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ORIGINAL ARTICLE

Muscle architecture in patients with primary Sjögren syndrome

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ABSTRACT

Objectives: This study aims to investigate skeletal muscle architecture and strength in patients with primary Sjögren syndrome (pSS).

Patients and methods: Between July 01, 2017 and November 30, 2017, 19 pSS patients (19 females; mean age: 54.1±6.6 years; range, 42 to 62 years) and 19 age-, body mass index-, and sex-matched healthy controls (19 females; mean age: 53.2±6.7 years; range 42 to 61 years) were included. Sjögren symptoms were assessed with the European Alliance of Associations for Rheumatology (EULAR) Sjögren's Syndrome Patient Reported Index (ESSPRI). Muscle thickness, pennation angle, and fascicle length were measured at quadriceps femoralis, gastrocnemius and soleus muscles. Isokinetic muscle strength tests were performed at 60 and 180°/sec for knee and at 30 and 120°/sec for ankle. Anxiety and depression evaluated with the Hospital Anxiety and Depression Scale (HADS), fatigue with Multidimensional Assessment of Fatigue scale (MAF), and functionality with Health Assessment Questionnaire (HAQ).

Results: In the pSS group, the mean ESSPRI was 7.70±1.17. The mean scores of depression (10.05±3.09 *vs.* 4.47±2.29; p<0.0001), anxiety (8.26±4.28 *vs.* 3.79±2.42; p<0.0001), functionality (0.94±0.78 *vs.* 0.22±0.26; p<0.0001), and fatigue (37.69±5.47 *vs.* 17.69±5.26; p<0.0001) were significantly higher in patients with pSS. Only, the pennation angle of vastus medialis in dominant leg was significantly greater in healthy controls (p=0.049). Peak torques/body weight of knee and ankle muscles were found to be similar.

Conclusion: Excluding a minor decrease of the pennation angle at vastus medialis, muscle structure of lower extremity of pSS patients were similar to healthy controls. In addition, isokinetic muscle strength did not significantly differ in patients with pSS compared to healthy controls. In patients with pSS, disease activity and fatigue level were negatively correlated with isokinetic muscle strength measurements.

Keywords: Disease activity, muscle architecture, muscle strength, primary Sjögren syndrome.

Sjögren syndrome (SS) is a systemic autoimmune disease with a wide range of clinical manifestations. The disease spectrum is ranged from autoimmune exocrinopathy to a systemic process.[1] Patients with primary SS (pSS) often complain of joint pain, myalgia, increased fatigue, and impaired physical capacity and function.[2-4] This may result in decreased ability to perform daily living activities, working disability and deterioration of health-related quality.[5-7] Although patients with pSS frequently suffer from arthralgia and myalgia, myositis is rarely reported.[8,9]

Although there are clinical trials and case reports about clinical and microscopic evidence of skeletal muscle involvement in patients with pSS, there is no information about the macroscopic structure of skeletal muscle of patients with

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pSS.[10-13] Muscle architecture, arrangement of muscle fibers within a muscle relative to the axis of force generation, is the primary determinant of muscle function.[14] The understanding of the relationship between structure and function is important for clarifying the physiology of force production and movement. Commonly used parameters in architectural muscle analysis are fascicle length, pennation angle and cross-sectional area. The fascicle length represents the number of sarcomeres in series and longer fascicles are associated with a higher peak shortening velocity.[15,16] Pennation angle is the angle of the insertion of muscle fascicles into the deep aponeurosis and positively correlated with muscle thickness.[17] Lower leg muscle thickness is valuable predictor of the muscle cross sectional area and muscle volume and, thus, muscle strength.[18] The most common method of measuring muscle architecture is B-mode ultrasound (US), which has been previously shown to be a reliable and valid method.[19,20]

To the best of our knowledge, there are no studies evaluating muscle architecture in pSS. Objective evidence on muscle architecture and strength in pSS may lead to a better understanding of its role in health-related parameters in this disease. In the present study, we, therefore, aimed to assess the muscle architecture in pSS compared to healthy controls. The secondary aim was to determine the relationship between muscle architecture, strength and mood status, fatigue, disease activity in patients with pSS.

