Review

Clinical utility of salivary and lacrimal gland ultrasonography in primary Sjögren's syndrome

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ABSTRACT

This review discusses the clinical utility of salivary gland ultrasonography (SGUS) and lacrimal gland ultrasonography (LGUS) in primary Sjögren's syndrome (SjS). Several studies have shown that SGUS findings improve the diagnostic performance of the recent SjS classification criteria. Lacrimal gland ultrasonography findings can also aid in the diagnosis of SjS. However, SGUS and LGUS findings correlated with salivary or lacrimal gland function and minor salivary gland biopsy findings. A better treatment response to rituximab and salivary stimulants was observed in SjS patients with lower SGUS scores. In addition, the clinical implications of Doppler ultrasonography and ultrasound elastography of the salivary and lacrimal glands were investigated in patients with SjS. This review highlights the advantages of SGUS and LGUS in the diagnosis and prediction of salivary and lacrimal gland functions and treatment response in patients with SjS. Additionally, modalities other than B-mode ultrasonography, such as Doppler ultrasonography and ultrasound elastography, have been actively studied to demonstrate the clinical utility of SjS. Ultrasonography has great advantages such as immediate performance and interpretation, no harmful complications, and no discomfort to patients. Therefore, SGUS and LGUS are potentially useful diagnostic and predictive tools for SjS.

Introduction

Primary Sjögren's syndrome (SjS) is a systemic autoimmune disease primarily accompanied by sicca symptoms, dry eyes, and dry mouth in affected patients (1). Approximately 50% of patients with SjS have extra-glandular manifestations, such as haematologic, renal, respiratory, neurologic, and musculoskeletal manifestations (2), and patients with SjS have a six-fold higher risk of non-Hodgkin's lymphoma than the general population (3). The disease activity and damage index for SjS are based on systemic manifestations (4, 5); however, the classification criteria for SjS are still based on exocrine dysfunction and autoimmunity. The diagnostic or classification criteria for SjS have been published since 1965 (6), and the most recent classification criteria were developed in collaboration with the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) in 2016 (7). The recent 2016 ACR/EULAR classification for SjS excluded subjective signs of sicca symptoms and nonspecific findings, such as salivary scintigraphy in components of classification criteria, and finally included five components as follows: histologic findings of labial salivary gland biopsy, anti-Sjögren's-syndrome-related antigen A (SSA)/Ro antibody, ocular staining score/van Bijsterveld score, Shirmer's test, and unstimulated whole-saliva flow rate (7). However, labial salivary gland biopsy is an invasive procedure, and 21% of patients experience long-standing sensory impairment (8). Furthermore, a delay in SjS diagnosis is inevitable, owing to histological staining and interpretation of the focus score in labial salivary gland biopsy. Lissamine green for the conjunctiva and fluorescein for the cornea are required to evaluate the ocular staining score, which can induce stinging eyes and irritation (9). Furthermore, the poor inter-rater repeatability of the ocular staining score, even among trained ophthalmologists, can cause misdiagnosis and reduce the usefulness of the ocular staining score in the outcome measurement of SjS treatment

(10). Ultrasonography of the salivary and lacrimal glands has the advantages of immediate performance and interpretation, no harmful complications, and no discomfort to patients. Salivary gland ultrasonography (SGUS) and lacrimal gland ultrasonography (LGUS) were not included in the classification criteria for SjS because experts did not agree that sufficient validation of SGUS in the diagnosis of SjS was conducted at that time (7). However, several recent studies on SGUS and LGUS in patients with SjS have been conducted to evaluate their diagnostic utility and outcome measurements. In this study, we reviewed the clinical utilities of SGUS and LGUS in SjS.

