ORIGINAL INVESTIGATIONS

Ultrasonography of the salivary glands in Sjögren's disease: own data analysis

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Objective: *to investigate feasibility of using ultrasonography (US) to evaluate structural changes of salivary glands (SG) in patients with Sjögren's disease (SD).*

Material and methods. *The study included 159 patients who were examined in V.A. Nasonova Research Institute of Rheumatology from 2016 to 2022 who met V.A. Nasonova Research Institute of Rheumatology 2001, and/or ACR 2012, and/or ACR/EULAR 2016 criteria for SD, and who had not previously received immunosuppressive therapy. All patients underwent a comprehensive classical examination (ophthalmological, dental, immunological) to diagnose SD. Disease activity was determined using ESSDAI index. US of the parotid gland (PG) and submandibular SGs was performed using a GE LOGIQ 9 device, and the images obtained were scored according to the OMERACT SGUS scoring system (SGUS SS).*

Results and discussion. *All SGUS SS scores statistically significantly correlated ($p<0.05$) with mouth sicca symptoms, enlargement of PG, ESSDAI activity index, presence of lymphohistiocytic infiltrate and focus score in labial SG biopsy, and parenchymatous parotitis according to sialography. No significant correlation was found with the results of sialometry. There was a significant correlation between the changes detected by US and sialography ($r=0.422$; $p=0.001$). Considering the data obtained, the consistency of the results of the different examination methods was analyzed. Bland-Altman diagrams were created to reflect the dependence of the differences between the results of US and sialography. At various stages of the comparison, not all data points were within the standardized range. In addition, 5% of the parameters were not within the interval of two standard deviations. The Bland-Altman analysis revealed a systematic discrepancy indicating a low degree of agreement between the two methods for determining structural changes in SG. According to the ROC analysis, sensitivity of ultrasound was 94% and specificity 51%. The area under the curve (AUC) was 0.787 (95% confidence interval 0.700–0.875).*

Conclusion. *SG US and sialography are not interchangeable, but complement each other in the assessment of SG structure. SG US is a safer and non-invasive method of SG examination that does not require contrast agent administration and is likely to play an important role in the dynamic monitoring of patients during the therapy. However, sialography is a more accurate method of diagnostics and assessment of the extent of SG lesions.*

Keywords: *Sjögren's disease; Sjögren's syndrome; ultrasonography of salivary glands; hypoechogenic lesions; sialography; parenchymatous parotitis.*
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For reference: *Khvan YuI, Torgashina AV, Volkov AV, Glukhova SI. Ultrasonography of the salivary glands in Sjögren's disease: own data analysis. Sovremennaya Revmatologiya=Modern Rheumatology Journal. 2024;18(5):38–43.* ***DOI:*** *10.14412/1996-7012-2024-5-38-43*

Sjögren's disease (SD), or primary Sjögren's syndrome (pSS), is a systemic chronic autoimmune disease characterized by a wide range of clinical manifestations: from exocrinopathy with the development of chronic parenchymal sialoadenitis and keratoconjunctivitis sicca to severe systemic disorders in the form of damage to the kidneys, blood vessels, lungs, nervous system, and lymphoproliferative complications [1, 2].

When diagnosing a SD, it is important to evaluate the parenchyma of the salivary glands (SG) and determine the changes corresponding to SD. Visualization of SG damage is accompanied by a number of difficulties. Currently, the main method for detecting changes in the structure of the SG is sialography. To assess the structure of the SG using sialography, the Rubin and Holt scale is used [3]: Stage I (punctuate) – parenchyma in the form of clouds; Stage II (globular) – multiple small and medium cavities with a fluid level are visible in the parenchyma; Stage III (cavitary) – large and medium cavities with a fluid level, dilated ducts; Stage IV (destructive) – confluent spots of contrast agent with unclear boundaries, destruction of the parenchyma. This method has disadvantages: catheterization of the SG duct can cause pain, there may be intolerance to water-soluble iodine-containing contrast agent, poor quality of the X-ray image, in some cases the procedure is impossible due to severe xerostomia.