PATIENTS AND METHODS

This cross-sectional study was conducted at Gazi University Faculty of Medicine, Department of Physical Medicine and Rehabilitation, Division of Rheumatology between July 01, 2017 and November 30, 2017. Nineteen pSS patients (19 females; mean age: 54.1±6.6 years; range, 42 to 62 years) who fulfilled 2016 American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) classification criteria[21] and 19 age- and sex-matched healthy controls (19 females; mean age: 53.2±6.7 years; range 42 to 61 years) were included in the study. Patients who had a history of concomitant rheumatic disease, peripheral or central nervous system disease, other systemic diseases (hyperthyroidism, hypothyroidism, diabetes mellitus), myositis, overt trauma of the muscles, and surgery of the lower limb were excluded. Demographic and clinical characteristics were recorded.

In the pSS group, disease activity was evaluated with the EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI). The ESSPRI is a self-assessment questionnaire to measure symptoms including pain, fatigue, and dryness. Each individual symptom is measured with an 11-point numerical scale (0: no symptoms and 10: worst possible symptoms). The final ESSPRI score is calculated by taking the average scores of these domains. While the final ESSPRI score <5 indicates low disease activity, ≥5 indicates high disease activity.[22,23]

The Hospital Anxiety and Depression Scale (HADS) was administered to assess anxiety and depression. This patient completed questionnaire compromises two subscales: anxiety (HADS-A) and depression (HADS-D). Both subscales consist of seven questions and each question is scored on an 4 point (0-3) scale. The HADS questionnaire indicates that a score between 8 and 10 is possible, between 11 and 14 probable and between 15 and 21 extreme cases of depression and anxiety.[24]

The Multidimensional Assessment of Fatigue scale (MAF) was applied to assess fatigue. This patient-reported questionnaire consists of 16 items and measures four dimensions of fatigue, including severity, distress, timing and degree of interference in activities of daily living. The final MAF score ranges from 0 to 50, with higher scores reflecting more severe fatigue.[25]

The Health Assessment Questionnaire (HAQ) was used to evaluate how the disease affects movements and activities in daily life over the past week. It contains 20 questions in eight categories including dressing, arising, eating, walking, hygiene, reach, grip and activities. Each question scores from 0 to 3 and a lower score represents a better outcome. In scoring the category, the highest score among the items was accepted as the category score. The HAQ score was calculated by dividing the total score of categories into 8.[26]

Ultrasonographic assessment

A single rheumatologist, who had experience in musculoskeletal US and blind to the participant's group assignment, performed US examinations using a multi-frequency linear probe (6-12 MHz; MyLab 70 XV, EsaoteBiomedica, Genoa, Italy). While obtaining images, a generous amount of water-soluble gel was applied between the transducer and the skin to aid acoustic coupling and to avoid compression or deformation of the muscle fibers. All measurements were done on quadriceps femoris, gastrocnemius, and soleus bilaterally. For quadriceps femoris measurement, participants lied supine with their legs extended and their muscles relaxed. Rectus femoris images were taken at 50% of the distance between the anterior superior iliac spine and the superior border of the patella. Vastus lateralis images were taken at the middle of the thigh length (the distance between the most prominent portion of the greater trochanter and the lateral femoral epicondyle). Vastus medialis images were taken at 30% the length of a reference line connecting the anterior superior iliac spine to the proximal edge of the patella; the probe was placed just medial to the border between vastus medialis and the rectus femoris. For gastrocnemius and soleus measurement, the participants lied prone with the feet hanging off the edge of the table and knees fully extended. Images were taken at the level of the maximum girth of muscles.

Muscle thickness was measured as the perpendicular distance between the deep and superficial aponeurosis. Pennation angle was measured as the angle of the insertion of muscle fascicles selected for length measurement into the deep aponeurosis. Fascicle length is the linear fascicular path between the insertion into the deep and superficial aponeurosis. It was calculated as muscle thickness/sin (pennation angle).[27]

Isokinetic strength measurement

Isokinetic measurements of muscles were done by a calibrated isokinetic testing machine (Cybex-NORM isokinetic machine) with standard attachments. Isokinetic knee muscle strength tests were performed bilaterally at 60 and 180°/sec and isokinetic ankle muscle strength tests were performed bilaterally at 30 and 120°/sec as peak torque/body weight (Nm/kg) and work. Before performing the isokinetic test, all participants conducted the submaximal repetitions. Isokinetic knee muscle strength test was performed, while the participants were sitting on the chair with their knee flexed at 90° and the ankle in neutral position. Isokinetic ankle muscle strength test was performed as the participants lied on the table with their knee at 0° extension and ankle at 90° of dorsiflexion.

