Review Article

Diagnostic value of major salivary gland ultrasonography in primary Sjögren's syndrome: the role of grey-scale and colour/power Doppler sonography

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Abstract: Primary Sjögren's syndrome (pSS) is an autoimmune connective tissue disease characterized primarily by chronic inflammatory involvement of the exocrine glands, particularly the salivary glands. The use of ultrasound in the study of salivary glands (SGUS) has expanded considerably in recent years. The ultrasound can document structural alterations that can be visualized as hyperechogenic and hypoechogenic areas, or as areas with non-homogeneous echogenicity. To date, several systems of SGUS scoring systems of abnormalities during pSS are available. From the studies published in recent decades, it has been possible to document the high sensitivity and specificity of the pathological findings that can be documented by SGUS. SGUS can also provide added value in identifying patients at risk for developing disease complications such as lymphoma. The Doppler technique can also supply information about glandular tissue vascularization, which is very useful for diagnostic and differential purposes. In this review we will present the state of the art of SGUS, with a prevailing focus on diagnostic use and possible future developments.

Keywords: Salivary gland ultrasonography (SGUS); Sjögren's syndrome (SS); colour/power Doppler sonography (C/PDUS)

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Introduction

Sjogren's syndrome (SS) is a systemic autoimmune disease whose main target is the exocrine glands, mainly the salivary and tear glands (1). The term primary SS (pSS) refers to those conditions that are not associated with other connective tissue diseases, particularly rheumatoid arthritis. It mainly affects middle-aged women, with an estimated prevalence between 0.02% and 0.1% (2). More rarely it concerns men, the elderly or children.

The clinical presentation of pSS can be heterogeneous, ranging from symptoms of oral and ocular dryness, to systemic and multi-organ disease, to a condition that predisposes to the onset of lymphoproliferative disorders (1,3). The pathophysiological mechanism underlying pSS is the immune-mediated destruction of the epithelium of the exocrine glands, involving B and T cell responses. Classically, autoantibody biomarkers are directed against the antigens Ro/SSA and La/SSB. The diagnostic criteria for pSS include the presence of autoantibodies in the serum, but the diagnostic cornerstone remains histological analysis