Techniques of salivary and lacrimal gland ultrasonography

Salivary gland ultrasonography is performed on both the parotid and submandibular glands. A linear probe with a frequency of 5–12 MHz, which is similar to that used in thyroid gland ultrasonography, is typically used. First, patients are asked to lie in the supine position and place a small pillow behind their neck to hyperextend the neck. Hyperextension of the C-spine exposes the submandibular gland. The head is rotated ipsilaterally to assess the parotid and submandibular glands. The parotid gland is placed perpendicular to the mandibular ramus, which is usually located immediately in front of the ear tragus (Fig. 1a) (11). The external carotid artery and retromandibular vein are visible on ultrasonography B-mode imaging of the parotid gland; however, the excretory duct (Stensen's duct) is not visible unless it is dilated due to pathological conditions (11). The submandibular gland is located in the submandibular triangle, with the margins of the anterior and posterior bellies of the digastric muscle and body of the mandible (11). However, identifying the digastric muscles using B-mode ultrasonography is challenging. Therefore, a more useful technique for assessing the submandibular gland is as follows: 1) find the inferior pole of the parotid gland, which is placed at the angle of the mandible; 2) move the ultrasonography probe forward along the body of the mandible; and 3) find the oval-shaped submandibular gland (Fig. 1a). In cases of severe fibrosis of the submandibular gland, the echotexture of the submandibular gland can be indistinguishable from the adjacent soft tissue. Doppler ultrasonography can be used to detect Doppler signals in the facial arteries and veins, which are always visible inside the submandibular gland (Fig. 1b) (11). Additionally, the excretory duct of the submandibular gland (Wharton's duct) is not visible under normal conditions. The normal echogenicity of the parotid and submandibular glands are similar to that of the thyroid parenchyma; therefore, the thyroid gland should be assessed using ultrasonography. The thyroid gland is located between the trachea and carotid artery/internal jugular vein (Fig. 1c). The Outcome Measures in Rheumatology (OMERACT) ultrasound working group recommends assessing the parotid and submandibular glands in both longitudinal and transverse views. The sublingual gland is excluded from the standard process of the OMERACT ultrasound working group because it is too small to establish a reliable assessment (11).

The bilateral lacrimal glands are located on the superior-lateral side of the orbit, and the probe is placed obliquely and cranially along the lateral side of the supraorbital margin of the frontal bone to visualise the lacrimal fossa (Fig. 2a) (12). Patients are placed on the bed in the supine position with their eyes closed. The lacrimal glands are found between the orbit and supraorbital margin of the frontal bone (Fig. 2b). Longitudinal view of the lacrimal glands is available; however, a transverse view is usually difficult to obtain because of the anatomical curves of the eyelids. In addition, longitudinal view with eyelids closed state can achieve sufficient view for lacrimal glands because elevator palpebrae aponeurosis expose most of the lacrimal glands when eyelids are closed (13).

Scoring system of the salivary glands

Various scoring systems for the salivary glands in SjS have been developed since the 1990's (14-17). De Vita *et al*. suggested a semi-quantitative scoring system that assesses the inhomogeneity of the bilateral parotid and submandibular glands (14). This method graded each salivary gland as follows; 0: normal; 1: mild inhomogeneity (isolated and small hypo/anechoic areas without hyperechoic bands); 2: evident inhomogeneity (multiple scattered hypo/anechoic areas and/or a few hyperechoic bands); and 3: gross inhomogeneity (large and confluent hypo/anechoic areas and/or diffuse hyperechoic bands) (14). Higher grades on one side of the parotid and submandibular glands were summed and interpreted as normal for 0–1, moderate change for 2–4, and severe change for 5–6 (14). Ariji *et al*. suggested a grading of the bilateral parotid glands according to grades 0–4 using contours, hypoechoic areas, and hyperechoic bands (18). The third scoring system developed by Salaffi *et al*. considers the degree of parenchymal inhomogeneity (15). This method measures the overall change as a grade between 0–4 in each salivary gland (bilateral parotid and submandibular glands) and uses the sum of the grades (range, 0 to 16) with a cut-off value of seven (15). El Miedany suggested another scoring system using the homogeneity and size of the hypoechoic areas of the bilateral parotid glands (19). Hocevar *et al*. used five factors, including parenchymal echogenicity (0: echogenicity comparable with that of the thyroid gland; 1: decreased echogenicity than that of the thyroid gland), homogeneity (0–3), hypoechogenic area (0–3), hyperechogenic reflection (0–3 in the parotid glands and 0–1 in the submandibular glands), and delineation of the salivary gland border (0–3) (16). The total sum of grades in the bilateral parotid and submandibular glands ranged between 0–48, and a sum of >17 was assumed to be a compatible ultrasonographic finding for SjS (16). The Hocevar scoring method can duplicate the total score because patients with higher scores on the components of the hypoechogenic area or hyperechogenic reflection have higher scores on homogeneity, echogenicity, and delineation of the salivary gland border components (16). Milic *et al*.

