HOW IMPORTANT IS EARLY DIAGNOSIS OF SUBCLINICAL ATHEROSCLEROSIS IN PRIMARY SJOGREN’S SYNDROME PATIENTS?

TOLGA KURT1, FERHAT GOKMEN1, GURHAN ADAM1, SEDAT OZCAN1, ERSAN OZBUDAK1, AYLA AKBAL2, AHMET TEMIZ3, MUSTAFA SACAR4

1School of Medicine, Department of Cardiovascular Surgery, Canakkale Onsekiz Mart University - 2School of Medicine, Department of Physical Medicine and Rehabilitation, Canakkale Onsekiz Mart University - 3School of Medicine, Department of Radiology, Canakkale Onsekiz Mart University - 4School of Medicine, Department of Cardiovascular Surgery, Canakkale Onsekiz Mart University - 5Asist.Prof.Dr., School of Medicine, Department of Physical Medicine and Rehabilitation, Canakkale Onsekiz Mart University - 6Asist.Prof.Dr., School of Medicine, Department of Cardiology, Canakkale Onsekiz Mart University - 7Asist.Prof.Dr., School of Medicine, Department of Cardiovascular Surgery, Canakkale Onsekiz Mart University, Turkey

ABSTRACT

Introduction: Cardiovascular (CV) disease is observed with increasing frequency in patients with systemic vasculitis. The use of carotid intima media thickness (CIMT) and ankle brachial pressure index (ABPI) may help to identify high-risk primary Sjogren’s syndrome (PSS) patients. The objective of this study is to determine abnormal ABPI and CIMT values in the patient group with PSS and compare them clinically and serologically with a control group.

Materials and methods: Our study comprised a total of 124 patients who were diagnosed with PSS according to the American-European Consensus Group Sjogren’s syndrome classification criteria and monitored for more than 3 years, and a control group. CIMT and ABPI measurements were completed by specialists. The patients were also evaluated serologically.

Results: All of the PSS patients had xerophthalmia findings, the second most common symptom was xerostomia. The mean disease duration was 80.4±25.6 months.

Nine PSS patients (41%) had ABPI less than 0.9. In the control group 11 (11%) patients had ABPI less than 0.9. When the two groups were compared, the difference was found to be significant (p<0.05). PSS patients also exhibited a statistically significant increase in mean CIMT values (mm; p<0.05).

When the PSS patients with ABPI less than 0.9 were compared with other PSS patients and the control group, there was no significant difference in terms of anti-Sjogren’s syndrome related antigen A (anti-SSA) and anti-Sjogren’s syndrome related antigen B (anti-SSB), C-reactive protein (CRP), rheumatoid factor (RF) or Anti-Cyclic Citrullinated Peptide (anti-CCP) positivity (p>0.05).

Conclusion: Similar to patients with systemic vasculitis, PSS patients should be assessed for subclinical peripheral arterial diseases in the early stage and monitored closely with ABPI and CIMT measurements. The atherosclerotic process observed in PSS patients may be due not only to the inflammatory effect, but to many multifactorial issues such as immunological and genetic effects.

Key words: Primary Sjogren’s syndrome, carotid intima media thickness, ankle brachial index.

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Introduction

In recent years, an increase in atherosclerosis in autoimmune diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) has been observed. Moreover, it appears that there has been a resulting increase in cardiovascular (CV) risk and mortality.

Compared with the general population, it is known that this patient group has high mortality linked to cerebrovascular and coronary artery disease. In patients with systemic autoimmune diseases, these risk factors frequently cause subclinical atherosclerosis such as increased intima media thickness and plaque progression. As a result of these issues, the incidence of cerebrovascular dis-
Eases increases in this patient group\(^4\). The increase in atherosclerosis observed in chronic inflammatory and autoimmune rheumatoid diseases is obvious; however, the prevalence and the contribution of traditional risk factors in CV disease causing atherosclerosis have not been fully explained\(^5\). Immunological disorders, genetic factors, persistent multisystemic inflammation and vascular damage may be listed among these factors\(^6\)-\(^8\).

