitus, hypertension, CVD and cerebrovascular diseases, evidence of overt atherosclerotic diseases such as angina pectoris, myocardial infarction, malignancy, active infection, anemia and pregnancy. Only patients who were receiving hydroxychloroquine and a maximum of 7.5 mg/day corticosteroid were included. Exclusion criteria were as follows: systolic blood pressure >140 mmHg, diastolic blood pressure >90 mmHg, overnight fasting plasma glucose >100 mg/dL, total cholesterol (TC) >200 mg/dL, LDL >150 mg/dL, triglyceride (TG) >200 mg/dL, body mass index (BMI) >30 kg/m^2, those receiving treatment with lipid-lowering drugs, antihypertensive, antiaggregant drugs, nitrates or estrogens, and presence of a family history of CVD. All these exclusion criteria were applied to the control group. All patients were examined and interviewed with the standardized questionnaire by a single rheumatologist. Patients' demographic data and medical history, disease related clinical and laboratory data were recorded. Blood pressure was measured, and BMI (body weight in kilograms divided by square of height

in meters) was calculated in all participants. A written informed consent was obtained from each participant. The study protocol was approved by the Dışkapı Yıldırım Beyazıt Training and Research Hospital Ethics Committee (date-no: 22.07.2019-68/12). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Disease severity

The EULAR Sjögren Syndrome Disease Activity Index (ESSDAI) was used for the assessment of the disease activity. It consists of 12 domains related to organ systems as follows: constitutional, articular, renal, respiratory, cutaneous, muscular, peripheral nervous system (PNS), central nervous system (CNS), hematological, glandular, lymphadenopathic, biological with a score ranging from 0-123. For each domain, features of disease activity are classified in three to four activity levels (no, low, moderate, or no, low, moderate, and high). Scores <5 are classified as "low disease activity"; 5 to 13 are a "moderate disease activity", and ≥14 are "high disease activity".[12]

Laboratory assessment

All patients and healthy controls underwent routine laboratory assessment including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), TC, LDL cholesterol, high-density lipoprotein (HDL) cholesterol, TG, and fasting plasma glucose level. Blood samples were drawn after an overnight fast. Serum samples for Lp-PLA2 measurement were obtained from all participants by centrifugation of venous blood and stored at -80°C until analysis.

Lp-PLA2 analysis

The levels of Lp-PLA2 (ng/mL) were measured by Creative Diagnostics enzyme-linked immunosorbent assay (ELISA) kit (Abbexa, 11/2020, Cambride, UK). Concentrations were determined from the curve obtained with the standards.

Carotid ultrasonography (USG)

The CIMT was measured using the USG device, functioned on a MyLab 60 platform (Esaote SpA, Genoa, Italy) with a high-resolution 12-MHz linear sequence transducer (LA523). All participants lied in the supine position with the head 45-degree up and horizontally 30-degree turned contralateral to the side being examined. The measurements were obtained from the posterior wall of the vessel, by detecting the lumen-intima and media-adventitia interfaces, using automated software program. The images were recorded in the longitudinal plane of the carotid system by B-mode USG. The CIMT was measured at 10-mm distal to the common carotid artery where no plaque was visualized. The plaque was defined as a focal protrusion into the vessel lumen of at least 1.5-mm. Imaging was performed by a single radiologist in each participant based on the same imaging parameters such as gray-scale and frequency of scanning probe.

Statistical analysis

Statistical analysis was performed using the SPSS for Windows version 11.5 software (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed in mean ± standard deviation (SD) or median (min-max), while categorical variables were expressed in number and frequency. The Kolmogorov-Smirnov test was used to assess the assumption of normality. The independent samples t-test or the Mann-Whitney U test was used for continuous variables, and the chi-square test was used for categorical variables. The receiver operating characteristic (ROC) curve analysis was used to examine the cut-off value of Lp-PLA2. When a significant cut-off value was achieved, the sensitivity, specificity, positive and negative predictive values were calculated. The association between Lp-PLA2, CIMT and clinical and laboratory data was evaluated using the Spearman correlation coefficient. A two-sided p value of <0.05 was considered statistically significant.

