Endothelial Dysfunction in Primary Sjögren Syndrome

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ABSTRACT

Objective: In this study, we aimed to investigate endothelial functions in primary Sjögren syndrome.

Methods: Thirty-five patients with primary Sjögren syndrome and 20 age and sex-matched healthy volunteers were recruited to the present study. Flow mediated dilatation of brachial artery and carotid intima-media thickness were measured in the study population.

Results: Carotid intima-media thickness values were similar between groups (0.50 ± 0.10, 0.053 ± 0.08, $p > 0.05$). Flow mediated dilatation of the brachial artery was disrupted in the primary Sjögren syndrome group (7% vs 12%, $p = 0.002$).

Conclusion: There is endothelial dysfunction in patients with primary Sjögren syndrome, although they had comparable carotid intima-media thickness with the healthy control group.

Keyword: Endothelial dysfunction, flow mediated dilation, Sjögren syndrome

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INTRODUCTION

Sjögren syndrome (SS) is a relatively frequent systemic autoimmune disease. It primarily affects lacrimal and salivary glands, but can also have different organ involvement (1, 2).

The endothelium is the inner lining of the vascular bed, and it plays a crucial role in vascular homeostasis. Any disruption in endothelial function is closely related with increased mortality and morbidity (3). Endothelial function is closely related with the general inflammatory status of a patient and it is disrupted in various inflammatory diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis [RA] (4, 5).

Brachial artery flow mediated dilatation (FMD) is widely accepted as a marker of endothelial dysfunction. Its measurement is non-invasive, relatively easy and cheap and it gives valuable information about the vascular bed.

By this study, we aimed to investigate the FMD of the brachial artery in patients with primary SS. As for as the authors are aware, this is the first study evaluating endothelial function in this patient group.

SUBJECTS AND METHODS

In total, 55 individuals were recruited to the present study. Thirty- five of them were patients with primary SS and 20 of them were age and sex-matched healthy volunteers. All patients met the American European consensus criteria for primary SS (6). Any disease other than primary SS and smoking were accepted as exclusion criteria. The control consisted of asymptomatic healthy volunteers. The study was approved by the local ethics committee and informed consent was obtained from all study participants.

Endothelial functions were evaluated by FMD of the right brachial artery in response to reactive hyperaemia. The method has been described previously (7). In brief, studies were performed in a temperature controlled room (20–25°C) between 08 and 11 am after a 12-hour overnight fasting. The

measurements were performed with a high resolution B-mode Doppler with a 5–12 MHz linear array transducer (General Electric Company, Fairfield, CT, USA) by an experienced ultrasonographer. Patients were rested for 10 minutes before study. Afterwards, the clearest longitudinal image of the brachial artery was obtained approximately five cm proximal to the antecubital fossa and the widest diameter at end diastole was measured. Accordingly, a blood pressure cuff was inflated on the upper arm to above 200 mmHg for five minutes. Measurement of the maximal diameter of the brachial artery was performed one minute after cuff release. The FMD of the brachial artery was calculated according to the following formula: [(maximum diameter during reactive hyperaemia – baseline diameter)/baseline diameter] x 100%.

Carotid intima-media thickness (CIMT) was measured with the same probe as above by the same physician. Approximately 2 cm proximal parts of both carotid arteries were evaluated in longitudinal scans and two seperate images were taken from both common carotid arteries. The CIMT was accepted as the distance between lumen-intima interface and media-adventitia interface (8). The mean value of the four CIMT values was accepted as the CIMT value of the patient.

Statistical analysis

Statistical analysis was performed by SPSS for Windows version 17.0 (SPSS Inc, Chicago, IL, USA). Kolmogorov-Smirnov test was used for normality distribution. Student's *t*-test, Chi-square test or Fisher's exact test and Mann-Whitney U test were used, as appropriate. Statistically significant level was set at $p < 0.05$.