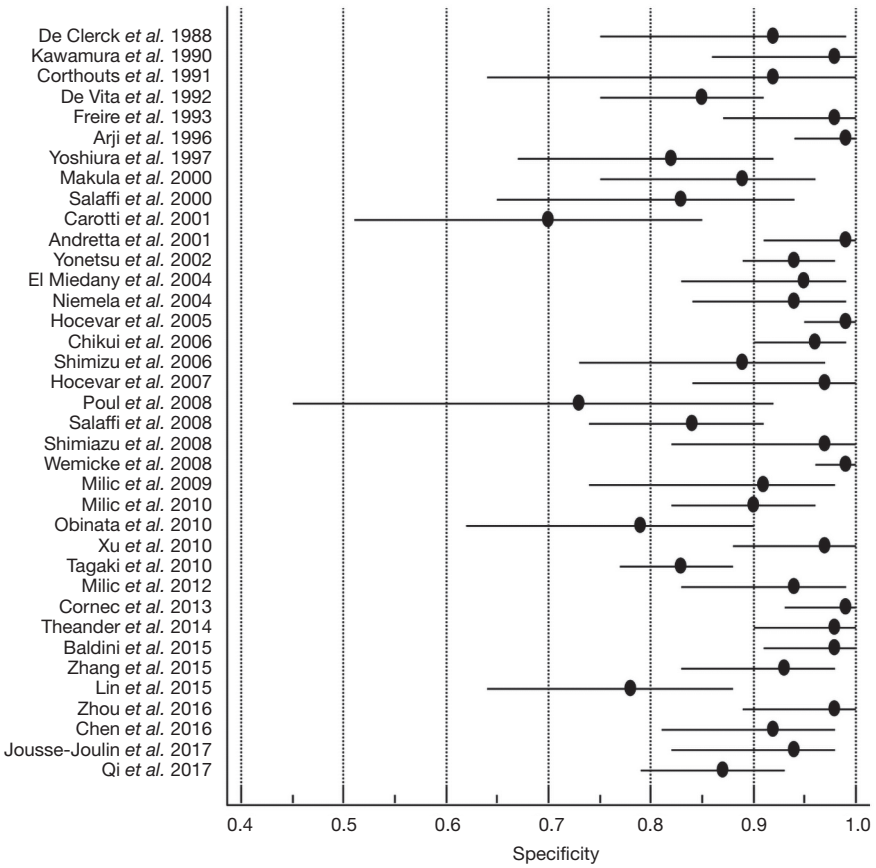

Figure 1 Forest plot showing study-specific and specificity of ultrasonography in diagnosing Sjogren's syndrome (SS). The point estimates of specificity for each study are shown as solid circle. Error bars are 95% confidence intervals (CI). Pooled specificity 0.91% (95% CI: 0.88–0.93%).

of the tissue of the minor salivary glands (4). Salivary gland ultrasonography (SGUS) is a recently introduced imaging technique to evaluate the involvement of the major salivary glands in pSS. Over the past few years, SGUS has received some interest, as it does not use ionizing radiation, is non-invasive, and is easily performed in daily clinical practice (5). According to the criteria of the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) (criteria ACR/EULAR), some patients without sicca symptoms may be classified as suffering from pSS (4). The inclusion of SGUS in the ACR/EULAR criteria would seem to improve its sensitivity from 64.4% to 84.4%, without changing its specificity (89.3% *vs.* 91.0%) (6). According to some researchers, SGUS may soon lead to the replacement of more complex techniques such as sialography and salivary scintigraphy (7,8).

SGUS as a diagnostic tool for pSS

SGUS allows to identify ecostructural anomalies characteristic of the disease (7,9-11) and its high sensitivity compared to other methods has already been demonstrated (7,11,12). The diagnostic accuracy of SGUS is also high in the early stages of pSS (13-18). In this review we identified 37 studies that examined the properties of SGUS for the diagnosis of pSS. Most of these contributions used a case-control design. A meta-analysis revealed that the common denominator of the studies is high specificity (pooled specificity 0.91%; 95% CI: 0.88–0.93%) (*Figure 1*), demonstrating how SGUS successfully reveals unaffected subjects. On the other hand, sensitivity was also considerably high (pooled sensitivity 0.83%; 95% CI: 0.78–0.87%) (*Figure 2*) (18). The main limitation in the interpretation of the pooled data is however represented by