Ultrasound has become important for determining changes in the SG. In the last decade, the international scientific community has been actively discussing the use of ultrasound as an alternative method for diagnosing SG lesions in SD/SS, as well as for assessing the effectiveness of various treatment methods over time. Ultrasound is a well-tolerated, non-invasive, inexpensive, radiation-free imaging method [4], which can be used repeatedly to determine the patient's condition over time. In some cases, ultrasound can replace invasive diagnostic tests, such as minor salivary gland (MSG) biopsy, or compete with sialography [5–7], and can also be used in a complex of examinations for diagnosing SD/SS [5–14]. Some authors discuss the possibility of including ultrasound data in the ACR/EULAR (American College of Rheumatology / European Alliance of Associations for Rheumatology) 2016 classification criteria [15, 16]. In addition to the structure of the SG, ultrasound is used to evaluate intraglandular lymph nodes and their differentiation disorders, which allows one to suspect the presence of MALT-lymphoma.

In SD, the parenchyma structure of the parotid SG is inhomogeneous, with increased blood flow and multiple small oval hypo- or anechoic areas.

It is generally accepted that these hypo- and anechoic areas represent disturbances in the structure of the parenchyma and

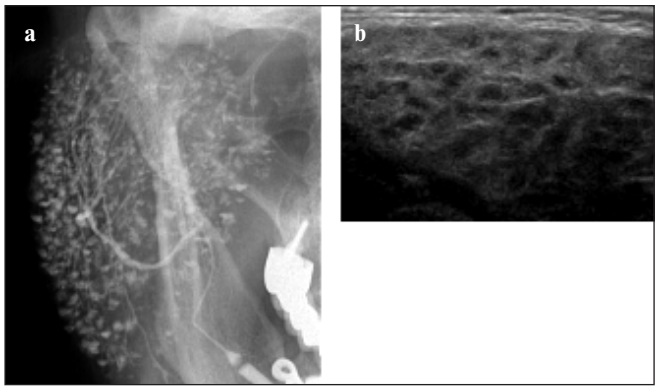

Fig. 1. *Sialography (a) and ultrasonography (b) of the SG in patient B., 55 years old*

Table 2. Characteristics of patients, n (%)

Parameter	N (%)
Oral dryness	127 (80.0)
Ocular dryness	114 (72.0)
Recurrent parotitis	32 (20.1)
Retention pain	48 (30.1)
Enlargement of parotid salivary glands	40 (25.2)
ESSDAI 0	35 (22.0)
ESSDAI 1	80 (50.3)
ESSDAI 2	34 (21.2)
ESSDAI 3	10 (6.3)
Rheumatoid factor >30 IU/ml	93 (58.5)
Anti-SSA/Ro positive (>25 IU/ml)	134 (84.3)
Anti-SSB/La positive (>25 IU/ml)	76 (48.0)
ANA ≥1:320	159 (100)
Stimulated Schirmer's test <10 mm/5 min	109 (68.5)
Tear breakup time <10 seconds	97 (61.0)
Positive staining with fluorescein and lissamine green	73 (46.0)

correspond to foci of lymphoid infiltration and altered, dilated ducts surrounded by lymphoid infiltrate [17]. When examining SG in patients with SD using ultrasound, it is difficult to understand which changes correspond to inflammation and are potentially reversible, and which indicate damage and only progress with the course of the disease [18].

For the ease of assessment of SG, various indices have been developed in which ultrasound signs are assigned a certain number of points. The indices differ in specificity, sensitivity and ease of calculation [19]. One of the convenient indices is OMERACT SGUS SS (Outcome Measures in Rheumatology Clinical Trials Salivary Gland Ultrasonography Scoring System) [20].

