considered responsible for glandular hypo function [3]. Currently, PSS diagnosis can be made using the ACR-EULAR 2016 PSS classification criteria [4].

Ultrasound (US) has been increasingly used in the practice of rheumatology, since it is a simple exam, in real time, without ionizing radiation and less expensive than other diagnostic imaging methods [5]. Therefore, in order to improve the diagnosis [6] and monitor the therapeutic response [7], salivary gland ultrasound (SGUS) has revealed to be an instrument capable of assessing the involvement of salivary glands in a less invasive manner [8,9]. Several assessment systems have been developed for the use of SGUS, all of them highly specific, regardless of the score used [10]. SGUS's weight can be considered similar to the minor criteria of the ACR-EULAR consensus [11].

The spectral Doppler (SD), in addition to the gray scale (GS), is used to assess glandular vascularization [12,13]. The inflammatory process, by increasing glandular perfusion, generates hypervascularization and stimulates angiogenesis, resulting in hemodynamic changes measured by the variation in the resistance index (RI) [10].

The objective of this study was to evaluate the diagnostic potential and the supplementary use of SGUS plus SD to correlate SGUS+SD with the presence of glandular inflammatory process in patients with pSS.

MATERIALS & METHODS

Study population

This cross-sectional study was carried out at the Rheumatology Outpatient Clinic of the Pontifical Catholic University of Campinas from March 2017 to December 2019. High-resolution SGUS images of 17 patients diagnosed with PSS were evaluated using SD.

The diagnosis of PSS was performed according to the ACR-EULAR 2016 classification criteria. The added score ≥4 of the following items determines the diagnosis: labial salivary gland with focal lymphocytic sialoadenitis and focus score ≥1 (3 points), anti-Ro/SSA positive (3 points), ocular staining score ≥5 (or van Bijsterfeld score ≥4) in at least one eye (1 point), Schirmer's test ≤ 5 mm/5 min in at least one eye (1 point) and total unstimulated saliva flow ≤0.1 ml/min (1 point).

Patients with a previous diagnosis of any of the following conditions were excluded from the study: history of head and neck radiation therapy, active hepatitis C infection (positive C-RP), Acquired Immuno Deficiency Syndrome (AIDS), Sarcoidosis, Amyloidosis, graft versus host or IgG4-related disease.

This study was approved, on May 2, 2016, by the Human Research Ethics Committee of the Pontifical Catholic University of Campinas (opinion number 1.526.307).

Clinical and laboratory assessment

A standardized clinical evaluation was carried out and the following data was collected: Gender, age, ethnicity, duration of illness since diagnosis, clinical history of xerophthalmia and xerostomia.

The laboratory evaluation was performed by collecting the qualitative and quantitative values of autoantibodies Anti-Ro/SSA and Anti-La/SSB, Rheumatoid Factor (RF) and ANA. Nonspecific inflammatory markers were quantitatively assessed using the erythrocyte sedimentation rate (ESR) and C-reactive protein (C-RP).

Salivary gland scintigraphy

Scintigraphy of salivary glands was performed with sodium pertechnetate solution [99mTc] in all patients by the nuclear medicine service of Campinas. "Positive scintigraphy" was considered under the following circumstances: (1) delayed uptake, (2) reduced concentration and/or delayed radio tracing substance secretion, as described by the American European Criteria Group (AECG) 2002 [14].

Minor salivary gland biopsy (MSGB)

MSGB was performed in all patients by an experienced pathologist, from the pathology service of PUC-Campinas Hospital. The histopathological material was obtained from a sample of the lower lip region and classified according to the focus score described in previous studies, with ≥ 1 being considered as a positive biopsy and associated with the diagnosis of SS [15].

Ultrasound evaluation of salivary glands

For the SGUS exam, a high-resolution US equipment, MyLab50 (Esaote S.p.A., São Paulo, Brazil), with a 12 MHz high frequency linear probe, B mode, was used. The investigation was complemented with SD, using the following configurations: a frequency of 6.6-8.0 MHz, frequency repetition pulse, which varied from 0.5 Hz to 1.0 MHz and a low wall filter. US was used with all patients by the same operator, with 12 years of experience in SGUS tests, blind to the patients' clinical data. The clinical evaluation was performed by another rheumatologist.

