

ULTRASOUND ELASTOGRAPHY FINDINGS OF SALIVARY GLANDS IN SJÖGREN'S SYNDROME

SJÖGREN SENDROMUNDA TÜKÜRÜK BEZLERİNİN ULTRASON ELASTOGRAFİ BULGULARI

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ABSTRACT

Aims: In Sjögren's syndrome, the basic histopathology in all affected organs is progressive lymphocyte infiltration, which causes a change in tissue elasticity in the major salivary glands. The purpose of this study was to investigate salivary gland stiffness in primary Sjögren's syndrome using shear wave elastography.

Material and Method: According to the 2016 American European Consensus Group criteria, 47 female patients were included in the study as the "patient group" by two rheumatologists. A total of 41 healthy female volunteers, who were in a similar age group and had no symptoms of dry mouth or sicca, and no diagnosis of salivary gland disease, constituted the "control group" of the study. The paired parotid and submandibular glands of all subjects were examined using shear wave elastography. The study was conducted between October 2018 and October 2019

Results: In our study, there were a significant difference in the elasticity values of the tissue of both parotid glands in both speed and shear wave elasticity values in patients with primary Sjögren's syndrome compared with the control group. However, when the submandibular glands were evaluated, no significant difference was found between the two groups. In our study, no relationship was found between the duration of symptoms and elasticity values.

Conclusion: The fact that elasticity values are higher in the evaluation of the parotid gland using shear wave elastography in patients with primary Sjögren's syndrome than in the control group makes it an easy, non-invasive, and effective imaging method in Sjögren's syndrome.

Keywords: Sjögren's syndrome; salivary glands; shear wave elastography; tissue elasticity

ÖZET

Amaç: Sjögren sendromunda etkilenen tüm organlarda temel histopatolojik bulgu lenfosit infiltrasyonudur. Bu durum tükürük bezlerinin doku esnekliğinde değişikliğe neden olur. Bu çalışmanın amacı primer Sjögren sendromunda tükürük bezlerinde oluşan doku sertliğindeki değişikliğin shear wave elastografi ile değerlendirilmesidir.

Gereç ve Yöntem: 2016 Amerika-Avrupa uzlaşma grubu kriterleri kullanılarak iki romatolog tarafından tanısı konan, 47 kadın hasta çalışmaya dahil edildi. Kontrol grubu için 41 gönüllü; benzer yaş grubu ve cinsiyette (hepsi kadın) ağız kuruluğu veya sikka semptomu olmayan; tükürük bezi etkilenimi yapan hastalık tanısı bulunmayan kişilerden seçilmiştir. Bütün vakaların her iki parotis ve submandibular bezleri shear wave elastografi ile değerlendirildi. Çalışma Ekim 2018- Ekim 2019 tarihleri arasında yapıldı.

Bulgular: Çalışmamızda her iki parotis bezinin doku elastisite değerlerinde kPa değerlerinde kontrol grubuna kıyasla anlamlı fark mevcuttu. Fakat submandibuler bezler değerlendirildiğinde hasta ve kontrol grubu arasında anlamlı fark saptanmadı. Bizim çalışmamızda semptom süresi ile elastisite değerleri arasında ilişki bulunmamıştır

Sonuç: Primer Sjögren sendromlu olgularda parotis bezinin shear wave elastografi tekniği ile değerlendirilmesinde shear wave elastisite değerlerinin, kontrol grubuna göre daha yüksek olması, Sjögren sendromunda shear wave elastografiyi kullanımı kolay, noninvasiv ve efektif bir görüntüleme yöntemi yapmaktadır.