In many systemic autoimmune diseases such as RA, SLE and Wegener’s granulomatosis, CV diseases linked to atherosclerosis are observed. Sjogren’s syndrome is a chronic systemic autoimmune inflammatory disease characterized by lymphocytic infiltration of exocrine glands. It can be presented itself, primary Sjogren’s syndrome (PSS), or with another autoimmune disease secondary Sjogren’s syndrome. PSS exhibits a more moderate progression compared to RA or SLE, and generally does not require immunosuppressive treatment. Primary Sjogren’s syndrome (PSS) has a strong female propensity (female to male ratio varies from 20:1 to 9:1) with the mean age onset usually in the 4th to 5th decade. It is estimated that the annual incidence of pSS at 3.9 per 100,000. The reported prevalence ranges from 0.09%-0.60%\(^9\)-\(^10\).

There are studies showing that traditional CV risk factors such as hypertension (HT) and dyslipidemia appear with increased rates in PSS\(^11\). In this, regard these patients appear to have increased risk of CV. While the CV incidence and survival rates are not fully known in PSS patients, they are still listed among the most important causes of mortality in this population\(^12\). Similar to many autoimmune diseases like SLE and RA, subclinical atherosclerosis is frequently observed with PSS\(^13\)-\(^15\).

ABPI and carotid intima media thickness (CIMT) measurements are accepted as simple, non-invasive, easily applied and cheap but effective methods to determine subclinical atherosclerosis. CIMT is strictly recommended by the American Heart Association, American Society of Echocardiography and Society for Vascular Medicine as a screening test for heart disease in healthy individuals\(^16\)-\(^17\). We compared PSS patients with a healthy age and sex-matched control group to determine the increased incidence of subclinical atherosclerosis in this patient group using the clinically easy and routinely used CIMT and ABPI measurements aiming to provide early diagnosis.

**Materials and methods**

The study protocol was approved by the local ethics committee (Canakkale Onsekiz Mart University Ethical Committee). Written informed consent was obtained from all of the PSS patients and control patients. Our study comprised a total of 124 patients, including patients applying to the rheumatology clinic between January 2012 and August 2014, diagnosed with PSS according to American–European Consensus Group Sjogren’s syndrome classification criteria and monitored for more than 3 years and a control group.

The patients were later called to the CV surgery clinic for prospective ABPI and CIMT measurements\(^18\). The age- and sex-matched control group included 102 patients without PSS or peripheral vascular disease (normal ABPI). Young patients (below 18 years) were excluded from the study. All patients completed a questionnaire including detailed history, and after a detailed physical examination, blood samples were taken. Those with systemic inflammatory diseases other than PSS, cerebrovascular diseases (transient ischemic attacks or history of thrombotic cerebrovascular events), peripheral vascular diseases (or history of intermittent claudication), active infection, anemia (hemoglobin ≤9.0 g/dl for women and ≤10 g/dl for men), severe renal failure (receiving dialysis and/or a glomerular filtration rate ≤30 ml/min/m\(^2\)) and those who could not have ABPI or CIMT measurements taken due to lack of patient cooperation or anatomical reasons were excluded from the study. Estimated glomerular filtration rate was calculated according to the modification of diet in renal disease equation (MDRD-7).

The patients’ age, gender, clinical situation (xerostomia, xerophthalmia), disease duration, immunological profiles (anti-SSA and anti-SSB antibodies), erythrocyte sedimentation rate (ESR) levels, C-reactive protein (CRP) levels and biopsy findings were obtained from hospital notes and electronic patient records. Family history of atherosclerotic diseases and other data were obtained during patient interviews. If within one year before participation, the patient smoked at least one cigarette per day, they were recorded as a smoker.

Blood pressure measurements were completed on the same day as ABPI measurements. Before measurements, the patient rested sitting down for 5 minutes. Measurements were taken on each arm separately at 5 minute intervals. HT had to be newly diagnosed and/or patients had to be receiving hyper-
tensive therapy or to have been diagnosed by a doctor during assessment (systolic blood pressure [SBP] ≥140 mmHg and/or diastolic blood pressure [DBP] ≥90 mmHg in three measurements at intervals of 3-5 min). The lowest value from measurements taken at the same visit was recorded.

For diabetes mellitus (DM), patients who were newly diagnosed and/or receiving antidiabetic therapy were included (fasting plasma glucose ≥126 mg/dl or blood glucose ≥200 mg/dl at any time). Blood samples for fasting glucose and lipid profiles were taken on the same day as ABPI measurements or on the following day. ABPI was measured routinely by the same CV surgeon.