The four major salivary glands (bilateral parotid and submandibular glands) were studied based on De Vita et al. criteria [9], as well as on the study by Cornec and his collaborators [10] and rated on a scale of 0 to 4 for echotexture, exemplified in **Figure 1**. Grade 0 represents normal gland. Grade 1 is attributed to glands that have small hypoechogenic areas without echogenic bands. When there are multiple hypoechogenic areas measuring <2 mm with hyperechogenic bands, grade 2 is ascribed. Multiple hypoechogenic areas measuring 2-6 mm with hyperechogenic bands are scored grade 3. Finally, grade 4 is attributed to glands with multiple hypoechogenic areas measuring> 6 mm or multiple calcifications with echogenic bands. The highest

value for each patient was considered to determine the patient's US classification. Scores ≥2 are considered positive for SGUS, illustrating echo graphic changes that suggest SS.

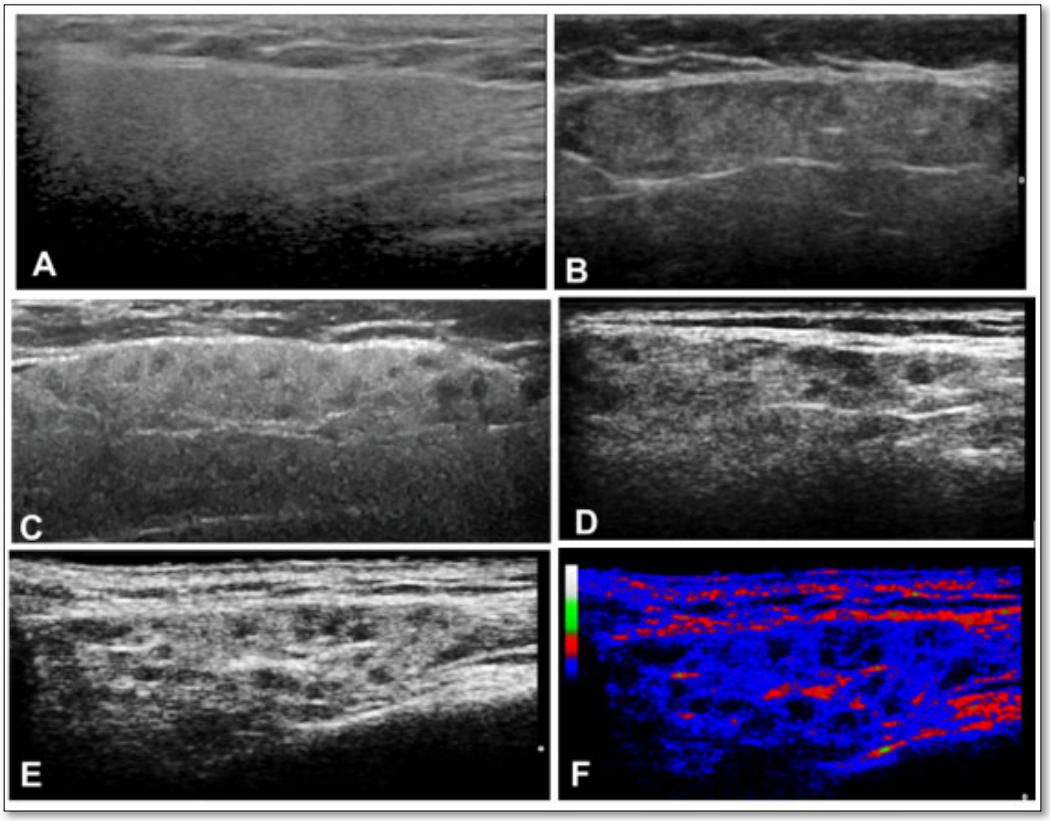

Figure 1. (A-E): Grayscale ultrasound images of the major salivary glands illustrating the semi-quantitative scoring system from 0 to 4. Grade 0 (A), Grade 1 (B), Grade 2 (C), Grade 3 (D) and Grade 4 (E). F: Stained glandular parenchyma (grade 4) for better resolution of hypoechogenic rounded areas.