Anahtar kelimeler: Sjögren sendromu; tükürük bezleri; shear wave elastografi; doku elastisitesi

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Makale Geliş Tarihi / Submitted: Ağustos 2021 / August 2021

Makale Kabul Tarihi / Accepted: Nisan 2022 / April 2022

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INTRODUCTION

Primary Sjögren's syndrome (pSS) is an autoimmune disease that presents with dry mouth and eyes, polyarthralgia, and fatigue. In the literature, the prevalence varies according to the diagnostic criteria used. According to a meta-analysis published in 2014, the overall incidence is 7 per 100 000; the incidence has been reported as 43 per 100 000 in Europe and Asia.¹ The diagnostic criteria established by the American-European Consensus group in 2016 are extensively used (Table 1).

Table 1. American-European Consensus Group Classification

I. Ocular symptoms, A positive answer to at least one of the following questions:
1. For at least three months, have stubborn dry eyes?
2. Is there a recurring foreign body sensation in the eyes such as sand or gravel?
3. Use artificial tears at least three times a day?
II. Oral symptoms, A positive response to at least one of the following questions:
1. Symptoms of dry mouth for at least three months
2. Recurrent or persistently swollen salivary glands
3. Need for liquids to swallow dry foods
III. Ocular symptoms, a positive result for at least one of the following two tests as objective evidence of eye involvement:
1. Schirmer's test score (without anesthesia; ≤ 5 mm/5 minutes)
2. Rose Bengal test score or other eye pain test score (≥ 4 according to Van Bijsterveld Scoring System)
IV. Histopathology: Observing of focal lymphocytic sialadenitis in the minor salivary gland (detected with the appearance of normal acini), observed by an expert histopathologist. The focus score should be ≥ 1. The focus score is the number of foci formed by at least 50 lymphocytes in the 4 mm^2 gland tissue adjacent to the normal -appearing acini tissue.
V. Salivary gland involvement: Observing a positive result for at least one of the following diagnostic tests as objective evidence of salivary gland involvement.
1. Amount of unstimulated saliva (15 minutes ≤ 1.5 mL)
2. Diffuse sialectasis (punctate, cavitory, or destructive pattern) without obstruction in the main canals in parotid sialography.
3. Delayed uptake, decreased salivary concentration, delayed excretion in salivary gland scintigraphy.
VI. Autoantibodies: Positivity of the following autoantibodies in serum
1. Positivity for antibodies against Ro (SSA) and La (SSB) antigens, or both

Salivary glands are the main target organ, and focal lymphocyte infiltration, gland destruction, and fibrosis are observed in pathologic analysis.² The diagnosis of pSS can be made by evaluating clinical, laboratory, histologic, and imaging findings together because there is no single specific diagnostic criterion. B mode ultrasonography (US), sialography, scintigraphy, and minor salivary gland biopsy methods can be used in the evaluation of the involvement of the salivary glands, but US is the first choice among these because it is fast, inexpensive, does not contain radiation, and is reproducible for evaluation of salivary glands. However, although parotid sialography is a criterion according to the American-European Consensus Criteria for pSS, B mode US has not yet been included in the diagnostic criteria.³

There is limited research about shear wave elastography findings in pSS. In this study, we investigated whether shear wave elastography (SWE), one of the advanced US methods, could contribute to the diagnosis process of patients with pSS.

MATERIAL AND METHOD

In this prospective study, according to the 2016 American European Consensus Group criteria, 47 female patients were included in the study as the "patient group" by two rheumatologists. Patients with a history of head and neck irradiation, HIV or hepatitis C infection, lymphoma history, sarcoidosis, or graft-versus-host diagnosis, and use of anticholinergic drugs were excluded from the study. All patients had undergone Schirmer testing for ocular involvement.

A total of 41 healthy female volunteers, who were in a similar age group and had no symptoms of dry mouth or sicca, and no diagnosis of salivary gland disease, constituted the "control group" of the study by rheumatologists. Patients with a history of head and neck irradiation, HIV or hepatitis C infection, lymphoma history, sarcoidosis, or graft-versus-host diagnosis, and use of anticholinergic

drugs were excluded from the study; two volunteers were excluded due to anticholinergic drug use. Individuals in both groups had no other endocrinologic or rheumatologic disorders.