**ABPI Measurement**

Patients’ ABPI measurements were taken after a resting time of 15 minutes. The ankle pressure was measured in the dorsalis pedis and tibialis posterior artery bilaterally. The brachial pressure was measured in both of the arms. The ABPI for each lower extremity was calculated by dividing the higher recorded ankle pressure (dorsalis pedis and tibialis posterior artery). After this measurement, the patients underwent comprehensive CIMT examination on the same day.

**CIMT Measurement**

CIMT was measured using a Vivid 7 (GE Vingmed Ultrasound AS, Horten, Norway) with a linear array of 10 MHz probes. All patients lay in supine position. The transducer probe was manipulated so that the near and far walls of the carotid artery were parallel, and the lumen diameter was maximized in the longitudinal plane. The section 10 mm proximal to the carotid bifurcation was identified, and the CIMT of the far wall was evaluated as the distance between the lumen intima interface and the media intima interface. The CIMT was measured on a frozen frame capturing a suitable longitudinal image, with the image magnified to achieve a higher resolution of detail.

Following selection, patients were divided into two groups, namely the PSS and control groups. Disease scores (the 9-item fatigue severity scale [FSS], 8-item visual analogue scale [VAS] xerostomia questionnaire), CRP, erythrocyte sedimentation rate and rheumatoid factor levels were also recorded. FSS is a self-reported questionnaire with 9 items which was first administered to 25 multiple sclerosis patients in 1989(19). The VAS is used in many areas to assess pain; it is commonly used in a wide range of areas relating to pain. The advantage over dichotomous/categorical measures of xerostomia is its ratio properties, which could be useful in analyzing relative changes in salivation over time.(20,21)

A Framingham risk score was derived for each subject using the gender-specific prediction formulae proposed by Wilson et al. based on conventional CV risk factors (age, total and high-density lipoprotein [HDL] cholesterol categories, blood pressure categories, diabetes and smoking status)(22,23).

**Statistical analysis**

Statistical analysis was performed using Statistical Package for the Social Sciences (version 15.0, SPSS, Chicago, Illinois, USA). Quantitative variables were expressed as mean value ± standard deviation (SD) or median (minimum–maximum) and qualitative variables as percentages (%). The groups were compared using the Kolmogorov–Smirnov test. Comparison of parametric values between the groups was performed using the Mann-Whitney U test. Categorical variables were compared using the Chi-square test, and p<0.05 was considered statistically significant.

**Results**

The study included 24 PSS patients between the ages of 25 and 70 and 105 controls aged 26-69 for a total of 129 patients. Five patients were excluded from the study for a variety of reasons. Two patients did not agree to participate in the study (both had PSS). In the control group, three patients were excluded for a variety of reasons (two patients had active infections of cellulitis and pneumonia). One patient was receiving treatment for RA. Care was taken that the age and gender profiles of the PSS and control group patients were similar. The clinical symptoms, serological values, and disease scores (FSS, VAS) of PSS patients are given in Table 1. All of the PSS patients had findings of xerophthalmia with the second most common symptom being xerostomia. The mean disease duration was determined to be 80.4±25.6 months. The demographic comparison of PSS patients with the control group and Framingham risk scores are shown in Table 2. While the HT history of PSS patients was not significant, it was found to be higher than in the control group; similarly, SBP values were also higher.

Nine PSS patients (41%) had ABPI lower than 0.9. In the control group, 11 patients (11%)
had ABPI lower than 0.9. When both groups were compared, the difference was found to be significant (p<0.05).

<table>
<thead>
<tr>
<th>Demographic Parameters</th>
<th>pSS Group 1, N=22</th>
<th>Control Group 2, N=102</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean±SD</td>
<td>57.2±12.3</td>
<td>58±10.4</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Gender (F/M), n</td>
<td>22/0</td>
<td>22/0</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>BMI kg/m², mean±SD</td>
<td>28.7±4.6</td>
<td>29.6±5.4</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>DM n (%)</td>
<td>2/22(9.09)</td>
<td>12/102(11.7)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Smoker n (%)</td>
<td>7/22(31.8)</td>
<td>33/102(32.3)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>HTN, n (%)</td>
<td>6/22(27.2)</td>
<td>15/102(14.7)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Known coronary artery disease, n (%)</td>
<td>4/22(18.1)</td>
<td>18/102(17.6)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>History of stroke, n (%)</td>
<td>2/22(9.09)</td>
<td>9/102(8.8)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>FHs of atherosclerosis, n (%)</td>
<td>2/22(9)</td>
<td>8/102(7.8)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Framingham risk scores, % by Mann-Whitney test</td>
<td>1.8 (0.72-2.4)</td>
<td>1.6 (0.8-2.6)</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

Table 1: Clinical, serological features and signs of the patients with primary Sjögren’s syndrome.