RESULTS

There was no significant difference in the mean age between the groups (p=0.096). The median disease duration was 20 (range, 10 to 120) months. Thirty (90.9%) patients presented with low disease activity, while three patients (9.1%) presented with moderate disease activity. Two (6.1%) patients were antinuclear antibody (ANA)-negative. Granular pattern of ANA was observed in 26 (78.8%) patients, homogeneous in five (15.1%) patients. Granular pattern was positive

Table 1. Demographic, clinical, and laboratory data of study population

	Primary Sjögren syndrome (n=33)					Healthy controls (n=37)					
	n	%	Mean±SD	Median	Min-Max	n	%	Mean±SD	Median	Min-Max	*p*
Age (year)				46	23-60				41	25-54	0.096
Body mass index (kg/m^2)			26.4±2.6					23.5±2.8			<0.001
Smoking	10	30.3				4	10.8				0.042
Duration of pSS from diagnosis (month)				20	1-120				-	-	-
ANA											-
Negative	2	6.1				-	-				
Positive	31	93.9				-	-				
Granular	26	78.8				-	-				
Homogen	5	15.1				-	-				
Anti SSA											-
Negative	3	9.2				-	-				
Positive	30	90.8				-	-				
Anti SSB											-
Negative	21	63.6				-	-				
Positive	12	36.4				-	-				
Rheumatoid factor											-
Negative	14	42.4				-	-				
Positive	19	57.6				-	-				
ESSDAI											-
Low disease activity	30	90.9				-	-				
Moderate disease activity	3	9.1				-	-				
High disease activity	-	-				-	-				
White blood cell			6.2±1.7					6.2±1.5			0.978
Platelet			268.2±81.5					273.4±57.2			0.754
Fasting blood glucose (mg/dL)			81.6±15.5					87.5±6.7			0.048
Total cholesterol (mg/dL)			168.5±27.4					171.5±22.8			0.615
Triglycerides (mg/dL)				88	41-187				85	33-150	0.417
Low density lipoprotein (mg/dL)			112.6±24.8					108.6±18.4			0.452
High density lipoprotein (mg/dL)				51	37-98				55.5	36.2-100.9	0.290
Erythrocyte sedimentation rate (mm/h)				17	3-56				7	2-2	<0.001
C-reactive protein (mg/L)				2.40	0.4-34				1.67	0.3-6.56	0.023

SD: Standard deviation; pSS: Primary Sjögren syndrome; ANA: Anti-nuclear antibody; SSA: Sjögren syndrome related antigen A; SSB: Sjögren syndrome related antigen B; ESSDAI: The EULAR Sjögren's Syndrome Disease Activity Index.

Table 2. Cardiovascular parameters of study population

	Primary Sjögren syndrome			Healthy controls			
	Mean±SD	Median	Min-Max	Mean±SD	Median	Min-Max	*p*
Lp-PLA2 (ng/mL)		560	108 -1,222		328	0-1,280	0.024
CIMT right (mm)	0.6±0.2			0.6±0.2			0.726
CIMT left (mm)	0.6±0.2			0.6±0.2			0.538
CIMT (mean) (mm)	0.6±0.1			0.6±0.2			0.595

SD: Standard deviation; Lp-PLA2: Lipoprotein-associated phospholipase A2; CIMT: Carotid intima-media thickness.

in five (15.2%) patients at a serum dilution of 1/100-1/320, in eight (24.2%) patients at a serum dilution of 1/320-1/1000, in nine (27.3%) patients at a serum dilution of 1/1000-1/3200, and in four (12.1%) patients at a serum dilution >1/3200. Homogeneous pattern was positive in one (3.0%) patient at a serum dilution of 1/100-1/320, in three (9.1%) patients at a serum dilution of 1/320-1/1000, and in one (3.0%) patient at a serum dilution of 1/1000-1/3200. Thirty (90.8%) patients had anti-Sjögren syndrome-related antigen A (anti-SSA) autoantibodies and 12 (36.4%) had anti-Sjögren syndrome related antigen B (anti-SSB) antibodies. Nineteen (57.6%) patients were rheumatoid factor (RF)-positive. Two (6.1%) patients were not taking any drugs for pSS. Twenty-three (69.7%) patients were taking hydroxychloroquine, while eight (24.2%) patients were taking hydroxychloroquine and low-dose steroid. Demographic and clinic characteristics of the study population are shown in Table 1.

The median serum Lp-PLA2 level in patients with pSS was significantly higher compared to controls (560 ng/mL; range, 108 to 1,222 *vs.* 328 ng/mL; range, 0 to 1,280, respectively; p=0.024) (Table 2). The ROC curve analysis revealed that optimal cut-off value for Lp-PLA2 for patients with pSS was 549.5 ng/mL, with a sensitivity, specificity, negative predictive, and positive predictive value of 51.5 (95% confidence interval [CI]: 35.2-67.5%), 81.1% (95% CI: 65.8-90.5%), 65.2 (95% CI: 52.8-75.9%), and 70.8 (95% CI: 58.6-80.8%), respectively (area under curve [AUC]=0.658, 95% CI: 0.528-0.788; p=0.024) (Figure 1).

There were no statistically significant differences between the patient and control groups in terms of the measurements of CIMT (p>0.05) (Table 2).