Approval for the study was obtained from Keçiören Training and Research Hospital ethics committee (24.10.2018 No:2012-KAEK-15/1776). Each participant received oral information on the study and read an information sheet explaining the study procedures and objectives. A consent form was obtained from everyone included in the study.

All evaluations were performed by a single radiologist (OG, with 13 years US experience) using a Toshiba Aplio 500 device (Canon Medical Systems, Tustin, CA) and a multifrequency linear 7.2-14 MHz probe (Canon Medical Systems, Tustin, CA, USA). The radiologist was unaware of the diagnosis and laboratory test results. Two hours before the examinations, patients were asked not to eat, drink or smoke. The examination was performed in all cases in the supine position and with the neck extended. The evaluation of each participant was completed within approximately 15 minutes. The left parotid gland, left submandibular gland, right parotid gland, and right submandibular gland were examined using SWE. Each salivary gland was examined for the presence of a space-occupying lesion, and B mode US features were noted. Parenchymal homogeneity or heterogeneity, hypoechoic areas, and hyperechoic bands were noted. Then, SWE was applied on the long axis of each salivary gland, ensuring that the probe did not apply pressure to the skin. When the appropriate image for SWE was obtained, the image was frozen with the patient holding their breath for a few seconds. In the propagation mode, the contour lines displayed the quality and validity of the images. Homogeneous images had parallel contour lines. Then, in each salivary gland, round and same-sized regions of interest (ROIs) were placed at four different points in the gland, and SWE values were measured. The median elasticity value (kPa) of these four measurements was obtained, and this value was named E1 (Figure 1).

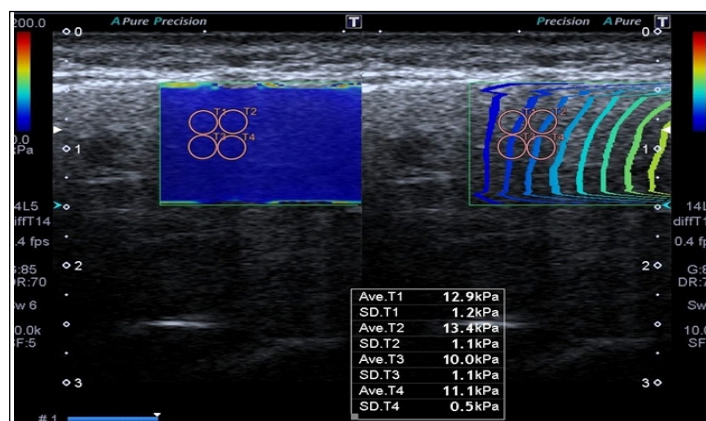


Figure 1: Shear wave elastography in the parotid gland. Four small round ROIs were used and the median value of these four shear wave values except E1. Afterward, the measurement was repeated with a single ROI that included all four measurements, and the elasticity value (kPa) was re-recorded, and this measurement was named E2 (Figure 2).

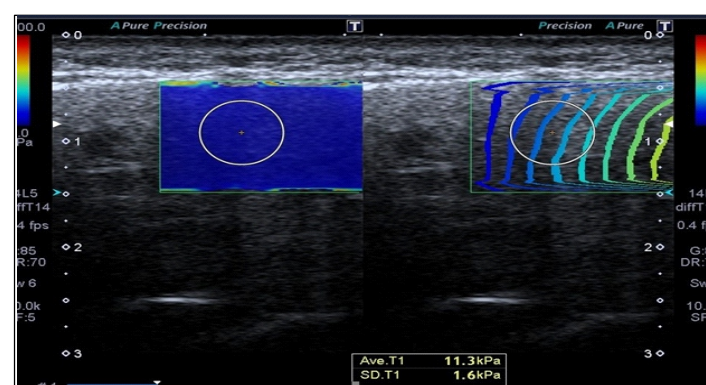


Figure 2: Shear wave elastography in the parotid gland. One large round ROI used and shear wave value excepted as E2

Thus elasticity value (kPa) values were obtained for each salivary gland, two for each and eight for each patient in total.