- Anti-CCP: Anti- Cyclic Citrullinated Peptide, Anti-SSA/Ro: Anti-Sjögren’s-syndrome-related antigen A, also called anti-Ro. Anti-SSB/La: Anti-Sjögren’s-syndrome-related antigen B, also called anti-La. CRP: C-Reactive Protein, FSS: Fatigue Severity Scale, RF: Rheumatoid factor, VAS: Visual Analogue Scale

Comparing the PSS patients with the control group in terms of traditional CV risk factors, no significant difference was found (p>0.05; Tables 2 and 3). There was no significant difference in the demographic data (age, gender, body mass index [BMI]) of the patients (Table 2).

Table 2: Comparison of demographic parameters, primary Sjögren’s Syndrome patients and control group.


Comparing the PSS patients with the control group, there was no significant difference in terms of anti-SSA or anti-SSB antibodies, CRP, RF or anti-CCP positivity (p>0.05). The ABPI and CIMT values of PSS patients with ABPI less than 0.9 were examined, it was found to be 110.6±28.4. When this group of patients was compared with PSS patients, a significant association with duration of disease (month, mean±SD, 80.4±25.6) was present (p<0.05).

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Comparing the PSS patients with ABPI less than 0.9 with all PSS patients and the control group, there was no significant difference in terms of anti-SSA or anti-SSB antibodies, CRP, RF or anti-CCP positivity (p>0.05).

Table 3: Comparison of the blood tests parameters, primary Sjögren’s Syndrome patients and control group. FPG: Fasting plasma glucose, HDL-C: High density lipoprotein - cholesterol, Hgb: Hemoglobin, LDL-C: Low density lipoprotein cholesterol, pSS: Primary Sjogren’s syndrome, TG: Triglyceride

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Comparing the PSS patients with ABPI less than 0.9 with all PSS patients and the control group, there was no significant difference in terms of anti-SSA or anti-SSB antibodies, CRP, RF or anti-CCP positivity (p>0.05).

Table 4: Comparison of the pressure values and CIMT parameters, primary Sjögren’s Syndrome patients and control group.

- ABPI: ankle-brachial pressure index, CIMT: Carotis Intima Media Thickness, DBP: Diastolic blood pressure, pSS: Primary Sjogren’s Syndrome, SBP: Systolic blood pressure

PSS patients also exhibited a statistically significant increase in CIMT mean values (mm; p<0.05). The ABPI and CIMT values of PSS patients were statistically significantly different.
when compared to the control group (p<0.05; Table 4). This leads to the consideration that this patient group appears to have increased risk of stroke and peripheral artery disease (PAD).

**Discussion**

The frequent observation of premature atherosclerosis with diseases such as SLE and RA with chronic inflammation and systemic autoimmunity similar to PSS led us to consider that the same disease may be observed in the PSS patient group. We aimed to use the low-cost and easy-to-apply tests of CIMT and ABPI on patients from the PSS patient group to provide early diagnosis and prevent PADs and cerebrovascular incidents that may develop.

Chronic inflammation plays a key role in premature atherosclerosis. In addition, comparing CRP levels with the general population in terms of CV risk, a close relationship was found between RA patients and early stage endothelial damage. Chronic inflammation in PSS, characterized by exocrine gland involvement, may be considered to play a role in atherosclerosis development similar to that in SLE and RA patients. An increase in classic CV risk factors has been observed in SLE patients. Pro-atherogenic lipid profiles (increased low-density lipoprotein [LDL], triglyceride levels) have been identified in SLE patients. This increased lipid profile may be linked to corticosteroid treatment.