RESULTS

Baseline characteristics of patients are summarized in the Table. Mean ages of participants were similar: 48.1 ± 7.8 years in the control group and 47.6 ± 8.0 years in the primary SS group ($p = 0.827$). Most patients were female (88.6%). Body mass indices were similar between groups and there was no significant difference in laboratory parameters.

The CIMT values were similar in the control group and primary SS group (0.50 ± 0.10, 0.053 ± 0.08, respectively, $p = 0.345$) [Fig. 1].

The brachial artery FMD values were significantly reduced in the primary SS group compared to the control group (7%, 12%, respectively, $p = 0.002$) [Fig. 2].

DISCUSSION

In the present study, we found that although the CIMT values of primary SS patients were similar with CIMT values of healthy volunteers, there was significant disruption in the FMD of the brachial artery against reactive hyperaemia in the primary SS group compared to the control group.

The endothelium is a very important element of the body, especially for the establishment of vascular health. By its anatomy and by molecules secreted from the endothelium (like nitric oxide), it plays a crucial role in cardiovascular dynamics. Any disruption in anatomy or functional properties of the endothelium results in increased morbidity and mortality (9).

Response of blood vessels to an increase in flow by dilatation is called flow mediated dilatation. It is a well-known marker of endothelial dysfunction. Disturbed FMD is closely related with adverse vascular events. It has been shown that FMD is disturbed in patients who have cardiovascular risk factors like hypertension, hypercholesterolaemia and diabetes mellitus (9, 10). It has also been shown to be reduced in chronic systemic infections (11).

Recently, it has been shown that FMD of the brachial artery was disturbed in some rheumatologic diseases. For example, Kiss and colleagues showed that FMD of the brachial artery was disturbed in patients with SLE (12). In another study, it was shown that endothelial dysfunction in SLE patients remained significant even after adjustment for other classic cardiovascular risk factors (13). Ferreira and colleagues reported that atorvastatin can improve endothelial dependent vasodilatation in SLE patients (14). In a study, it was shown that endothelial function was disturbed in patients with rheumatoid arthritis and this disruption was closely related with disease duration (15). In another study, it was shown that FMD could be reduced even in the early stages of rheumatoid arthritis (16).

Sjögren syndrome is an inflammatory autoimmune disease. Inflammation is one of the cornerstones of the disease. Because our patient group was devoid of classical cardiovascular risk factors, we think that inflammation may play a role in the disruption of endothelial functions. Although we found that CIMT

values were normal, it did not mean that the endothelial functions were normal in patients with primary SS. Functional abnormalities can precede anatomic changes. This means that disruption of FMD can precede overt atherosclerosis or increment in CIMT like in our patient group.

There is still little knowledge about the cardiovascular endpoints in primary SS. Because endothelial dysfunction is a marker of untoward vascular endpoints, cardiovascular complications may be more frequent than we assumed in primary SS. More studies are needed to be conducted in order to highlight this issue. Assessment of FMD from the brachial artery is an easy method to evaluate endothelial function. This method is safe, cheap and useful and it can easily be used in patients with primary SS.