The assessment of the glandular anatomical region with greater vascularization was complemented with SD, which characterized the flow of the smaller parenchymal vessels responsible for the nutrition of the glandular lobes. The RI was calculated as the difference between the peak final systolic and diastolic rate over the peak systolic rate. Normal flow at the level of soft tissues exhibits high resistance, in which the diastolic speed is considered null and the RI is closer to 1. In situations of glandular inflammatory process, due to tissue structural damage, there is a decrease in RI. **Figure 2** illustrates the use of SD in a patient with PSS.

In carrying out the examination, the transducer was used longitudinally to examine the parotid gland, and was placed slightly ahead of the ear, covering the entire length of the gland. For the submandibular glands, the patients were examined seated with the neck slightly extended and the probe was placed parallel to the jaw line and manipulated to a horizontal position, until the gland was located.

STATISTICAL ANALYSIS

Statistical analyses were performed using the SPSS software package for Windows v. 17.0 (SPSS Inc., Chicago, IL, USA). Quantitative variables were described as mean and standard deviation and the qualitative variables as number and respective percentage. Correlations between the SGUS score, RI values and different pSS parameters were assessed using Spearman's correlation coefficient. The results were considered statistically significant when p value <0.05.

RESULTS

All patients were female and Caucasoid. The mean age was 45.76±16.61 years and the average disease duration after diagnosis was 4.35±3.21 years; 100% exhibited xerostomia and xerophthalmia.

In the laboratory evaluation, we obtained: titration of the ANA that varied from 1/160 to 1/1280 with a thick speckled nuclear pattern; 88.23% had positive anti-Ro/SSA titration and 64.70% had positive anti-La/SSB and RF. In **Table 1** we

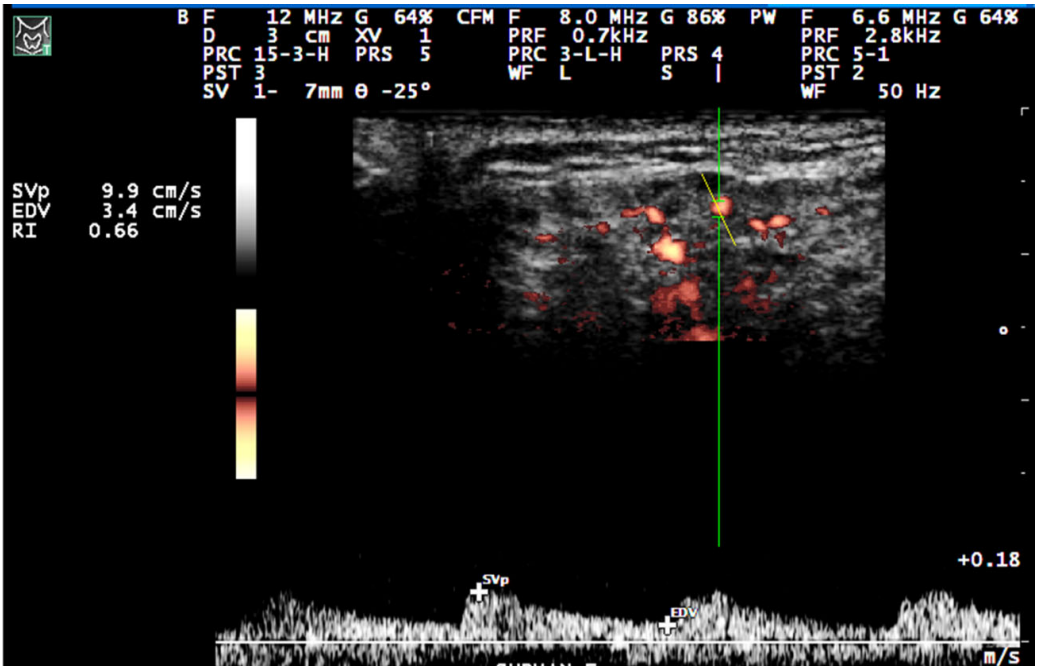

Figure 2. Spectral Doppler image of submandibular gland with grade 4 echo textural damage. Patient with xerostomia, scintigraphy with glandular secretion depression and negative minor salivary gland biopsy (MSGB) showing a decreased resistance index (RI) due to the characteristic hemodynamic alteration of glandular inflammatory activity.