Ultrasound of the SG, especially in patients with immune-inflammatory rheumatic diseases, significantly reduces the need for a classification test (biopsy), since such an invasive and

Table 1. Characteristics of SG changes according SGUS SS

SGUS SS grade	Definitions
0	normal parenchyma
1	minimal change: mild inhomogeneity without anechoic/hypoechoic areas
2	moderate change: moderate inhomogeneity with focal anechoic/hypoechoic areas
3	severe change: diffuse inhomogeneity with anechoic/hypoechoic areas occupying the entire gland surface

Table 3. Instrumental characteristics of SG changes, n (%)

Parameter	N (%)
SGUS SS:	
SGUS SS grade 0	16 (9.4)
SGUS SS grade 1	11 (6.4)
SGUS SS grade 2	31 (18.2)
УЗИ SGUS SS grade 3	101 (59.4)
Stimulated SFT < 2.5ml/5 min	102 (64.1)
Sialectasia on Sialography:	
Stage 1	43 (25.3)
Stage 2	96 (56.5)
Stage 3	14 (8.2)
Stage 4	6 (3.5)
>50 elements of lymphohistiocytic infiltrate (1 focus)	146 (85.0)

unpleasant method cannot be used for screening. At the same time, the results of the study of dysfunction of SG and lacrimal glands are not highly specific.

Other radiation methods are also used in the diagnosis of SG diseases, but they are not readily available due to their high cost and, in addition, are associated with radiation exposure and are not validated for the diagnosis of SD.

The purpose of the study is to investigate the feasibility of using ultrasound to assess structural changes of the SG in patients with SD.

Material and methods. The study included patients who met the criteria of the SD of V.A. Nasonova Research Institute of Rheumatology 2001 [2], and/or ACR 2012 [21], and/or ACR/EULAR 2016 [22], who had not previously received immunosuppressive therapy. All patients underwent a comprehensive classical examination to diagnose SD: 1) ophthalmological – unstimulated and stimulated Schirmer test; tear break-up time with determination of precorneal layer stability by the rate of formation of dry spots of the tear film on the cornea; staining of the conjunctival/corneal epithelium with fluorescein and lissamine green and semiquantitative assessment of eye damage adopted by ACR in 2012 (Ocular Staining Score, OSS); 2) dental – unstimulated and stimulated saliva flow test (SFT), sialography (Fig. 1, a), biopsy of minor SGs with assessment of lymphohistiocytic infiltrate and calculation of the focus score; 3) determination of disease activity using the ESSDAI index (EULAR Sjögren's syndrome disease activity index) [23]; 4) Ultrasound of the parotid glands (PG) and submandibular (SM) SG (SMG) using the GE LOGIQ 9 device (Fig. 1, b). To assess the changes detected during ultrasound, the OMERACT SGUS SS index was used, which has gradations from 0 to 3 degrees (Table 1) [20].

The immunological blood test included determination of antinuclear factor (ANA) by indirect immunofluorescence using human Hep2 cells as a substrate, antibodies to Ro (anti-Ro) and La (anti-La) antigens by enzyme immunoassay. Levels of IgM rheumatoid factor (RF), CRP, C3, C4, IgG, IgM, IgA were assessed by a highly sensitive immunonephelometric method.

For statistical processing of data, the program Statistica for Windows version 12.0 and SPSS version 10.0 were used.

Results. The study included 159 patients, observed at V.A. Nasonova Research Institute of Rheumatology from 2016 to 2022. Characteristics of the patients are presented in Table 2. The study group consisted of 158 women and 1 man, whose mean age was 47.3±12.8 years, the median duration of the disease from the first complaints to diagnosis was 4 [2; 10] years. The mean age of disease onset was 43± 14.3 years, the mean age of diagnosis was 51±14.1 years.

Disease activity according to ESSDAI varied from low to high. All patients were positive for ANA, 84.3% of them had anti-Ro, and 48% had anti-La. RF was detected in 58.5% of cases. In 68.5% of patients, a decrease in the function of the lacrimal glands was noted according to the stimulated Schirmer test, in 73% – epithelial dystrophy of the cornea.