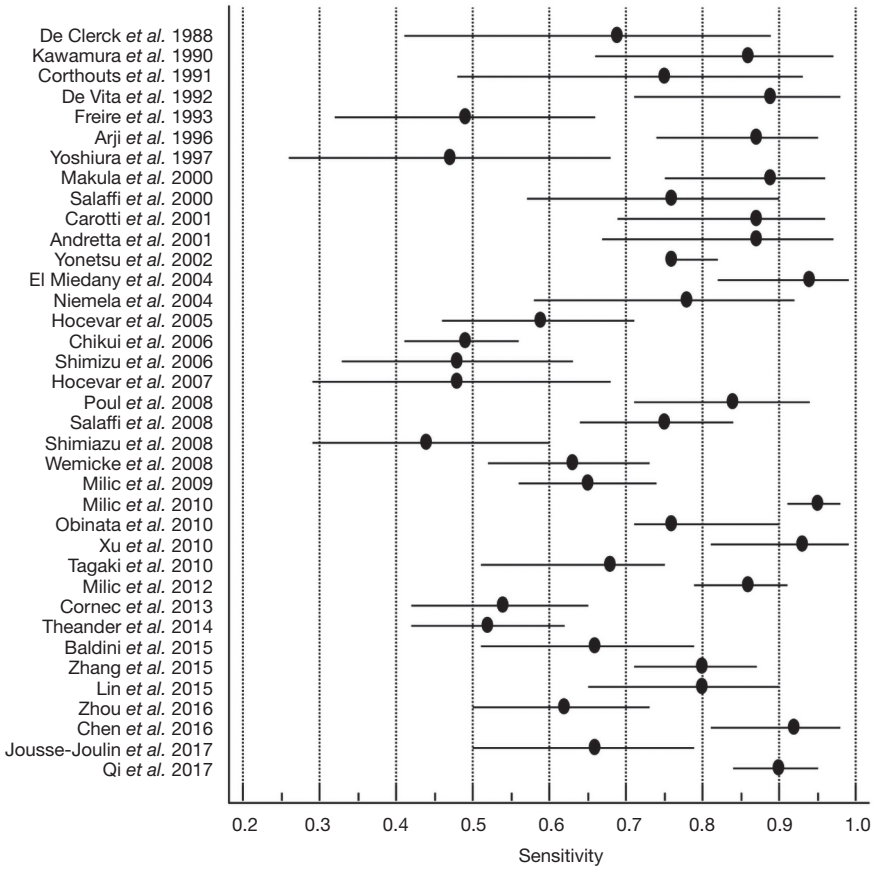

Figure 2 Forest plot showing study-specific and sensitivity of ultrasonography in diagnosing Sjogren's syndrome (SS). The point estimates of sensitivity for each study are shown as solid circle. Error bars are 95% confidence intervals (CI). Pooled sensitivity 0.83% (95% CI: 0.78–0.87%).

the low quality of the studies included and their clinical and methodological heterogeneity.

Echostructural abnormalities detectable on SGUS

The principal ecostructural abnormalities detectable by SGUS are the following: parenchymal non-homogeneity, hypo-anechoic or hyperechoic areas (due respectively to cysts or calcifications), size variations, irregularities in glandular profiles and the presence of intra- or periglandular lymph nodes (19) (*Figures 3-5*). As highlighted by several authors (9,20), the most relevant SGUS alteration of pSS is the parenchymal inhomogeneity detectable bilaterally. This ultrasound finding, is the one that has shown the greatest agreement with the alterations documented with the scintigraphy of the salivary glands, sialography, and minor labial salivary gland biopsy (LSGB) (21,22). At the level of the parotid and submandibular glands, SGUS shows the best relationship of sensitivity to specificity, with a positive predictive value of 72.0% and a negative predictive value of 96.0% (23). Compared to contrast sialography and to salivary gland scintigraphy, SGUS showed higher sensitivity (75.3%, 72.7% and 70.1%, respectively), with similar specificity (83.5%, 84.9% and 82.3%, respectively) (7). Ultrasound findings of hypoechoic, multiple, circumscribed or confluent areas and/or multiple cysts correspond to a histological pattern of ductal ectasia surrounded by lymphocyte infiltrate or dilated glandular lobes surrounded by lymphocyte aggregates. In particular, Kawamura *et al.* (24) and Salaffi *et al.* (7,12) demonstrated that the anomalies documented at SGUS are strongly related to histological changes (12), and that the SGUS score proposed for classification is well correlated with

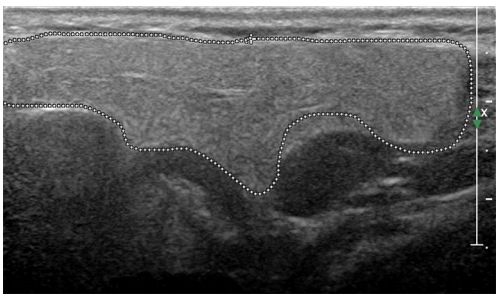

Figure 3 US scan of parotid gland in healthy subject. Note the normal echostructure and the homogeneity of parenchyma.