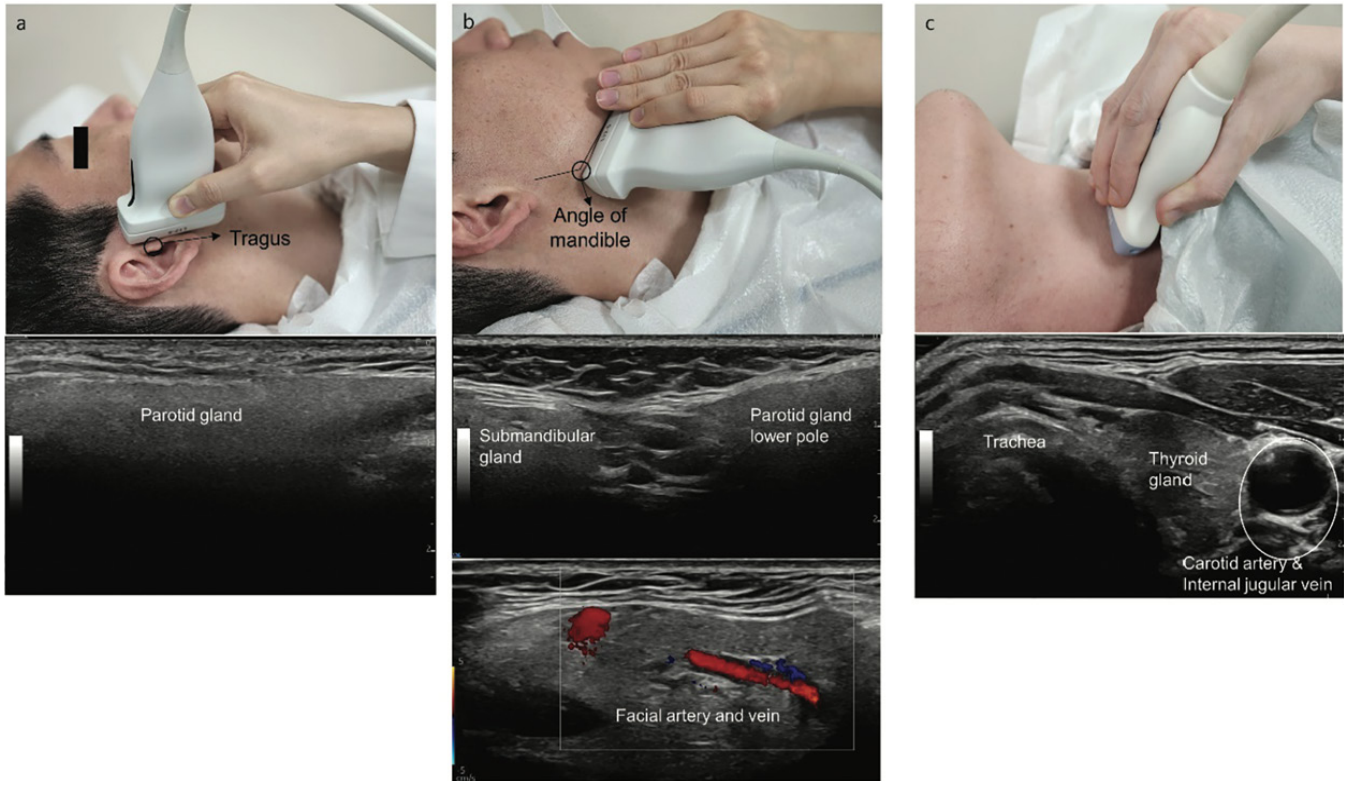

Fig. 1. Ultrasound probe positioning and technique to access the parotid, submandibular, and thyroid glands.
a: The probe should be placed in front of the tragus of the ear, which is parallel to the mandibular ramus. **b**: The inferior pole of parotid gland can be found at the angle of the mandible, then the probe should move forward along the body of mandible. In case of diffuse fibrous change in the submandibular gland, the Doppler signal of the facial artery and vein can aid to distinguish the submandibular gland. **c**: To find the thyroid gland (the echogenicity of the thyroid gland is comparable with that of the normal parotid and submandibular glands), the probe should be placed adjacent to the cricoid cartilage, the thyroid gland is placed between the trachea and carotid artery/internal jugular vein.