Analyses were performed using the IBM SPSS Statistics 23 and R program (IBM Corp, Armonk, NY, USA). Whether the numerical variables showed normal distribution was examined using normality tests and graphics. Whether there was a difference between the two independent groups in terms of numerical variables was examined using the "Mann-Whitney U Test," one of the non-parametric methods, because the assumption of normal distribution was not provided. Relationships between numerical variables were analyzed using Spearman's correlation coefficient. Receiver operating characteristics (ROC) analysis was performed to determine the appropriate cut-off values for separating patient and control groups by using measurement values. It was decided to give cut-off values for variables found to be significant in terms of areas under the ROC curve (AUC). It was preferred to select cut-off values with high sensitivity because the measurement values would be used for screening.

RESULTS

Because the study is observational, patients who presented within the date range of the study were included in the study.

The average age of the patient group was 52.23±10.25 (mean±SD) years. In the control group, the mean age was 48.97±7.54 years. There was no difference in terms of age between the patient and control groups (p>0.05). The mean duration of illness in the patient group was 31.8±33 months.

When the clinical histories of the patients were questioned, it was found that either one or both of the mouth and eye dryness symptoms had been present in all patients. All patients had positivity for antibodies against Ro (SSA) or La (SSB) antigens or both.

In B mode US, inhomogeneity was observed in 53.19% of these patients, multiple hypoechoic areas, and multiple hyperechoic bands were observed in 51% of these patients.

E1 and E2 values for each salivary gland of the patients are shown in Table 2. A correlation was found between the elasticity value (kPa) for both E1 and E2 (Table 3). There was no significant correlation between the duration of the disease and the SWE values of the salivary glands (Table 4).

Table 4: Spearman's rho correlation coefficient between duration of the disease and the SWE values

	Left submandibular E1	Left submandibular E2	Left parotid E1	Left parotid E2	Right submandibular E1	Right submandibular E2	Right parotid E1	Right parotid E2
Correlation coefficient	0,188	0,159	0,192	0,150	0,107	0,086	0,128	0,093
p	0,205	0,286	0,197	0,315	0,472	0,567	0,392	0,535

There was no significant difference between the E1 and E2 values obtained from the right and left submandibular glands between the patient and control groups (p>0.05) (Table 2).

Table 2: Elasticity values of patient and control groups

	Patient			Control			Z	p
	Median	25%	75%	Median	25%	75%		
Left parotid kPa E1	25.50	12.40	62.30	14.90	10.10	29.10	-2.546	0.011
Left parotid kPa E2	27.70	12.60	62.00	14.80	10.20	30.10	-2.247	0.025
Right parotid kPa E1	24.20	9.90	57.60	12.60	8.20	20.60	-2.282	0.023
Right parotid kPa E2	24.60	11.30	57.00	15.40	9.00	22.80	-2.338	0.019
Left submandibular kPa E1	18.40	11.60	32.90	15.20	10.10	27.20	-1.536	0.125
Left submandibular kPa E2	18.70	12.70	33.50	14.70	9.90	28.70	-1.813	0.070
Right submandibular kPa E1	16.40	10.10	25.80	12.50	11.00	17.70	-0.907	0.365
Right submandibular kPa E2	15.40	10.40	28.00	13.20	11.10	18.80	-1.063	0.288

kPa E1: median shear wave value of four small round ROI

kPa E2: shear wave value of one large ROI

In the evaluation of SWE of the right and left parotid glands (Table 2), there was a significant difference between the patient and control groups in terms of tissue elasticity (p<0.05)

The correlation coefficient was calculated between E1 and E2 obtained using SWE from each salivary gland. When the SWE of the parotid and the submandibular gland was evaluated in both groups, high correlation values were obtained between E1 and E2 (Table 3).