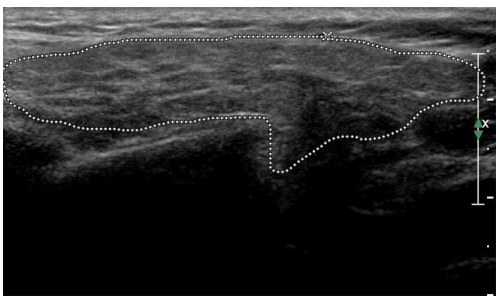

Figure 4 US longitudinal scan of parotid gland in a pSS patient. The parenchyma is completely heterogeneous with hypoechogenic areas and echogenic bands due to replacement of connective fibrous tissue. The borders of the glands are not well defined. pSS, primary Sjögren's syndrome.

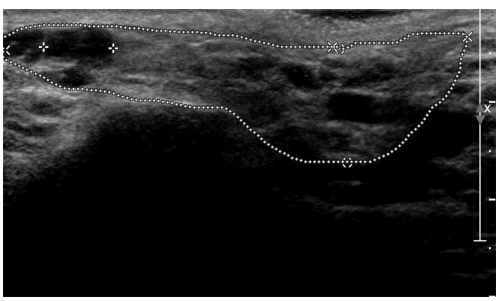

Figure 5 US longitudinal scan of parotid gland in a pSS patient. The parenchyma shows irregular contour, multiple large confluent hypoechogenic areas (>6 mm), and multiple cysts with echogenic bands, resulting in severe damage to the glandular architecture, decreased glandular volume and posterior glandular border not well visible. pSS, primary Sjögren's syndrome.

sialographic classifications (12). Cornec *et al.* (15) have verified that morphological abnormalities of the salivary glands can be detected early in the course of pSS. The diagnostic characteristics of the SGUS also seem not to vary during the disease. Applying an ultrasound cut-off of 5, the proposed SGUS scoring system was slightly less specific (85.7% *vs.* 77.9%) but more sensitive (94.9% *vs.* 98.7%) compared to the AECG criteria (4,13).

Comparison of SGUS semiquantitative scoring systems

To date, several scoring systems are available in the literature for assessing the severity pSS on the basis of SGUS. In a meta-analysis, Delli *et al.* have identified 33 scoring systems used to assess the involvement of the major salivary glands in the course of pSS (18). Among them, the scoring systems are rather heterogeneous, and this heterogeneity is related to several factors: type of salivary glands examined, ultrasound features evaluated, and cut-off applied. Hocevar *et al.* have defined a methodology widely used in several contributions (9,10,25-27). This method dates back to 2005, and is based on five components (echogenicity scored from 0 to 1, homogeneity, presence of hypoechoic areas, presence of hyperechoic reflexes, and clarity of the edges of the glands scored from 0 to 3) with a sensitivity of 58.8%, and a specificity of 98.7%. However, this scoring system is time-consuming and difficult to apply in daily clinical practice. Consequently, over the years the literature is proposing simpler scoring systems (15,20,28,29).

Alongside the Hocevar scoring system (9), the most widely used systems have been developed by De Vita *et al.* (30), whose system is the oldest available in literature, by Salaffi *et al.* (7), and by Milic *et al.* (10). The scoring system of De Vita *et al.* (30) dates back to 1992, and has been developed to define in a simplified way the parenchymal structural anomalies on the basis of a semi-quantitative score from 0 to 3: from normal to marked parenchymal inhomogeneity.

In 2008, Salaffi *et al.* (7) modified the De Vita scoring system (30), evaluating different hypo- or anechoic areas in different glands. This scoring system summarizes the changes of SGUS in each of the four main salivary glands, recording the alterations of these ultrasound findings:

Table 1 Features of the main semiquantitative scoring systems

Salaffi *et al.* (7): 0–16 final score, 0–4 for each parotid and submandibular gland. Abnormal if at least both parotids or both submandibular show a score at least of 1. US grading:
Grade 0 = normal glands
Grade 1 = regular contour, small hypoechoic spots/areas, without echogenic bands, regular or increased glandular volume (mean values 20+3 mm for the parotids and 13+2 mm for the submandibular glands) and ill-defined posterior glandular border (definite echogenic border with respect to the neighbouring structures)
Grade 2 = regular contour, evident multiple scattered hypoechogenic areas usually of variable size (<2 mm) and not uniformly distributed, without echogenic bands, regular or increased glandular volume and ill-defined posterior glandular border
Grade 3 = irregular contour, multiple large circumscribed or confluent hypoechogenic areas (2–6 mm) and/or multiple cysts, with echogenic bands, regular or decreased glandular volume and no visible posterior glandular border
Grade 4 = irregular contour, multiple large circumscribed or confluent hypoechogenic areas (>6 mm), and/or multiple cysts or multiple calcifications, with echogenic bands, resulting in severe damage to the glandular architecture, decreased glandular volume and posterior glandular border not visible
Milic *et al.* (10): 0–48 final score for parotids and submandibular glands given by the sum of the following US features:
Echogenicity = grade 0 if isoechogenic to the thyroid, grade 1 if decreased
Parenchymal homogeneity = graded from 0 (homogeneous parenchyma) to 3 (grossly inhomogeneous gland)
Hypoechogenic areas = graded from 0 to 3
Hyperechogenic reflections = graded from 0 to 3 in parotid glands, from 0 to 1 in submandibular glands
Clearness of the salivary glands posterior borders = graded from 0 to 3
Hocevar *et al.* (9): 0–48 final score for parotids and submandibular glands given by the sum of the following US features:
Echogenicity = grade 0 if isoechogenic to the thyroid, grade 1 if decreased
Parenchymal homogeneity = graded for 0 homogeneous gland, grade 1 for mild inhomogeneity, grade 2 for evident inhomogeneity, grade 3 for grossly inhomogeneity
Hypoechoic areas = grade 0 absent, grade 1 few, grade 2 several, grade 3 numerous
Hyperechoic foci = in parotid glands grade 0 absent, grade 1 few, grade 2 several, grade 3 numerous; in submandibular glands grade 0 absent, grade 1 present
Visibility of glandular borders = grade 0 well defined borders, grade 1 slightly less defined borders, grade 2 ill-defined borders, grade 3 borders not visible
De Vita *et al.* (30): 0–6 final score, 0–3 single scores for each pair of parotid or submandibular glands. US features:
For parotid glands: mild inhomogeneity scored 1
For parotid and submandibular glands: evident inhomogeneity scored 2; gross inhomogeneity scored 3

parenchymal homogeneity, echogenicity, gland size, posterior glandular boundary. Each of these parameters was evaluated according to the scoring system described in *Table 1*. The final score ranges from 0 to 16, obtained by adding the scores [0–4] for each parotid and submandibular gland. A pathological pattern is defined by a score of at least 1 in both parotids or in both submandibulars (grade 1). Grade 2 is a clear parenchymal inhomogeneity, characterized by multiple hypoechogenic areas of varying sizes (<2 mm), distributed unevenly. Using a cut-off of 6, the best ratio between sensitivity (75.3%) and specificity (83.5%) was obtained, with a positive likelihood ratio of 4.58. Applying a cut-off of 8 gains in specificity, but pays for a clear loss of sensitivity (sensitivity 54.5%, specificity 97.5%, positive likelihood ratio 21.5) (7). Milic *et al.* (10) proposed in 2010 a total ultrasound scoring system between 0 and 48 (0–12 for each gland), revealing a sensitivity of 95.1% and a specificity of 98.1%.

The wide variability in the proposed scores and cut-offs led to a great diversity of sensitivity and specificity in the

available scoring systems (18). *Table 1* summarises the main characteristics of the four scoring systems mentioned above.