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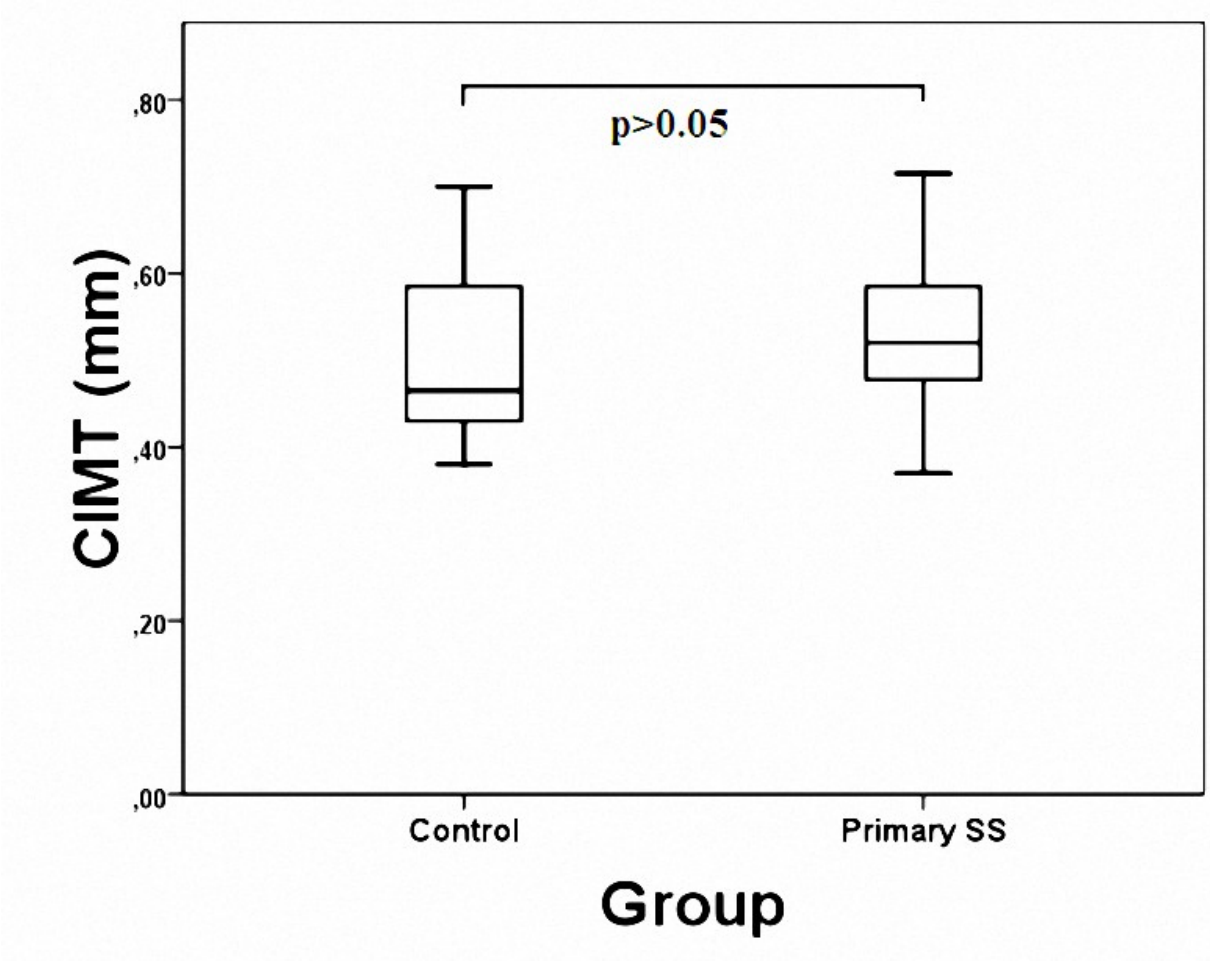

Fig. 1: Carotid intima-media thickness (CIMT) of the primary Sjögren syndrome (SS) and control groups.