developed a scoring method that only scores the severity of inhomogeneity in each salivary gland (bilateral parotid and submandibular glands); the total score ranged between 0–12 (0–3 for each salivary gland) (17). Cornec *et al*. simply modified the De Vita's method by using hypoechogenic area and size of the hyperechogenic bands (20). The last scoring system suggested by Theander modified the Milic's scoring system and graded the bilateral parotid and submandibular glands as grades 0–3 according to the severity of inhomogeneity (21). One study compared the distribution of SGUS scores according to the De Vita, Salaffi, Milic and OMERACT methods, and Milic method relatively overestimated grade of SGUS than three other methods (22). Recent meta-analysis evaluated diagnostic accuracy of each scoring system (0–4 scoring system, 0–16 scoring system, and 0–48 scoring system), and sensitivity was 75% (95% confidence interval [CI] 71–79%), 84% (95% CI 81–87%), and 75% (95% CI 70–80%), respectively, while the specificity was 93% (95% CI 90–95%), 88% (85–91%), and 95% (91–97%), respectively (23). The 0–4 scoring system showed the lowest heterogeneity and highest diagnostic odds ratio compared to the other scoring systems (23).

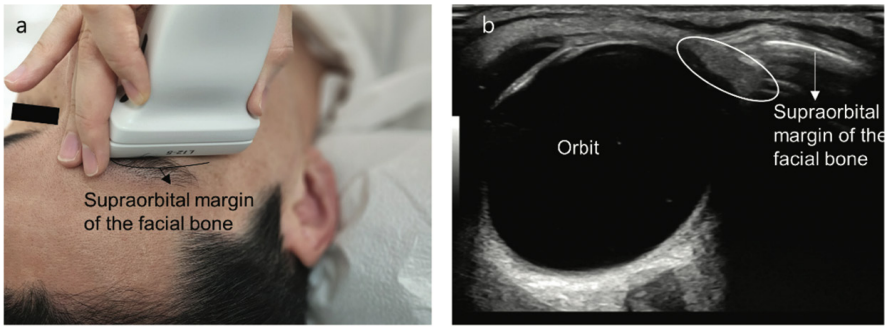

Fig. 2. Techniques of accessing the lacrimal gland.
a: The probe should be placed oblique and cranially along the supraorbital margin of the frontal bone. **b**: In a B-mode ultrasonography image, the lacrimal gland is placed between the orbit and bone margin of the frontal bone.

The OMERACT ultrasound working group developed a novel scoring system for major salivary glands (parotid and submandibular glands) in SjS (11). Twenty-five rheumatologists reached consensus after three rounds of Delphi (11). Severity of the anechoic/hypoechoic foci of each salivary gland was assessed and scored semi-quantitatively as follows: 0, normal parenchyma; 1, minimal change (mild inhomogeneity without anechoic/hypoechoic foci); 2, moderate change (moderate inhomogeneity with focal anechoic/hypoechoic

Table I. Scoring methods for salivary gland ultrasonography (SGUS).