Table 3: Evaluation of the correlation between E1 and E2 values

	Spearman's rho correlation coefficient
Left parotid E1 - left parotid E2 kPa	0.981
Right parotid E1 - right parotid E2 kPa	0.981
Left submandibular - left submandibular E2 kPa	0.976
Right submandibular - right submandibular E2 kPa	0.956

kPa E1: median shear wave value of four small round ROI

kPa E2: shear wave value of one large ROI

When we considered the right parotid and left parotid independently, there were no statistically significant differences in terms of parotid E1 kPa and parotid E2 kPa values (p>0.05). When evaluated separately in the patient and control groups, there was no difference between right and left parotid (p>0.05). When examined in terms of kPa, the area under the ROC curve for E1 was greater than for E2. It was evaluated that E1 was slightly better than E2 in differentiating patient and control groups. Therefore, cut-off values were calculated on 47 patients x2 (right-left parotid gland) +39 control x2 (right-left parotid gland). When the cut-off value for E1 kPa in the parotid gland was accepted as 8.45, the sensitivity was calculated as 0.904, selectivity 0.244, positive likelihood ratio 1.20, and the negative likelihood ratio as 0.39.

DISCUSSION

B mode US examination is a frequently used method in the evaluation of salivary gland pathologies. US findings of characteristic pSS are inhomogeneity, multiple hypoechoic areas, and multiple hyperechoic lines. Sallafive et al. used the American-European Consensus criteria in the diagnosis of 156 patients, and the

sensitivity of US examinations in the diagnosis of pSS was found as 75.3%, and the specificity was 83.5%.⁴ In a study conducted by Cornec et al., 45 patients were diagnosed by a rheumatologist, and the sensitivity was found as 60% [95% confidence interval (CI): 45.7-74.3%], and the specificity was 87.5 (95% CI: 78.8-96.2%).⁵ In a meta-analysis including 29 studies, the combined sensitivity was 69% (95% CI: 73.7-80.9%), and the specificity was 81.5% (95% CI: 77.6-85%).⁶ These differences in sensitivity and specificity make US's ability to diagnose pSS alone in some patients controversial. Probably, for this reason, B mode ultrasonography (US) findings were not included in the criteria for the classification of Sjögren's syndrome by the American-European Consensus Group.

SWE is a US method that provides a quantitative evaluation of tissue elasticity. Lymphocytic infiltration of exocrine glands and B lymphocyte hyperreactivity are present in the physiopathology of pSS. The basic histopathology in all affected organs is progressive lymphocyte infiltration², which causes a change in tissue elasticity in the major salivary glands. Evaluation of salivary glands with SWE can increase the sensitivity and specificity of B mode US and contribute to the diagnosis. In the study of Sezer et al., strain elastography findings supported the diagnosis of pSS in 13 patients (22%) whose B mode US findings were not-diagnostic.⁷ Similarly, in the study of Dejaco et al., strain elastography was found to be useful in patients with nonspecific B mode findings.⁸

There is no definite conclusion about the difference in SWE values between parotid and submandibular glands in the literature. In a previous study, Arslan et al. found a significant difference between patient and control groups in tissue elasticity values in the submandibular and parotid glands.⁹ Similarly, Zhang et al. found significantly higher 2D SWE values in parotid and submandibular glands in patients with pSS compared with the control group.¹⁰ In a study, Samier-Guerin et al. used acoustic radiation force impulse (ARFI) elastometry in 10 patients with pSS and found a significant difference in SWE in the parotid gland between the patient and control groups and found no significant difference in the submandibular gland, which was similar to our study.¹¹ Wierzbicka et al. evaluated 78 patients with different parotid gland pathologies and found no fibrosis in US findings in patients with pSS with mild symptoms. In addition, they found unusually high stiffness values in SWE and concluded that elastography examinations were especially valuable in patients with pSS.¹²