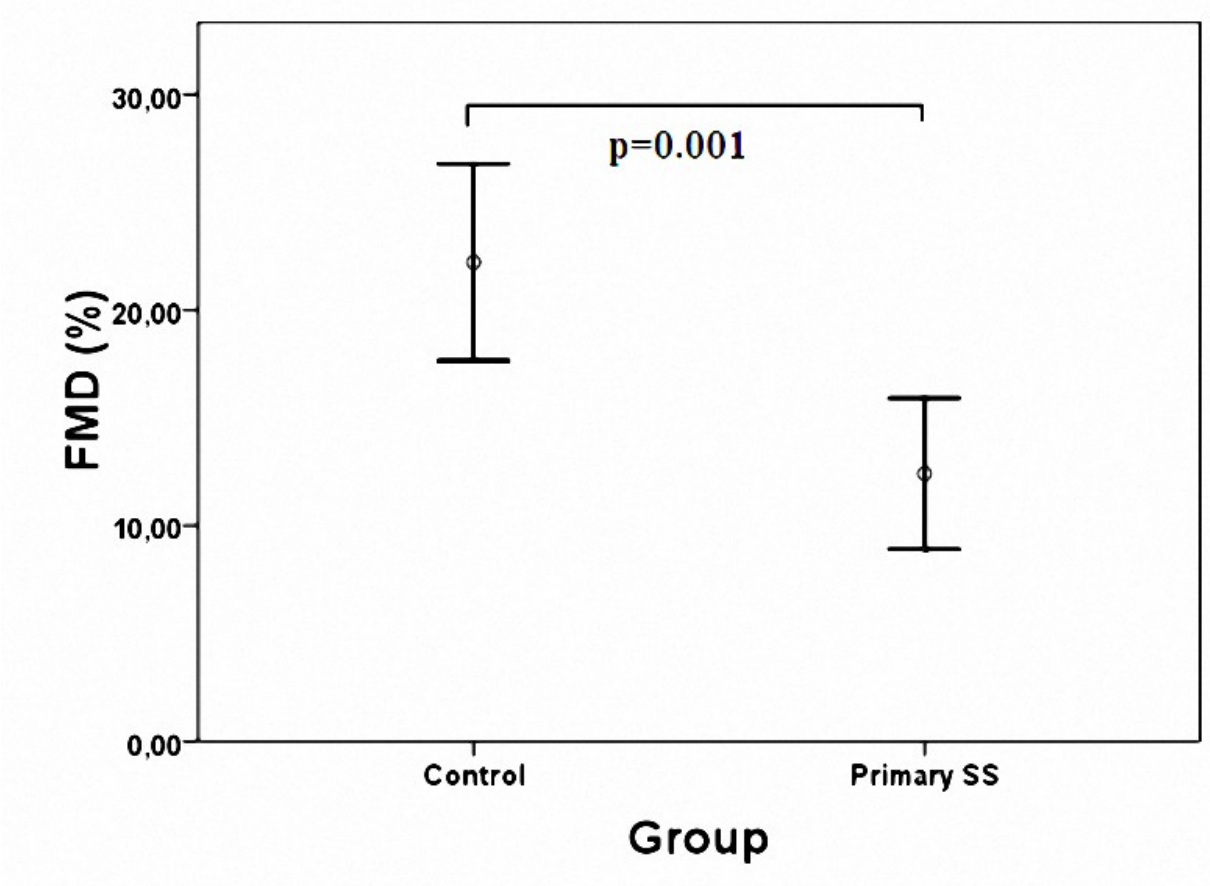

Fig. 2: Flow mediated dilation (FMD) of brachial artery is disrupted in primary Sjögren syndrome (SS).

Table: Basal characteristics of study participants

	Control group (n = 20)	**Primary SS (n = 35)**	***p*-value**
Age (years)	48.1 ± 7.8	47.6 ± 8.0	0.827
Female (%)	85.0	88.6	0.705
Creatine (mg/dl)	0.74 ± 0.05	0.72 ± 0.09	0.663
Total Cholesterol (mg/dl)	197.1 ± 35.1	197.3 ± 37.1	0.986
HDL (mg/dl)	46.2 ± 13.4	45.2 ± 11.5	0.800
LDL (mg/dl)	117.0 ± 29.8	123.1 ± 27.5	0.487
Triglyceride (mg/dl)	152.6 ± 99.5	135.3 ± 63.7	0.529
Body mass index (kg/m^2)	29.3 ± 5.2	30.4 ± 4.5	0.458

HDL: High density lipoprotein, LDL: Low density lipoprotein