Reproducibility of SGUS in pSS

Few researches have evaluated the reproducibility of SGUS in pSS. In the study by Salaffi *et al.* (7) the agreement measured on blind evaluations performed by two radiologists was high, with a kappa of 0.88 for the submandibular glands and 0.93 for the parotid glands respectively. Hocevar *et al.* (9) also documented an excellent interobserver agreement (0.90 kappa) with two blind operators. Both in the evaluation of echogenicity, inhomogeneity and presence of hypoechoic areas it is possible to document an excellent interobserver agreement (k =0.88, 0.90 and 0.88, respectively). El Miedany *et al.* (31) confirmed an excellent agreement (kappa 0.8 for the parotid gland) in assessing intraobserver reproducibility. In order to evaluate interobserver reproducibility, Salaffi *et al.* (7) studied patients with sicca symptoms without pSS or with pSS, obtaining a kappa of 0.85 for parenchymal homogeneity, 0.82 for echogenicity, 0.80 for gland size and posterior glandular boundary clarity. Interobserver reproducibility was lower than the overall score, suggesting the importance of establishing a common method for measuring scores. The reliability of interobserver readings of the submandibular glands was lower: 0.46 for homogeneity and 0.38 for echogenicity. Some authors (27), in order to increase the feasibility of ultrasound examination in daily clinical practice, proposed to evaluate the hypoechoic areas in a parotid and submandibular gland. However, in our opinion, it is of fundamental importance to carry out an ultrasound examination of all four major salivary glands in order to document the presence of neoformations or lithiasis.

Probably the scoring defined by Jousse-Joulin *et al.* (17) seems to have the best balance between simplicity and diagnostic accuracy. This scoring system also has its limits, in particular cysts are considered the only criterion of heterogeneity of the glandular parenchyma with respect to fat involution, a rather frequent condition in the submandibular glands. Fat involution can compromise the ability to visualize the salivary gland correctly. With fat involution, the edges of the glands become poorly defined and numerous thick hyperechoic bands can be seen.

SGUS as a prognostic tool

The possibility of performing outcome measurements and prognostic predictions in patients with pSS is very important for patients with pSS in view of the fact that the disease may evolve into severe extraglandular manifestations such as lymphoma.

Repeated SGUS may be useful for the early diagnosis of this serious complication, but also for highlighting possible therapeutic outcomes (32,33).

Theander *et al.* (28) investigated the prognostic value of SGUS during pSS. These authors observed hypoechoic lesions in 52% of pSS patients versus 1.8% of controls (P<0.001), with a specificity and a positive predictive value both of 98.0%, while sensitivity and negative predictive values were 52.0% and 53.0% respectively. Subjects with a pathological SGUS had more frequently significant systemic complications, increased disease activity and markers of lymphoma development, such as skin vasculitis, salivary gland swelling, detection of central germ structures in LSGB, and CD4+ T cell lymphopenia. Therefore, ultrasound parenchymal inhomogeneity may add real-time information useful in characterizing patients at high and low risk of complications. Lee *et al.* (34) confirmed the high sensitivity and specificity of SGUS in distinguishing patients with pSS from those with idiopathic sicca syndrome, also revealing in a linear regression model that the combination of SGUS positive and the presence of anti-SSA/Ro antibodies optimally predicts the classification of pSS according to the AECG, ACR and ACR-EULAR criteria (27). Astorri *et al.* (35) have also demonstrated that SGUS can stratify patients who are extractable nuclear antibodies (ENA)-negative: in ENA-negative patients without sonographic signs of pSS, LSGB should not be performed, as it is unlikely that it will add further information.

Conversely, some authors argue that in ENA-positive patients, LSGB should be performed independently of the results obtained by SGUS to study the presence of ectopic structures similar to germination centers and to diagnose the most severe phenotype of pSS (36). In the comparison between SGUS and histopathology, a clear role is proposed for SGUS in the stratification of ENA-negative patients by reducing the number of useless LSGBs. El Miedany *et al.* (31) evaluated the use of SGUS as a predictor of LSGB histopathological score: the ultrasound score was significantly correlated with the histopathological score (r=0.82). There was a high correlation between SGUS and LSGB grading (r=0.84) (12). The receiver operating characteristic curves (ROC) showed the good diagnostic properties of SGUS, followed by the semi-quantitative score of focus on LSGB. Attempts to

evaluate the independent contribution of fractional LSGB composition since the predictor of the SGUS score showed a significant contribution of both fractional composition of inflammatory infiltrates and intralobular ducts. These results suggest that the ultrasonographic findings are strongly related to pSS (12).