In our study, there was a significant difference in parotid glands tissue elasticity values in kPa values in patients with pSS compared with the control group. However, when the submandibular glands were evaluated, no significant difference was found between the two groups. Like our study, Golder and Stiller used sialography and found that the parotid gland's involvement was higher compared with the submandibular gland.¹³ In the study of Turnaoglu et al., the mean SWV values of the parotid and submandibular glands were significantly higher in patients with pSS than in the healthy control group.¹⁴ In the study of Knopf et al., there was a discrepancy in ARFI values between the parotid gland and submandibular gland, like in our study.¹⁵ The reason for this may be that the histologic structures of both salivary glands are different and therefore affected by pSS at different levels. The acini of the parotid gland are formed by pure serous cells, whereas the acini of the submandibular gland are mixed types.

In the study of Arslan et al., the measurement of salivary gland contours was made using a large ROI.⁹ Samier et al. placed 10 ROIs using the ARFI technique and used the average of these values for the evaluation.¹¹ The E1 measurement used in our study is the same technique used in studies in the literature. The E2 method shortens the examination time compared with E1 and obtains a similar value. Although E1 and E2 values have a high correlation, when we look at the AUC and effect sizes, we evaluated that E1 was slightly better than E2 in distinguishing patient and control groups. For this reason, we recommend measurements made using the E1 technique.

In the literature, the relationship between the duration of disease and parotid SWE values is controversial. Tatar et al. found a significant relationship between the elasticity values of parotid glands and the duration of symptoms.¹⁶ However, Arslan et al. found no significant relationship between the duration of symptoms and elastography values.⁹ Cindil et al. found no statistically significant differences between disease duration and elasticity scores or strain ratios in the pSS group.¹⁷ Similarly, in our study, no relationship was found between the duration of symptoms and elasticity values.

Chen et al. evaluated SWE values using both US and 2.19 m/s cut-off values and cited that the diagnostic accuracy increased in the differentiation of Sicca syndrome from Sjögren's syndrome using US and 2.19 m/s cut-off values

together.¹⁸ However, Hofauer et al. concluded that user-dependent evaluations such as real-time tissue elastography and virtual touch imaging did not contribute additionally to the evaluation of salivary glands in pSS.¹⁹ Because the SWE evaluation that we used in our study was not a user-dependent technique and there was a significant difference in the SWE values of the parotid gland between the patient and control groups, we think that it may be an additional diagnostic tool in the diagnosis of pSS. In our study, there was no elasticity value difference between left and right glands. The examination can be made on one side, which would decrease exam time by 50%. Our study's limitation is that the correlation between B-mode and SWE findings was not evaluated in the patient group. In the literature, different scoring systems have been proposed to evaluate US findings in Sjögren's syndrome. However, we decided not to include it in the study because there is no consensus on the scoring systems, and the sensitivity and specificities of the defined scoring systems are different in previous studies.

CONCLUSION

The fact that elasticity (kPa) values were higher in the evaluation of the parotid gland using SWE in patients with pSS than in the control group makes SWE an easy, non-invasive, and effective imaging method in Sjögren's syndrome. Because the elasticity measurements made by placing a large number of ROIs are better than the AUC and the effect size, we recommend making the measurement this way. In addition, we think that more comprehensive and multi-center studies will contribute to the literature.

Acknowledgments:

The authors declare that they have no competing interests. There is no financial support.

Author Contributions :Concept and Design: Dr.Özlem Güngör ,Data Collection:Dr.Özlem Güngör,Dr. Kubilay Şahin,Dr. Sevinç Can Sandıkcı ; Analysis:Merve Kaşıkçı; Literature review research:Dr.Özlem Güngör, Dr. Cansu Öztürk ;Writing of the article:Dr. Özlem Güngör;Dr. Selma Uysal Ramadan.

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