Table 1. Laboratory variables.

	Mean	Standard Deviation
Anti-Ro/SSA	211.76	±19.33
Anti-La/SSB	111.11	±34.12
RF	127.17	±308.56
ESR	29.82	±10.81
C-RP	0.70	±0.44

Considering the higher grades obtained in the US evaluation of each patient, through GS from 0 to 4, we obtained the following results: Grade 0 (0%), grade 1 and grade 2 (5.88%), grade 3 (23.52%) and grade 4 (64.7%). In other words, 94.11% of the patients had positive SGUS, that is, ≥ 2. In addition, of the total 68 glands that were evaluated, 3 glands were classified as grade 0 (4.41%), 14 glands as grade 1 (20.58%), 12 glands as grade 2 (17.64%), 13 glands as grade 3 (19.11%) and 26 glands as grade 4 (38.23%).

The SD provided the following RI mean values and standard deviations for the major salivary glands shown in **Table 2**. The overall mean RI of all glands was 0.57±0.10.

report the Anti-Ro/SSA means and standard deviations, anti-La/SSB, FR, ESR and C-RP.

Table 2. Salivary glands Internal Resistance Indices.

	Mean	Standard Deviation
Right parotid RI	0.57	±0.09
Left parotid RI	0.60	±0.15
Right sub mandibular RI	0.55	±0.07
Left submandibular RI	0.57	±0.10

Spearman's correlations provided the following results, statistically significant, ranging from p<0.00 to p=0.04 **(Table 3)**.

Table 3. Spearman's correlation between ultrasound and laboratory variables.

Variables	r	p value
Right parotid SGUS x ESR	r = 0.771	p<0.00
Left submandibular SGUS x ESR	r = 0.551	p=0.02
Right submandibular SGUS x ESR	r = 0.687	p=0.02
Left submandibular SGUS x Anti-La	r = 0.499	p=0.04
Left parotid RI x SGUS right parotid	r= -0.687	p=0.02
Left submandibular RI x Anti-La	r = -0.611	p=0.02
Right submandibular RI x C-RP	r= -0.647	p=0.01

The data also showed that 100% of the patients had affected salivary glands, as evidenced by the glandular scintigraphy exam. The deficit in salivary excretion was moderate to severe in all cases. In the histopathological evaluation, biopsy of the minor salivary glands, yielded positive results in about 41% of the cases.

DISCUSSION

Despite the fact that salivary gland scintigraphy is no longer part of the 2016 diagnostic criteria, this exam has been widely used in clinical practice. In our sample, 100% of the patients' scintigraphy exam revealed functional changes; this data reflects the high sensitivity of the exam, which goes up to 89%. However, it is not an exam capable of confirming a diagnosis of SS due to its low specificity, of around 50% [16] unlike another study [17] outcome, in this study no significant correlations were found between scintigraphy and auto antibodies.

The minor salivary glands biopsy (MSGB) is considered a major criterion in the diagnosis of PSS according to the ACR-EULAR 2016 consensus. The systematic review [18] shows that sensitivity could reach 93.7% and specificity varied up to 100%. However, as research described [19] MSGB has some limitations, such as the influence of the use of corticosteroids and the difficulty of histopathological evaluation in patients with chronic symptoms due to the development of fibrosis and atrophy. Most of the population in our study, 88.23%, was classified by SGUS as grade 3 or 4, that is, they were in more advanced stages of tissue destruction. In the comparison between MSGB and SGUS [20] there was an absolute agreement at 79.2%. Therefore, we expected to find a greater number of patients with positive salivary biopsy, but our result was positive only in about 41% of the cases.

Currently, there is a growing number of studies that investigate the diagnostic potential of SGUS in SS. Regardless of the studies design and relevant objectives, a good sensitivity and high specificity of SGUS was observed in the PSS diagnostic process, contributing to SGUS inclusion as a diagnostic tool [16]. SD, in turn, allows detecting blood flow abnormalities in the parotid and submandibular glands. The inflammatory process, by increasing permeability and glandular perfusion and stimulating angiogenesis, tends to generate hemodynamic changes that can be measured by the variation in RI [7,13].