Table 3 presents the instrumental characteristics of the changes in the SG. A decrease in function according to stimulated SFT was detected in 64.1% of patients. In sialography, sialectasia was detected in all patients. In 60.4% of them, undoubted sialectasia was found in the form of reliable focal cavities (stage II), in 27.0% – "clouds" (stage I), which are not quite typical of SD, in 8.8% – stage III and in 3.8% – stage IV.

The ultrasound examination assessed the homogeneity of the parenchyma structure of the glands, the presence or absence of hypo- and anechoic areas of different sizes. Changes in the structure of the SG were detected in 143 of 159 patients. In 63.5% of cases, typical hypo- and anechoic areas were determined. Loose structure of the SG (grade 1 according to SGUS SS) was detected in 6.9% of patients, small hypoechoic areas (grade 2) – in 19.5%. It is interesting that 16 patients had a normal structure of the SG (grade 0 according to SGUS SS), while in 11 of them according to sialography, sialectasia on the sialography stage I was determined, and in 5 – stage II.

A correlation was found between the SGUS SS indices and the presence of dry mouth (r=0.48, p=0.01), sialectasia according to sialography (r=0.48, p<0.01), lymphohistiocytic infiltrate and focus score in the MSG biopsy (r=0.38, p<0.01), with an increase in the PG (r=0.32, p<0.01), the ESSDAI activity index (r=0.27, p<0.01; Fig. 2, 3). No statistically significant correlation was observed with the SFT results.

Considering the fact that in 16 patients ultrasound did not reveal any changes in the SG structure, an analysis of the consistency of the results obtained by ultrasound and sialography was performed. Bland-Altman plots were plotted (see Fig. 3). To simplify comparison,