In our study, when the PSS and control groups were compared, no significant change in lipid profiles (LDL, triglyceride, HDL) was observed. While the other traditional CV risk factors of HT, DM, smoking and obesity are among the significant causes of early atherosclerosis in SLE and RA patients, even if these factors are kept under control, it is clear that a diagnosis of SLE is among the strongest risk factors for CV. In this regard, the importance of assessing all of these factors in PSS patients and a control group in our study is clear.

Atherosclerosis may be identified through many non-invasive techniques such as Doppler ultrasound (US), intravascular US, electron beam computed tomography scan, magnetic resonance angiography and assessment of carotid plaque and intima media thickness. Amongst these methods, the low-cost and wide application areas of ABPI and CIMT are important advantages for developing countries.

ABPI is a clinically easy-to-apply, non-invasive technique which aids in determining PADs. The high sensitivity (90%) and specificity (95%) of this test make it an ideal tool to identify PAD. It aids in determining the risk of developing coronary artery disease and stroke in the future. ABPI measurements are quick and easy, so patient compliance is at the highest level.

Studies have found that the predictive value of ABPI is 92.7% for coronary artery disease and 92.2% for stroke. The importance of ABPI measurements for those with ventricular dysfunction and coronary artery disease is undeniable; increased atherogenesis found in autoimmune inflammatory diseases and resulting ventricular dysfunction or arterial HT increases CV risk for autoimmune patients. When studies with PAD are investigated, it similarly appears to have high sensitivity in the patient group with ABPI less than 0.9; however, it has been found that correct detection may not be possible with a handheld Doppler at SBPs below 30 mmHg. In PSS patients with normal coronary flow reserves, endothelial dysfunction and sub-clinical atherosclerosis have been found, and an increase has been identified in plasma asymmetric dimethylarginine values.

There are two basic conclusions to be drawn from our study. The first is that when compared with a similar age group, patients with PSS and no history of PAD or cerebrovascular disease have significantly high CIMT and significantly low ABPI levels. These findings lead to the consideration that carotid Doppler US and ABPI may be surrogate markers to identify atherosclerosis. The second conclusion is that the lack of significant increase in inflammatory markers in patients with PSS is due to the immunological effects of the disease, and shows that it is caused by endothelial dysfunction, which is very important for the development of subclinical atherosclerosis.

Although in the age group included in our patient population, the incidence of PAD is about 3.5-4% in the general population, in our study group, 41% of PSS patients (9/22) had ABPI less than 0.9%, while 14% (3/22) had high ABPI. This proves that compared to the normal population, PSS patients exhibit a high rate of PAD. The observation of subclinical atherosclerosis in the PSS patients in our study group means that it is necessary to take preventative measures against PAD which may develop in the future.
In addition to CV risk factors in systemic vasculitis, it is thought that arterial wall damage may be caused in immune dysfunction disorders. A characteristic of systemic autoimmunity is that high amounts of autoantibodies (like RF, ANA, anti-SSA, anti-SSB antibodies) may be produced by many PSS patients\(^{38}\). While reactive antibodies to some autoantigens play a role in the development of atherosclerosis, their atherogenic role in autoimmune disorders is still not known\(^{40-43}\). In our PSS patient group, there was no statistically significant association found between these autoantibodies and subclinical atherosclerosis.

In addition to these results, when we examined laboratory tests showing inflammation, no significant difference was found in CRP and white blood cell values in comparison with the control group. This suggested that the developing subclinical atherosclerotic process does not just involve inflammation, but rather multiple issues like genetic and immunological factors. A study of 34 PSS patients predicted that there may be a progressive consumption of the endothelial pool during disease progression, possibly resulting in restoration of damaged vein walls and endothelial dysfunction. Release of endothelial microparticles (CD31+/CD42-) induces production of endothelial progenitor cells which increases as the severity and duration of disease in PSS patients increases, thereby facilitating the development of subclinical atherosclerosis\(^{44}\).

In systemic vasculitis, it has been shown that vascular endothelial cells are stimulated by their tissue-specific antigens by cytokine-triggering inflammation. Expressions of interleukin-1 and tumour necrosis factor (TNF) adhesion molecules are stimulated\(^{45,46}\).