Therefore, based on the results [10] indicating that the scoring system from 0 to 4 shows less heterogeneity and less variations in specificity than other systems, we chose this score for use in this study. The cutoff values ranged from 1 to

2, with ≥2 being chosen for our US analysis. According to research [21], the integrated ACR-EULAR scoring system, when added to the US evaluation, produced 93% accuracy, compared to the criteria used alone that discriminated patients with PSS with 79% accuracy. Recent studies also show that the inclusion of US among the ACR-EULAR criteria increases sensitivity to 91.1% [22] or 95.6% [6]. In the latter study, by Joulin et al. [6] the weight of SGUS could be considered similar to the minor criteria of ACR-EULAR, which enhances the validity of the integration of SGUS to the consensus.

Our patients showed acute phase reagents' value slightly above normal reference values indicating a mild systemic inflammatory process. As shown by the work of Gottenberg et al. [23] increased ESR is generally related to the amount of immunoglobulins in blood circulation, due to the activation of polyclonal B cells. In our statistical analysis, we obtained significant positive results in the correlation between SGUS and ESR. The results indicate statistical dependence between the two variables with r between 0.55 and 0.77 for $p < 0.05$, suggesting that the SGUS can identify the glandular inflammatory process manifested in the laboratory by the elevation of ESR. C-RP, on the other hand, despite its elevation being rare and associated with other secondary inflammatory processes, as shown in the literature, in our work it was possible to obtain statistically significant correlations with the RI of parenchymal glandular vessels, demonstrated by the statistically significant correlation equal to r=-0.647 and p=0.01, which allows us to state that this acute phase inflammation marker, even if nonspecific for the systemic inflammatory process, can be correlated with the hemodynamic changes of the glands in this study [23].

Anti La/SSB antibodies are detected in up to half the patients with SS and are often associated with the presence of anti Ro/SSA antibodies. As it did not affect the performance of the classification, anti-SSB/La positivity was excluded from the ACR-EULAR criteria, since its presence without anti-SSA/Ro did not demonstrate a significant association with the phenotype of a patient with SS. [4] In the work of [5] the investigators observed that there was an association between patients with SGUS scores ≥3 with the presence of anti-Ro/SSA, but no statistical significance was found for anti-La/SSB. However, in our sample, 64.70% of the patients were positive for anti-La/SSB and it was possible to verify a moderate but significant correlation between SGUS with r=0.499 and p=0.04, in which the higher the autoantibody titers, the higher were the SGUS grades, revealing greater eco-structural damage.

Through the analysis of the results of the study conducted by Nimwegen et al. [11], SGUS can be added to the ACR-EULAR criteria, with a weight of 1, remaining the ideal diagnostic cut off score ≥4. Originally, the sensitivity and specificity of the criteria were 95.9% and 92.2%, respectively. When added to SGUS, the sensitivity increased to 97.3% and the specificity dropped slightly, to 90.2%. Thus, a good performance of the criteria was observed when the ultrasound method was used. The validity of the criteria remains high with the inclusion of SGUS and allows an initial approach with the dosage of Anti-Ro/SSA and the US. Thus, the SGUS is suggestive, although it does not replace the lip biopsy; if added to the positive Anti-Ro/SSA it could help in establishing Sjogren's Syndrome, adding 4 points in the suggested modified diagnostic criterion. In our sample, 82.35% of patients presented double positivity for anti-Ro/SSA and SGUS. Thus, these patients would be diagnosed with pSS after the initial evaluation, avoiding a lip biopsy.

Spearman's statistically significant negative correlations were found between the vascular resistance of the parenchymal vessels and the dosage of the anti-La/SSB autoantibody. The RI of the left submandibular gland with Anti-La/SSB was r=-0.611 and p=0.02; data interpretation suggests that with the increase in Anti-La titers, indicating severity, the vascular RI is reduced, indicating a glandular inflammatory process. Thus, it is again possible to observe that the anti-La/SSB was relevant in our sample.