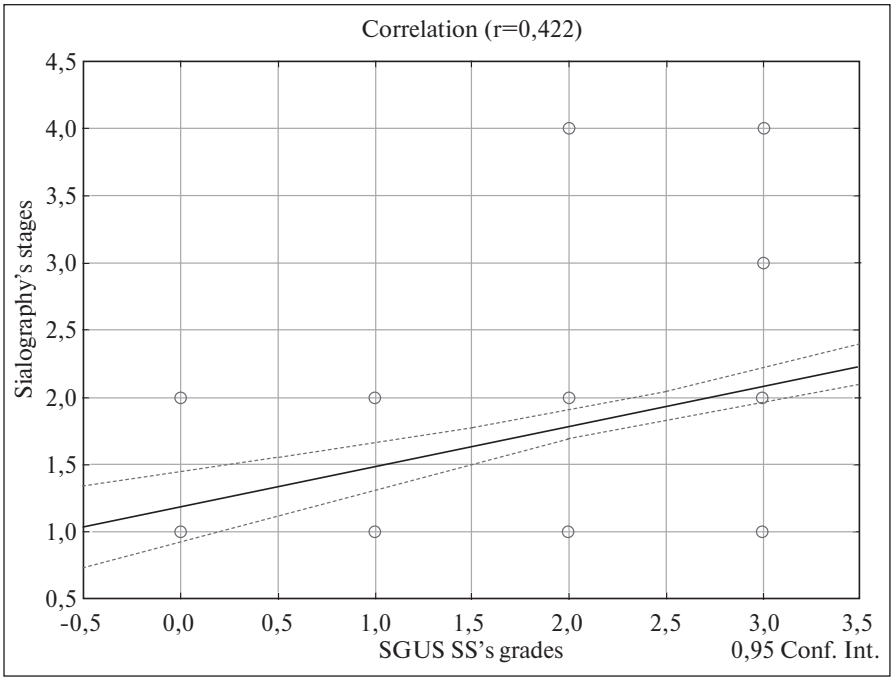

Fig. 2. *Pearson correlation analysis*

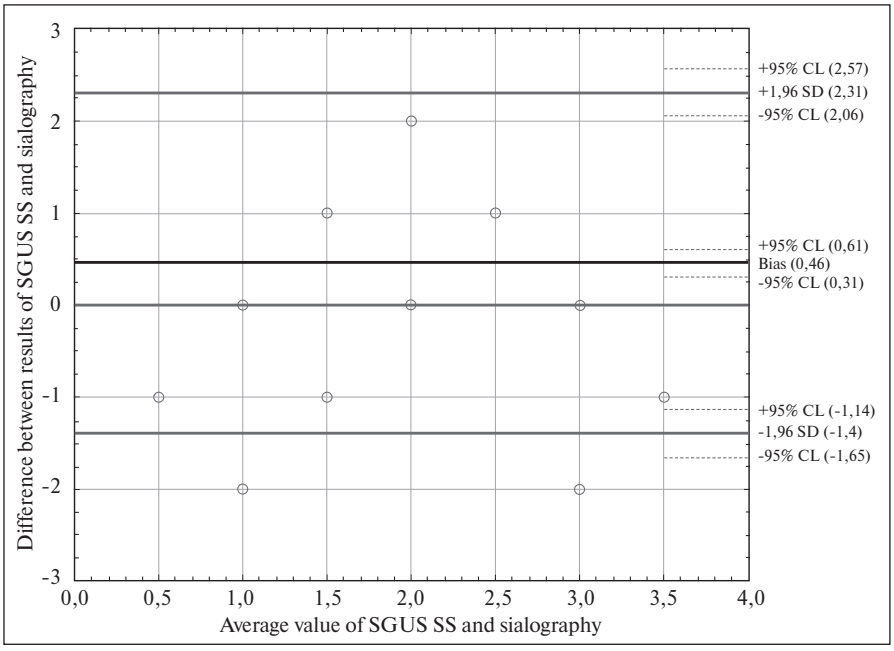

Fig. 3. *Correlation of SG changes detected by ultrasonography and sialography (Bland-Altman analysis)*

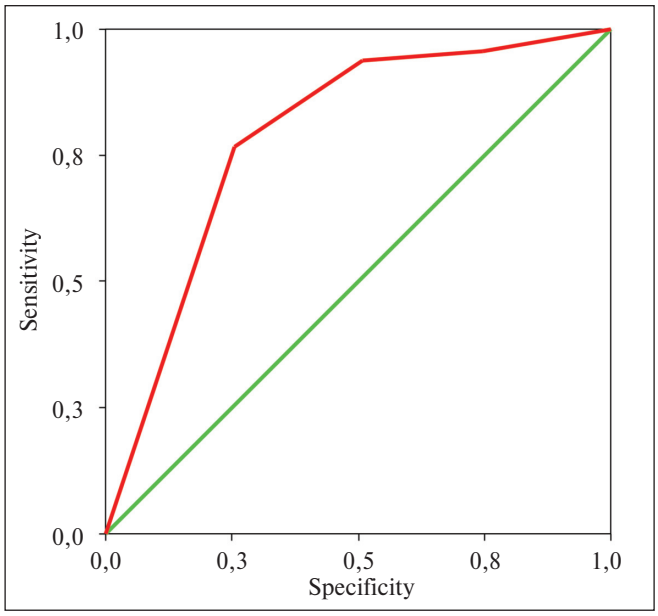

Fig. 4. *ROC analysis*

all plots were plotted in a standardized range: ±1.96*σ, which should represent the expected spread of the differences in the values of the two measurements. At different stages of comparison, not all data points fell within this standardized range. The mean deviation of the results of ultrasound compared with sialography was 0.4591, the range was from 0.3109 to 0.6073. The mean lower limit of the 95% confidence interval (CI) for ultrasound compared with sialography was -1.396, the range was -1.652 to -1.139. The average upper limit of the 95% CI for ultrasound compared to sialography was 2.314, the range was from 2.057 to 2.571. Also, 5% of the indicators were not included in the interval of two standard deviations. Thus, the Bland-Altman analysis revealed a systematic discrepancy, which indicates a weak degree of agreement between the two methods for determining structural changes in the SG.

According to the ROC analysis, the sensitivity of ultrasound was 94%, and the specificity was 51%. The area under the curve (AUC) was 0.787 (95% CI 0.700–0.875; Fig. 4).