Method	Component	Grading	Cut-off value and diagnostic accuracy
De Vita, 1992 (14)	Inhomogeneity of bilateral parotid and submandibular glands	0–3 (each gland) 0: Normal 1: Mild inhomogeneity 2: Evident inhomogeneity (evident multiple scattered hypoechogenic areas) 3: Gross Inhomogeneity (large circumscribed or confluent hypoechogenic areas, and/or gross linear densities) Total score: 0–6 Sum of higher score on each parotid and submandibular gland	≥2 Sensitivity, 88.8% Specificity, 84.6%
Ariji, 1996 (18)	Contour, hypoechoic area, hyperechoic bands of bilateral parotid glands	0–4 (each gland) 0: Regular contours with no internal echoes 1: Regular contours with small multiple hypoechoic spots/areas without hyperechoic bands 2: Regular contours with round multiple hypoechoic spots/areas without hyperechoic bands 3: Irregular contours with round multiple hypoechoic spots/areas with hyperechoic bands 4: Irregular contours with irregular multiple hypoechoic spots/areas with hyperechoic bands Select higher score from bilateral parotid glands	≥1 Sensitivity, 68.0% Specificity, 82.0%
Salaffi, 2000 (15)	Contour, size of hypoechoic area, hyperechoic bands, size of gland, cyst, delineation of posterior glandular border of bilateral parotid and submandibular glands	0–4 (each gland) 0: normal 1: Regular contour, small hypoechoic areas, without hyperechoic bands, regular or increased glandular volume, and ill-defined posterior glandular border 2: Regular contour, evident multiple scattered hypoechogenic areas usually of variable size (<2 mm) and not uniformly distributed, without hyperechoic bands, regular or increased glandular volume, and ill-defined posterior glandular border 3: Irregular contour, multiple large circumscribed or confluent hypoechogenic areas (2–6 mm) and/or multiple cysts, with hyperechoic bands, regular or decreased glandular volume, and no visible posterior glandular border. 4: Irregular contour, multiple large circumscribed or confluent hypoechogenic areas (>6 mm), and/or multiple cysts or multiple calcifications, with hyperechoic bands, decreased glandular volume, and no visible posterior glandular border Total score: 0–16 Sum of 4 glands	≥7 Sensitivity, 75.3% Specificity, 83.5%
El Miedany, 2004 (19)	Inhomogeneity, size of hypoechoic area of bilateral parotid glands	0 – 3 (each gland) 0: Normal 1: mild inhomogeneity as diffuse hypoechoic areolae less than 2 mm with blurred borders 2: moderate inhomogeneity as large hypoechoic areas (2–6 mm), with sharp borders 3: severe inhomogeneity as more than 6 mm circumscribed hypoechoic areas Select highest score from bilateral parotid glands	≥1 Sensitivity, 95.7% Specificity, 92.7%
Hocevar, 2005 (16)	Echogenicity, Inhomogeneity, Hypoechoic area, Hyperechoic eflection, Clearness of the gland border of bilateral parotid and submandibular glands	Echogenicity: 0–1 Inhomogeneity: 0–3 Hypoechogenic areas: 0–3 Hyperechogenic reflections: 0–3 in the parotid glands 0–1 in the submandibular glands Clearness of salivary gland borders: 0–3 0–13 (for each parotid gland) 0–11 (for each submandibular gland) Total score: 0–48 (sum of four glands)	≥17 Sensitivity, 58.8% Specificity, 98.7%
Milic, 2010 (17)	Inhomogeneity of bilateral parotid and submandibular glands	0–3 (each gland) 0: normal 1: mild inhomogeneity 2: moderate inhomogeneity 3: severe inhomogeneity Total score: 0–12 (sum of four glands)	≥6 Sensitivity, 95.1% Specificity, 90.0%

Method	Component	Grading	Cut-off value and diagnostic accuracy
Cornec, 2013 (20)	Inhomogeneity, size of hypoechoic area, hyperechoic bands of bilateral parotid and submandibular glands	0–4 (each gland) 0: normal 1: small hypoechogenic areas without hyperechoic bands 2: multiple hypoechogenic areas measuring <2 mm with hyperechoic bands 3: multiple hypoechogenic areas measuring 2–6 mm with hyperechoic bands 4: multiple hypoechogenic areas measuring >6 mm or multiple calcifications with hyperechoic bands Select highest score from 4 glands	≥2 Sensitivity, 62.8% Specificity, 95.0%
Theander, 2014 (21)	Inhomogeneity, hypoechoic area of bilateral parotid and submandibular glands	0–3 (each gland) 0: normal 1: mild inhomogeneity 2: several rounded hypoechoic lesions 3: numerous or confluent rounded hypoechoic lesions Select highest score from 4 glands	≥2 Sensitivity, 52.0% Specificity, 98.5%
OMERACT ultrasound working group, 2019 (11)	Mainly severity of hypoechoic areas of bilateral parotid and submandibular glands	0–3 (each gland) 0: normal 1: minimal change: mild inhomogeneity without a n/hypoechoic areas 2: moderate change: moderate inhomogeneity with focal an/hypoechoic areas but surrounded by normal salivary parenchyma 3: severe change: diffuse inhomogeneity with an/hypoechoic areas occupying the entire gland surface but surrounded with no normal tissue * Non-dominance of hypoechoic area - Grade 1: diffuse fatty change (diffuse hyperechoic gland parenchyma compared to adjacent tissue) Grade 3: diffuse fibrous change (diffuse hyperechoic bands which is indistinguishable from adjacent soft tissue)	≥2 (Select highest score from four glands)(29) Sensitivity, 72% Specificity, 91% ≥4 (sum of higher score from parotid and submandibular glands) (30) Sensitivity, 77.2% Specificity, 92.2%