The study conducted by Cornec et al. [9] performed an analysis of blood flow in the parotid gland, through the Doppler wave shape of the transverse facial artery, before and during stimulation with lemon juice. On the other hand, in the present study we performed an analysis of the intraparenchymal vasculature of the salivary glands and, therefore, we expected variations in the values found due to the difference in diameter of the explored vessels. In the observation of Cornec et al. [9] no differences were seen between patients with PSS and without PSS in terms of baseline RI or stimulated RI. In the analysis of the blood flow of the salivary glands, baseline RI of patients with Pss exhibited a mean value of 0.84±0.09 and, after stimulation, the mean RI was 0.77±0.10. The general RI mean in our analysis was 0.57±0.10, revealing greater impairment of the glandular vasculature, possibly explained by the high grades of GS observed in most of our sample.

Color Doppler images showed diffuse hypervascularity when alterations in the parenchymal echotexture were observed in the diseased glands [12]. Systolic peak rates increased dramatically, and arterial impedance decreased, causing a decrease in RI values. The heterogeneous pattern glands in the GS showed an increase in the Doppler flow signal. In 6 out of 11 patients with heterogeneous glands, the RI values were lower than 0.6, similar to the mean value of 0.57 found in our sample. Likewise, it can be proposed that the high percentage of patients with severe structural damage was responsible for determining low RI values in our study.

The following study by Jousse et al. [7] aimed to evaluate the ability of Doppler US to detect changes induced by the use of chimeric monoclonal antibody against CD20 in patients with pSS. When comparing the 9 patients in the control group with the group of 16 ill patients, the authors found baseline RI

values significantly lower in the ill patients (0.75±0.05) as compared to controls (0.81±0.42). After using Rituximab, no changes in parenchyma echogenicity or homogeneity were observed and the RIs were similar before (0.75±0.05) and after (0.77±0.1) treatment. However, a significant data was obtained after stimulation with lemon, when a higher systolic peak and a lower diastolic flow were observed in the Doppler wave, resulting in an increase in RI, which may reflect a decrease in glandular parenchymal inflammation due to possible depletion. Of B cells. Therefore, we may suggest again that the inflammatory process is responsible for the variations in the RI of the glandular vessels.

In connection with juvenile Sjogren's syndrome (JSS), in a previous case review by Guissa et al. [24] two cases are described. In the study in question, SGUS and SD showed consistency in the detection of chronic and active inflammatory processes of the salivary glands. The first patient had SGUS grade 4 and decreased RI, with a mean and standard deviation of 0.42±0.08. The second patient, with the same SGUS grade, also showed a decrease in the RI which mean value was 0.48±0.07. JSS can be described as a variant of PSS in adults and thus correlated as such. In our study, all patients followed up had a confirmed diagnosis of PSS and the vast majority of the population under review had SGUS with grades greater than 2, also contributing to the decreased RI results found in the present study. The RI averages for each gland assessed ranged from 0.60 to 0.55 with standard deviations ranging from ± 0.15 to ± 0.09.

Further, scientists [25] suggest that the increase in Doppler US signals without structural changes may indicate early stages of the disease. The authors also associate hyperemia of the salivary glands to the inflammatory process resulting from the pathology. In the present study, a moderate to strong negative correlation was found when correlating the RI of parotid gland vessels with SGUS ($r = -0.687$; $p = 0.02$). So, it is possible to say that with lower RI values we find higher SGUS grades, establishing a link between the echo textural and hemodynamic changes of the diseased glands. Thus, the low average of RI and the high degrees of SGUS verified in the study population allow characterizing the sample as homogeneous, despite being small.

Finally, our study had some limitations, mainly related to the sample size, which makes several inferences difficult. The fact that the studied population has high degrees of tissue destruction can influence the data obtained. To date, few articles in the literature have used RI data or used the same design as this investigation, making it difficult to establish other comparisons.

CONCLUSION

In conclusion, SGUS is useful in the diagnostic process of patients with pSS, even if it is not yet included as a diagnostic criterion. SD, through RI analysis, shows promising results in measuring the glandular inflammatory process, especially when related to acute phase inflammatory markers and serology. We then suggest the use of SD as a supplementary way to mode B for hemodynamic assessment of salivary glands. However, additional studies are needed to support SD as a monitoring tool.

CONFLICT OF INTERESTS

None of the authors have any potential conflict of interest.

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