The Lp-PLA2 was positively correlated with platelet count (r=0.411, p=0.018) and negatively correlated with ESR (r=-0.409, p=0.018). The Lp-PLA2 had no significant relationship with age and BMI (r=-0.159, p=0.376 and r=0.059, p=0.744, respectively). The value of right CIMT was mildly, positively correlated with disease duration (r=0.339, p=0.053), and negatively correlated with leucocyte and platelet count (r=-0.453, p=0.008; r=-0.386, p=0.026, respectively). The value of left CIMT was positively correlated with CRP (r=0.490, p=0.004). The value of mean CIMT was positively correlated with disease

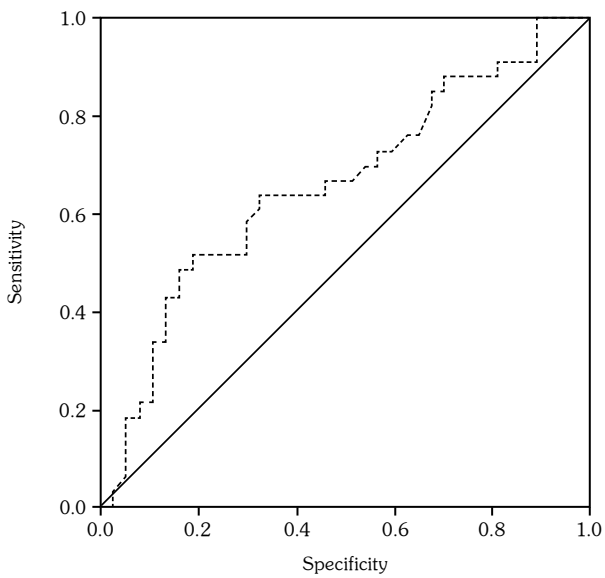

Figure 1. ROC curve for serum Lp-PLA2 levels between patients with pSS and healthy controls.

ROC: Receiver operating characteristic; Lp-PLA2: Lipoprotein-associated phospholipase A2; pSS: Primary Sjögren syndrome.

duration (r=0.316, p=0.074), and negatively correlated with the leucocyte count (r=-0.458, p=0.007). Neither Lp-PLA2 nor CIMT values were correlated with the levels of lipid parameters. Disease duration was negatively correlated HDL level (r=-0.414, p=0.017). In addition, CRP was positively correlated with TC (r=0.432, p=0.012).

DISCUSSION

In the present study, we demonstrated that a higher level of Lp-PLA2 among the pSS patients and similar CIMT values between the groups. We found no significant relationship between the Lp-PLA2 and CIMT. The Lp-PLA2 level was associated with the platelet count and ESR. Disease duration and leucocyte count were associated with the CIMT. To the best of our knowledge, this the first study to assess Lp-PLA2 level as a CV biomarker among pSS patients, through the measurement of the wall thickness of the carotid artery.

The Lp-PLA2 has an important value in predicting the risk of future CV events, in consequence of being independent of the CV risk factors such as smoking, age, BMI, and systolic blood pressure. It has been shown that Lp-PLA2 is correlated with coronary artery endothelial dysfunction. Despite potential differences in the ethnicity for Lp-PLA2 concentration, above 200 ng/mL is recommended as the threshold value for identifying CV events.[13] Based on these findings, higher Lp-PLA2 levels in our study may support the increased CV risk in pSS patients, despite similar CIMT measurements. These results indicate that pSS patients have a risk for CV events from the early stages of the disease. Considering the exclusion of traditional CV risk factors prior to this study, or that most of the patients had mild clinical manifestations, increased Lp-PLA2 levels in our study are an important outcome. Also, it has been well known that medications used for rheumatic disease can affect the CV risk. Antimalarials have a potential protective role in CVD, while corticosteroids have an effect that contributes to the development of CVD.[5,14] We believe that the finding of a high level of Lp-PLA2 despite the hydroxychloroquine use in most of our patients might make our results more valuable. Furthermore, our results suggest that the current treatment of pSS patients has no significant effect on the Lp-PLA2 levels of the patients. In our study, the Lp-PLA2 level was independent of age, BMI, the severity of the disease, and disease duration. It appears that closely monitoring patients with pSS for CV events would be beneficial, regardless of the disease duration, the effect of treatment, or additional CV risk factors.