foci surrounded by normal tissue); and 3, severe change (diffuse inhomogeneity with anechoic/hypoechoic areas occupying the entire gland surface) (11). When anechoic/hypoechoic foci were absent, diffuse fatty change (hyperechoic gland compared to adjacent tissue) was graded as 1, and diffuse fibrotic change (diffuse hyperechoic bands indistinguishable from adjacent soft tissue) was graded as 3 (11). The OMERACT scoring system focuses on the severity of anechoic/hypoechoic areas because homogeneity and anechoic/hypoechoic foci of the salivary glands show good inter- and intra-reader reliabilities (24-27). A strong correlation existed between homogeneity and anechoic/hypoechoic foci, indicating that the two components contained similar information (28). Scoring only anechoic/hypoechoic foci on one side of the parotid and submandibular glands showed a similar diagnostic value (area under the receiver operating characteristic curve [AUC-ROC] =0.846) compared to including all five components of the bilateral parotid and submandibular glands (AUC = 0.856) (28). Additionally, the correlation coefficient between the scores of the left and right parotid glands was 0.909 and 0.868 for the left and right submandibular glands, respectively (28). Therefore, the OMERACT ultrasound working group recommends scoring at least one parotid and submandibular glands (11). Applying the OMERACT scoring system with a cut-off value of ≥2 in at least one major salivary gland showed a sensitivity of 72% and specificity of 91% (29). Another study applied a total score of ≥4, including the OMERACT score on the left or right parotid and submandibular glands, and showed diagnostic values of 0.756 and 0.772, respectively (30). Salivary gland ultrasonographic scoring using the OMERACT ultrasound working group method showed excellent intra-reader (Light's kappa = 0.81) and good inter-reader (Light's kappa = 0.66) reliabilities (11). The reliability test for the OMERACT scoring system showed moderate to excellent intra- and inter-reader reliabilities, even by less experienced sonographers (27). The De Vita and OMERACT methods showed similar intra-rater reliability (Light's kappa 0.86 for De Vita method, and 0.87 for OMERACT method) and inter-rater reliability (Light's kappa 0.75 for De Vita method, and 0.77 for OMERACT method) (31). The ultrasonographic scoring methods for the salivary glands are summarised in Table I.

Doppler ultrasonography images of the major salivary glands have also been used to increase the diagnostic value of SGUS for SjS. One study showed that colour Doppler signals correlated with the degree of chronic inflammation in minor salivary gland biopsy (32). Although the Doppler ultrasonography index, which is graded by the intensity of blood flow in the major salivary glands, was significantly higher in patients with SjS than in HCs, the diagnostic value of the Doppler ultrasonography index was lower than that of SGUS (33). When SGUS scores in patients with SjS were followed-up at two-year intervals, 18.6% of patients had worsening SGUS scores, and in a group with worsening

SGUS scores, only the power Doppler score significantly worsened (34). Superb microvascular imaging can achieve more sensitive vessel imaging and detect and visualise smaller vessels than color or power Doppler imaging (35). Superb microvascular imaging of the parotid and submandibular glands demonstrated higher diagnostic value than power Doppler ultrasonography for SjS (AUC-ROC =0.906 for superb microvascular imaging and 0.817 for power Doppler imaging) (36). The OMERACT ultrasound work group only included grey-scale images as a standardised scoring system of SGUS in 2019 (11), and recently, they developed a novel scoring method for major salivary gland vascularity assessed by colour Doppler (37). The vascularity of the parotid and submandibular glands was assessed using a semi-quantitative method by scoring grades between 0–3 as follows: grade 0, no visible vascular signal; grade 1, focal, dispersed vascular signals; grade 2, diffuse vascular signals <50% of the gland parenchyma; and grade 3, diffuse vascular signals >50% of the gland parenchyma (37). Further studies are required to validate the clinical utility of Doppler SGUS signals in SjS.