In a 2005 study, Vaudo et al. clinically and serologically assessed 35 white women with nontreated PSS and an age-matched control group. The femoral and carotid artery intima media thickness was measured in patients, and a statistically significant increase was identified in nearly half of the patients compared to the control group (49% vs. 11% of controls). Similarly, in our study comparing a control group with a PSS patient group, 41% of patients had ABPI < 0.9. Nearly half of the age- and sex-matched PSS patients in both studies had subclinical atherosclerosis diagnosed. Again, when the serologic results in the same study were investigated, PSS patients with subclinical atherosclerosis were observed to have higher rates of leukopenia and circulating anti-SSA antibodies. However, in our study, we did not analyze the data for such an association. We did not find any association between low ABPI and CIMT values and anti-SSA or anti-SSB\(^{47}\). In a study comparing 25 PSS patients with an age, ethnicity and sex matched control group, Rachapalli et al. assessed ABPI and anti-SSB association; however, as in our study, they found no significant association\(^{48}\).

Leukopenia is a typical finding in connective tissue diseases. It expresses immune dysregulation in SLE and PSS patients\(^{49}\). Low numbers of leukocytes in circulation is a finding related to active disease in SLE, and an association has been found with subclinical aortic stiffness\(^{50}\). In PSS, an association has been found between low white blood counts and salivary gland involvement\(^{51}\).

In all of these studies, factors like increased inflammatory markers and cells in circulation were related to plaque instability in cases with RA and SLE, and similarities were revealed in PSS patients. In the PSS patient group, observation of autoimmunity supports the association with subclinical atherosclerosis; however, our data on CIMT and arterial wall cell infiltration have not been fully explained. Increased CIMT and anti-SSA and association with leukopenia may not be coincidental. In addition, the endothelial cell apoptosis cascade activation observed in SLE has been considered to cause atherosclerosis development and organ damage\(^{52,53}\). In this way, an independent role may be assumed between anti-SSA antibodies, leukopenia or genetics related to CIMT in PSS patients. Other researchers continue to work to confirm this interesting and very confusing hypothesis.

This study represents the first research to assess CIMT, ABPI and laboratory values in PSS cases to assess subclinical atherosclerosis, as has been done in SLE and RA patients, together with an age- and gender-matched control group. These vascular changes are not thought to be related to the inflammatory mechanism in PSS disease or classic CV risk factors, but may be due to immune system or genetic changes. The lack of certainty regarding these clinical findings continues. The relatively short disease duration in this study of PSS, which may be asymptomatic for many years, may have caused a lack of correlation.

Considering the increased stroke, PAD and cardiac risk mortality of PSS patients, a broader series patient groups and longer monitoring times are necessary. We intend to monitor these patients
at 6-month intervals to obtain data about mortality rates in the future. 

Deaths of PSS patients linked to CV diseases may be related to premature atherosclerosis of arterial walls; however, although reduced ABPI and increased CIMT assessed with ultrasound do not mean that CV diseases may develop, they increase our ability to estimate CV events which may occur in the future. In this way, comparing plaque percentages in PSS patients with a control group may be important for CV mortality which may develop later. These findings aid us in understanding the pathogenic characteristics of premature atherosclerosis in systemic autoimmune diseases. Contrary to invasive techniques, our study results used data from ABPI and CIMT measurements applied in an outpatient clinic, supporting their use as simple and beneficial methods.

**Study limitations**

Our study has several limitations. First, the sample size was small, leading to a limitation in the usefulness of the statistical methods. Future studies should be completed with larger patient populations. Second, the duration of disease in our study was an average of 80 months, which could be extended further to assess disease development. Third, this study was completed at a single research center; multiresearch center studies should be completed to increase environmental effects and numbers. Fourth, we did not measure total plaque area.

**Conclusion**

All patients with PSS should be assessed for subclinical CV risk using ABPI and CIMT, which are simple and easy to use in outpatient clinics. These cheap and non-invasive techniques will allow prevention of mortality and morbidity linked to CV diseases, and monitoring should be completed after early stage diagnosis. In conclusion, to our knowledge, this study is the first to assess CIMT, ABPI and laboratory values of subclinical atherosclerosis in PSS cases with age- and gender-matched groups.

**References**


Corresponding author
TOLGA KURT, Assist. Prof. Dr.
Assistant of Professor, School of Medicine, Department of Cardiovascular Surgery, Canakkale Onsekiz Mart University, Research and Training Hospital, Sahil yolu street, No: 5, 17110, Kepez
Canakkale (Turkey)