Statistical analysis

Statistical analysis was performed using the SPSS for Windows version 16.0 software (SPSS Inc., Chicago, IL, USA). The visual (histograms and probability plots) and analytical (Kolmogorov-Smirnov and Shapiro-Wilk's test) methods were used to determine whether the variables were normally distributed. Continuous data were expressed in mean ± standard deviation (SD) or median (min-max), while categorical data were expressed in number and frequency. The Student t-test was used for comparison of normally distributed data, and the Mann-Whitney U test was used for comparison of non-normally distributed data. The Spearman correlation coefficients were used to investigate correlation between patient's characteristics and clinical parameters. A p value of <0.05 was considered statistically significant.

RESULTS

There was no significant difference between the pSS patients and healthy controls for age,

Table 1. Demographic and clinical characteristics of participants

	pSS group	Control group	
	Mean±SD	Mean±SD	p
Age (year)	54.1±6.6	53.2±6.7	0.583
Weights (kg)	78.1±14.3	78.8±11.3	0.948
Heights (cm)	159.6±5.2	158.8±5.3	0.441
Body mass index (kg/m^2)	30.7±5.5	31.4±5.0	0.671
Depression	10.1±3.1	4.5±2.3	0.0001
Anxiety	8.3±4.3	3.8±2.4	0.0001
Fatigue	37.7±5.47	17.7±5.3	0.0001
Functional disability	0.9±0.8	0.2±0.3	0.0001

pSS: Primary Sjögren syndrome; SD: Standard deviation.

Table 2. Muscle ultrasound measurements of pSS patients and healthy controls

	Dominant leg			Non-dominant leg		
	pSS patients	Healthy controls		pSS patients	Healthy controls	
	Mean±SD	Mean±SD	*p*	Mean±SD	Mean±SD	*p*
Rectus femoris thickness	12.2±1.6	12.1±2.5	0.838	11.8±2.12	11.73±2.31	0.872
Vastus medialis						
Muscle thickness (mm)	12.5±2.0	12.5±1.7	0.977	12.6±1.9	12.1±1.7	0.350
Pennation angle (deg)	10.3±3.6	14.2±6.4	**0.049**	10.3±3.5	11.8±4.2	0.170
Fascicle length (mm)	80.8±39.1	60.8±22.5	0.112	78.5±29.4	66.8±26.1	0.199
Vastus lateralis						
Muscle thickness (mm)	14.2±1.6	13.6±1.9	0.189	13.7±1.7	13.2±2.3	0.456
Pennation angle (deg)	13.1±3.5	14.8±4.0	0.176	13.0±3.3	14.2±4.1	0.345
Fascicle length (mm)	66.4±16.5	55.0±14.8	0.082	64.5±17.5	56.9±16.9	0.274
Vastus intermedius						
Muscle thickness (mm)	10.5±2.3	9.9±1.6	0.422	10.6±2.3	10.7±2.1	0.942
Pennation angle (deg)	7.8±4.9	5.8±3.1	0.099	7.7±3.4	7.3±4.1	0.669
Fascicle length (mm)	89.9±39.4	114.9±42.4	0.073	90.3±34.1	96.6±41.9	0.649
Gastrocnemius medialis thickness (mm)	15.7±1.9	15.2±2.6	0.759	15.8±2.5	15.8±2.7	1.000
Gastrocnemius lateralis thickness (mm)	11.9±1.5	11.8±1.8	0.965	12.2±2.0	12.6±2.1	0.465
Soleus thickness (mm)	13.9±1.3	13.6±1.5	0.599	14.0±1.6	13.1±1.6	0.965

pSS: Primary Sjögren syndrome; SD: Standard deviation.

Table 3. Isokinetic muscle strength measurements of pSS patients and healthy controls

		Peak torque/body weight (Nm/kg)			Work		
Variables	Velocity	pSS patients	Healthy controls	*p*	pSS patients	Healthy controls	*p*
Dominant leg							
Knee extension	60	63.1±20.2	58.0±24.1	0.357	-	-	
	180	25.3±14.1	27.4±19.4	0.930	435.4±161.8	483.9±315.1	0.882
Knee flexion	60	37.4±11.0	36.5±15.0	0.826			
	180	23.3±9.9	23.7±13.0	0.878			
Ankle DF	30	18.3±6.3	14.5±5.9	0.104			
	120	16.4±6.0	14.9±7.3	0.426			
Ankle PF	30	39.5±16.6	37.8±17.0	0.977			
	120	13.7±8.6	15.2±10.1	0.713	116.82±64.58	154.71±108.94	0.524
Non-dominant leg							
Knee extension	60	58.7±26.9	62.5±29.5	0.693			
	180	25.1±11.0	30.2±18.1	0.421	429.9±231.0	591.8±359.7	0.276
Knee flexion	60	37.2±14.7	37.8±18.6	0.843			
	180	20.5±5.9	26.0±14.2	0.382			
Ankle DF	30	10.7±5.9	10.1±4.6	0.839			
	120	9.8±3.3	9.8±3.7	0.890			
Ankle PF	30	38.1±14.4	36.1±14.0	0.883			
	120	15.2±6.8	15.4±9.2	0.895	124.6±74.5	144.2±90.5	0.447