Contrary to our results, some authors have reported higher CIMT in pSS patients.[15,16] Similar CIMT values between the groups in our study may result from the range of disease duration from diagnosis that relatively shorter than these previous studies.[15,16] In line with our results, Akyel et al.,[17] Atzeni et al.,[18] and Zardi et al.[19] found no significant difference between the groups in terms of the CIMT values, despite longer disease duration. Although no significant difference in the CIMT, Akyel et al.[17] and Atzeni et al.[18] identified endothelial dysfunction as a precursor of subclinical atherosclerosis. Considering that Lp-PLA2 is related to endothelial dysfunction as mentioned previously, it may be thought that this may be the case for our study.

It has been reported that endothelial dysfunction and subclinical atherosclerosis have been related to CRP, anti-SSA, leukopenia, and longer disease duration.[14,15,20-22] Anti-SSA has a role in inducing leukopenia, which is a typical feature of rheumatologic diseases, through apoptotic mechanisms.[15] It has been suggested that there is an association between anti-SSA and leukopenia, and accelerated cell apoptosis on the arterial wall via induced apoptotic cascade, leading to atherosclerosis.[15] Vaudo et al.[15] reported that anti-SSA and leukopenia were the predictors of carotid artery thickening. The authors concluded that their findings supported the link between immune dysregulation and early stages of atherosclerosis in pSS. In a cohort, pSS patients with leukopenia had a higher risk of developing angina.[23] In our study, the CIMT (mean and right) was associated with leucopenia. We believe that our similar results emphasize that immune mechanisms may play a precious role in the development of atherosclerosis, rather than traditional risk factors. However, we could not find any association with the presence of anti-SSA. The differences in the study protocols and number of samples might have led to conflicting

results. In consistent with our results, the presence of anti-SSA was not associated with subclinical atherosclerosis in two other studies.[14,23] Valim et al.[22] showed that it was unknown why anti-SSA and anti-SSB were prone to have less traditional CV risk factors, although these antibodies are related to systemic and more severe clinical features. In addition, CRP is one of the associated risk factors for developing CVD. Considering CRP is usually within normal limits in pSS patients,[22] the relationship between CIMT (left) and CRP in the present study may be a warning sign. The link between thrombocytopenia and CIMT (right) may result from similar mechanisms as in association between leukopenia and CIMT. The other correlation with CIMT in our study was disease duration that could lead to the accumulation of immunological and inflammatory features. Disease duration was also related to low HDL levels in the present study. This could be an important finding, indicating that the suggestion about inflammatory diseases can potentiate or interact with traditional CV risk factors.[22] Low HDL levels have been shown in pSS patients with leukopenia and anti-SSA. This association can be attributed to autoimmune dysregulation.[22,24] Also, it has been hypothesized that anti-HDL cholesterol antibodies may lead to low HDL levels.[25]

The association between Lp-PLA2, which is formerly known as platelet-activating factor (PAF) acetylhydrolase,[8] and platelet count may be hypothesized as a result of interaction via PAF signaling pathways.[26] The Lp-PLA2 is produced by various inflammatory cells,[27] and platelet is one of these cells.[28] This association would be critical that platelet is an easily accessible laboratory parameter, as Lp-PLA2 is suggested as a potential therapeutic target.[29] Interestingly, our results showed a negative correlation of Lp-PLA2 with ESR. It would be of a statistically significance rather than of a clinically significance. Although it cannot be fully interpreted, it may be related to the hypothesis that Lp-PLA2 is more connected with atherosclerosis than systemic inflammation.[30]

The possible mechanisms of atherosclerosis in pSS are thought to be complex interactions between various factors including traditional cardiac risk factors, side effects of medications, immune-mediated mechanisms, and some triggers such as sedentary life due to fatigue.[3,22] Several pathways, including cytokines, chemokines, integrins, and subsets of T and B cells, mediate inflammatory vascular damage in pSS.[31] The higher levels of biomarkers of endothelial cell damage have been detected in pSS[15,22] related to atherosclerosis. Also, genetic susceptibility to atherosclerosis may contribute to the process.

Nonetheless, there are some limitations to this study. First, the sample size is relatively small, due to strict inclusion and exclusion criteria; as such, in our study protocol, we considered an estimated prevalence of pSS of ranging between 0.6 and 1.0%, as previously described.[32] Therefore, further multi-center studies are needed to obtain large series of patients. Second, we could not follow the patients to identify the rate of individuals who would experience CV events.

In conclusion, our study demonstrates that pSS patients have a potential risk of atherosclerotic CVD, independent of traditional CV risk factors and disease severity. Based on these findings, CV risk assessment should be a part of the care of pSS patients to prevent non-fatal and fatal CV events.

Acknowledgements

We thank the staff and participants for their contribution to the study. We are grateful to Gökçe Nebioğlu Erkek for the laboratory assistance.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

This study was financially supported by Dışkapı Yıldırım Beyazıt Scientific Research Project Coordination Unit with the Project No. 74/01.

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