Colour/power Doppler sonography (C/PDUS) of the salivary glands

Research has also focused heavily on the field of color/power Doppler US (C/PDUS) despite the fact that the salivary glands have a complex vascularization. With the C/PDUS technique, a hemodynamic study of the glands can be carried out and the vascularization characteristics of a possible lesion evaluated. The C/PDUS is a complementary technique to the ultrasound B-mode study, and with it we can analyze both the physiological changes that occur during saliva stimulation in normal subjects (37) and the alteration of blood flow in the pathological glands (19,38,39). In patients with pSS a glandular hypervascularisation has been described. Hypervascularization is generally a diffused pattern, deriving from the presence of small vessels, both peripheral and randomly distributed inside the glands, visible as punctiform signals. The hypervascular pattern seemed to be directly related to the extent of parenchymal changes, being greater in the glands with higher parenchymal heterogeneity and higher number of cystiform structures. It may also be interesting to evaluate the resistivity and pulsatility indices of the facial artery which are decreased in patients with pSS, with a less intense response to lemon juice stimulation in patients than in controls (37,39). Hypervascularisation may result in a reduction in the resistive index of the facial artery. Martinoli *et al.* (37) used the Doppler technique to evaluate the vascular anatomy of the salivary glands and the changes induced by lemon juice stimulation. Stimulation leads to a marked increase in colour signals within the glandular parenchyma and to the development of an aliasing artifact due to an increased flow rate; conversely, arterial impedance is decreased resulting in a decrease in the resistive index (37). The values of the resistive index seem to return to normal within 20 seconds of stimulation with lemon juice (37). The hypervascular pattern had already been described in the course of autoimmune diseases with exocrine glandular involvement (40). It probably represents a common and unspecific finding: hyperemia is associated with inflammation in this class of diseases. Lee and co-workers (34) documented reduced volumes in the parotid and submandibular glands, and the presence of a reduced C/PDUS signal in patients with advanced pSS. Hypervascularisation and increased glandular volume would be characteristic of the inflammatory and early phase of pSS, while a reduction in glandular volume associated with hypo-vascularisation are characteristic glandular late stages. Consequently, increasing the C/PDUS signal without definite SGUS structural changes might be characteristic of the early stages of pSS. Chikui *et al.* (39), dealing with vascularization indices, revealed that the waveform of patients with pSS was more uniform than in healthy subjects, corroborated by a reduction in resistivity and pulsatility indices, suggesting the presence of downstream hypervascularisation. After stimulation of salivary secretion, the facial artery of healthy subjects changed decreasing the resistive and pulsatility indices, waveform changes indicative of increased blood flow to the submandibular gland. In contrast, the facial artery of patients with pSS did not respond sufficiently to stimulation, showing changes in resistivity and pulsatility indices significantly lower than those of controls. Doppler waveform abnormalities are related to the severity of glandular damage, indicating a close connection between altered blood flow of the salivary gland and altered secretory function in pSS. Carotti *et al.* (41) documented that peak systolic velocity was more sensitive than the resistive index. Resistivity values of the parotids and submandibular glands did not show significant changes after lemon stimulation in patients with pSS or in controls.

Conclusions

In conclusion, ultrasound examination of the salivary glands contributes significantly to the diagnosis of pSS. The main advantages are the prompt availability, repeatability, and low cost of the method. In addition, all major salivary glands can be easily studied in a single examination, and it is also possible to identify a proportion of subjects at greater risk of extra-glandular complications. However, in the context of early detection of pSS, and probably for follow-up monitoring of the disease in the context of clinical trials and in the context of lymphoproliferative disease, more sophisticated scoring systems, including vascularization characteristics, will be needed. Within the imaging methods available for pSS, SGUS integrated with the C/PDUS technique is considered to be the first-line examination for both diagnosis and follow-up.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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