Discussion. In our work, for the first time in the Russian Federation, a comparison of structural changes in the SG detected by sialography and ultrasound was carried out. The diagnostic value of SGUS has been assessed in a number of studies. Thus, F. Salaffi et al. [5] compared SG ultrasound in SD with sialography and scintigraphy. When examining 79 patients without SD but with symptoms of dryness, false positive results were obtained in 21 cases in ultrasound, in 33 cases in scintigraphy and in 19 cases in sialography. In 77 patients with SD, the sensitivity of ultrasound was 75.3%, specificity was 83.5%, AUC was 0.863±0.030, which exceeded the indicators of sialography and scintigraphy. However, in this study, only 40% of patients were positive for ANA and it is unclear whether all of them had a reliable diagnosis of SD. The researchers believe that SG ultrasound is a useful method for assessing structural changes in the glands in patients with suspected SD and can be a first-line visualization tool in diagnosing the disease.

K. Obinata et al. [6] compared the diagnostic value of SG ultrasound, sialography and SG biopsy. In a study of 73 patients, a statistically significant difference ($p<0.05$) was found in the sensitivity of sialography (83.3%) and MSG biopsy. The correlation between sialography and ultrasound was higher than between ultrasound and MSG biopsy. Changes detected by ultrasound correlated more reliably with sialography data than with histological changes in MSG. As ROC analysis showed, of the three examination methods, sialography was the most reliable diagnostic tool, its accuracy was 89%. At the same time, a highly reliable agreement was found between sialography and ultrasound of the PG (k=0.81; 95% CI 0.75–0.85) and a reliable agreement between sialography and ultrasound of the SMG (k=0.76; 95% CI 0.69–0.80). The authors believe that sialography in SD has a higher diagnostic reliability than other instrumental methods of SG examination.

Y. Takagi et al. [7] compared the data of sialography of the PG, ultrasound of the PG and ultrasound of the SMG in 188 patients with SD and 172 without SD. A statistically significantly lower diagnostic value of ultrasound of the PG than sialography was shown ($p<0.001$), however, ultrasound of the SMG and sialography were comparable in this indicator ($p=0.153$). The authors believe that the assessment of the PG using sialography is much more convincing than using ultrasound, but ultrasound can be used as an alternative to visualization of the SMG.

It is important that in all studies ultrasound of the SG was used to compare patients with SS with healthy individuals (control). It is noted that ultrasound does not provide sufficient information for diagnosing SD, since patients with sarcoidosis, viral hepatitis C, human immunodeficiency virus can have signs that imitate changes in the SG that occur in SD [24–26].

In our study, using extensive statistical analysis using the Bland-Altman and Pearson methods, systematic discrepancies and a weak degree of agreement between the studied methods for determining structural changes in the SG were established. It is worth noting that in 16 patients with normal SG structure, according to ultrasound data, sialography revealed different stages of sialectasia. These data are in greater agreement with the results of studies by Japanese colleagues.

Comparison of ultrasound and sialography shows that ultrasound is a safer and non-invasive method that does not require the introduction of a contrast. According to the results of some studies, sialography has a higher sensitivity for detecting changes in the SG in patients with SD. However, ultrasound of the SG can be useful for monitoring the effectiveness of treatment and assessing disease progression.

Conclusion. Ultrasound of the salivary glands and sialography are not interchangeable, but complementary methods of assessing the structure of the salivary glands. Visualization of the salivary glands using ultrasound with the determination of the OMERACT SGUS SS index can be used to identify changes in their structure, but this requires the appropriate qualifications of the specialist performing the study.

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Received/Reviewed/Accepted
06.05.2024/21.07.2024/23.07.2024

Conflict of Interest Statement

The article was prepared within the framework of the basic research topic, registration № 1021051402790-6.

The investigation has not been sponsored. There are no conflicts of interest. The authors are solely responsible for submitting the final version of the manuscript for publication. All the authors have participated in developing the concept of the article and in writing the manuscript. The final version of the manuscript has been approved by all the authors.

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