pSS: Primary Sjögren syndrome; DF: Dorsiflexion; PF: Plantar flexion

Table 4. Correlation between disease activity, fatigue, anxiety, depression and isokinetic muscle strength measurements in patients with pSS

	Velocity	ESSPRI	Fatigue	Anxiety	Depression
Variables		r	r	r	r
Dominant Leg					
Knee extension	60	**-0.572***	-0.157	-0.081	0.122
	180	**-0.617***	-0.459	-0.294	0.277
Knee flexion	60	**-0.492***	-0.174	-0.031	0.377
	180	-0.289	0.030	0.255	0.292
Ankle DF	30	-0.266	-0.171	-0.124	0.305
	120	-0.092	0.006	0.161	0.307
Ankle PF	30	**-0.700***	-0.450	0.000	0.273
	120	-0.531	**-0.484***	0.143	0.177
Knee work		**-0.730***	**-0.603***	-0.109	**0.515***
Ankle work		**-0.519***	-0.372	0.154	0.206
Non-dominant leg					
Knee extension	60	**-0.575***	-0.335	-0.058	0.289
	180	**-0.508***	**-0.521***	-0.195	0.076
Knee flexion	60	-0.456	**-0.585***	0.004	0.337
	180	-0.319	-0.277	-0.086	0.007
Ankle DF	30	-0.142	-0.186	-0.248	0.163
	120	0.277	0.133	-0.318	0.110
Ankle PF	30	**-0.506***	-0.334	0.208	0.248
	120	-0.349	-0.280	-0.062	0.184
Knee work		-0.361	**-0.516***	0.241	0.099
Ankle work		-0.295	-0.339	0.149	0.357

pSS: Primary Sjögren syndrome; ESSPRI: EULAR Sjögren's Syndrome Patient Reported Index; DF: Dorsiflexion; PF: Plantar flexion; * p value <0.05.

body weight, height, and body mass index [BMI] (Table 1). In the pSS group, the mean disease duration was 27.68±30.93 months and mean ESSPRI was 7.70±1.17. Antinuclear antibody (ANA) positivity was seen in 11 (57.9%) of patients, anti-SSA in eight (42.1%) and anti-SSB in three (15.3%) patients. All participants in both study groups had normal levels of aspartate aminotransferase and creatinine phosphokinase. All patients with pSS were on a stable dose of hydroxychloroquine 200 mg/day during the previous six months. Patients with pSS had a significantly higher score for HADS (Table 1). In the pSS group, four (21.1%) patients scored more than 10 on the anxiety scale and 11 (57.9%) scored more than 10 on the depression scale. In the control group, no subject had a score of more than 10 on neither the depression nor the anxiety scale. The pSS group had significantly higher levels of fatigue on the MAF scale compared to the control group (Table 1). Similarly, according to the HAQ, pSS patients had significantly lower functional ability compared to healthy controls (Table 1).

In the dominant leg, pennation angle of vastus medialis was significantly greater in healthy controls than that in patients with pSS (p=0.049). Except for pennation angle of vastus medialis of the dominant leg, the other US measurements were similar between the two groups (Table 2).

Peak torque/body weight of knee and ankle muscles were found to be similar (Table 3). Correlation between disease activity, fatigue, anxiety, depression and isokinetic muscle strength measurement in patients with pSS are shown in Table 4.

DISCUSSION

According to our results, thicknesses and fascicle length of lower limb muscles of patients with pSS did not significantly differ from that of healthy controls. However, pennation angle of vastus medialis on the dominant leg was significantly lower in pSS patients. We found similar pennation angles of the other muscles in both groups at both dominant and non-dominant legs. Additionally, peak torque/body weight of knee and ankle muscles did not significantly differ in the pSS group form that of healthy controls. Some relationship was found between knee, ankle muscle strengths, ESSPRI, and fatigue in dominant and non-dominant leg.

Musculoskeletal involvement in patients with pSS may not only be in the form of arthritis and arthralgia, but also rarely in the form of myositis (particularly inclusion body myositis).[8,9] To the best of our knowledge, this is the first study that assesses the muscle architecture in patients with pSS. There are limited numbers of US studies concerning muscle architectural changes in inflammatory rheumatic diseases.[28,29] Kaya et al.[29] reported that, although systemic lupus erythematosus (SLE) patients had significantly greater muscle thickness and pennation angle of vastus lateralis than healthy controls, fascicle length was similar. The authors attributed the increased pennation angle to increased muscle thickness which may be due to edema. Also, SLE patients had similar muscle thickness, pennation angle and fascicle length of gastrocnemius muscle compared with healthy controls. Matschke et al.[28] reported that, compared to their age-sex- and BMI- matched healthy subjects, sarcopenic patients with rheumatoid arthritis (RA) had significantly less vastus lateralis muscle volume, but without differences in fascicle length, physiological cross-sectional area or pennation angle of vastus lateralis.[28] Similar to these studies, we found some differences in pennation angle and fascicle lengths in vastus medialis compared to healthy controls. This may be due to muscle involvement in pSS, or due to low physical activity levels of patients. However, we did not question the activity levels of the participants. The small sample size might have led to a type I error. All the patients with pSS were on hydroxychloroquine. These small changes of muscle architecture in patients with pSS can be related to hydroxychloroquine. However, serum creatinine and phosphokinase levels were normal in all the patients with pSS.

In our study, the mean age was 54.1±6.6 and 53.2±6.7 years in pSS group and healthy controls respectively. Sarcopenia of aging may have been the reason for finding similar muscle architecture results in both groups.[30]

In addition, we showed that the muscle strength was similar in both pSS and healthy control groups. Strömbeck et al.[4] investigated isokinetic strength of the flexors and extensors of the knee at the velocity of 60°/sec in pSS patients. Similar to our result, they found no difference in isokinetic muscle strength of the knee extensors between pSS patients and healthy controls. However, they reported that pSS patients had significantly reduced isokinetic muscle strength of the knee flexors in comparison to healthy controls at 60°/sec velocity. In addition, pSS patients had significantly reduced isokinetic endurance of the knee flexors, measured at 240°/sec velocity compared to that of healthy controls. As the muscle endurance is dependent on oxygen uptake, they thought that patients with pSS had a lower level of aerobic capacity or lower level of physical activity compared to healthy controls. There are studies that report worsened isokinetic lower limb muscle strength in various rheumatic diseases such as SLE, RA, ankylosing spondylitis and systemic sclerosis.[29,31,32] However, these studies do not mention about the possible effect of disease activity and current drug status such as corticosteroids on muscle strength.

In the current study, disease activity was assessed by the ESSPRI. In pSS group, on both legs, ESSPRI was negatively correlated with isokinetic muscle strength of the knee extensors at velocities of 60°/sec and 180°/sec, ankle plantar flexors at velocities of 30°/sec. In addition, on the dominant leg, ESSPRI was negatively correlated

with isokinetic muscle strength of the knee flexors at velocities of 60°/sec. We concluded that isokinetic muscle strength decreased in some muscles as disease activity increases.

Fatigue is one of the most common extraglandular manifestations of pSS and is associated with decreased aerobic capacity, lower physical activity levels, functional impairment, and impaired health related quality of life in pSS.[4,33-36] In our study, pSS patients had significantly higher fatigue score than the control group. Additionally, fatigue scores were correlated with some isokinetic muscle strength and work. Likewise, anxiety and depression are more common in patients with pSS compared to the healthy controls.[37,38] Similarly, in our study, depression and anxiety were more prevalent in the pSS group. However, we found no significant correlation between scores of anxiety, depression, and muscle strength.

There are several limitations to this study. Small sample size was an important limitation. Another limitation of the present study is that physical activity levels of participants were unknown. The cross-sectional design of this study precludes investigation the effects of medical therapy and change in disease activity on muscle architecture.

In conclusion, excluding a minor decrease of the pennation angle at vastus medialis, we found no structural muscle changes in patients with pSS. However, in patients with pSS, disease activity and fatigue levels were negatively correlated with the isokinetic muscle strength measurement.

Ethics Committee Approval: Approval for the study was obtained from the Committee on Human Research Ethics of Zekai Tahir Burak Women's Health Education and Research Hospital, Ankara, Türkiye (date: 20.06.2017, no: 91/2017). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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