Scoring system of the lacrimal glands

Lacrimal gland ultrasonography studies of SjS are less common than those of SGUS. The first study conducted in 2020 demonstrated that inhomogeneity and fibrous gland appearance of LGUS findings were more frequently present in patients with SjS than healthy controls (12). Kim *et al*. compared LGUS findings between patients with SjS and idiopathic sicca symptoms (38). They dichotomously assessed the area, length of the major/minor axis, detectable Doppler signal of the intraglandular branch of the lacrimal artery, inhomogeneity, hyperechoic band, hypoechoic area, and delineation of the lacrimal glands (38). The size of the lacrimal glands was larger in an SjS group, and inhomogeneity, hyperechoic bands, and Doppler signals of the intraglandular branch of the lacrimal gland were significantly more frequent in the SjS group (38). The diagnostic value of LGUS in SjS achieved by combining detectable Doppler signals of the intraglandular branch of the lacrimal artery and inhomogeneity showed best performance; however, the diagnostic value of LGUS was lower than that of SGUS (AUC-ROC = 0.852 for SGUS, AUC-ROC = 0.731 for LGUS) (38). Another study scored LGUS similar to the OMERACT ultrasound working group's scoring method for major salivary glands (11), and it showed an AUC-ROC of 0.769, with a sensitivity of 83.5% and specificity of 57.1% for the diagnostic performance (39). Further studies are needed to establish a standardised scoring system for LGUS and validate its clinical usefulness in SjS.

Ultrasound elastography of the salivary and lacrimal glands in SjS

Ultrasound elastography can evaluate tissue stiffness either by the strain or shear wave method, and is widely used in clinics to evaluate liver cirrhosis or malignancies of soft tissues such as the liver, breast, thyroid, kidney, prostate, and lymph nodes (40). Some studies have demonstrated the clinical potential of ultrasound elastography for SjS. A strain ratio (strain of adjacent soft tissue/strain of salivary gland parenchyma) >1 indicates that salivary glands are less compressive and have greater stiffness than adjacent soft tissues, and significantly higher strain ratios of the parotid and submandibular glands were observed in patients with SjS than in HCs (41). Shear wave velocity (SWV) and shear wave elastography (SWE) were higher in the major salivary glands of patients with SjS than in HCs, which also indicated stiffer salivary gland parenchyma in patients with SjS (42-51). Additionally, using strain ultrasound elastography, patients with SjS have larger areas of hardened parotid and submandibular gland parenchyma than HCs (52). The degree of stiffness in the salivary glands correlates with salivary gland dysfunction, as measured using salivary gland scintigraphy (52). Patients with SjS and a longer duration of sicca symptoms showed lower elasticity of the parotid and submandibular glands, which indicates that the elasticity of the salivary gland may decrease with disease progression (53). Another analytical technique was used to determine the area of soft and hard tissues of major salivary glands in patients with SjS, and the pixel analysis method showed that patients with SjS had a lower area of soft tissue in the major salivary glands than HCs (54). Pixel size of the hard tissue area did not correlate with SGUS score (54). The SWV and SWE moduli of the lacrimal glands were higher in patients with SjS than those in HCs, and elasticity modulus >10.4 kPa showed diagnostic values of AUC-ROC = 0.901, with a sensitivity of 70.6% and specificity of 97.6% (39). The diagnostic performance of the elastic modulus is superior to that of the LGUS grey-scale score (55). Patients with SjS consistently showed decreased elasticity and higher stiffness in the salivary and lacrimal glands than HCs; however, further validation and standardisation of the application and methods of ultrasound elastography are necessary.

Clinical use of ultrasonography in SjS

The American European Consensus Group (AECG) included sialography and salivary scintigraphy as objective items in the 2002 AECG classification criteria for SjS (56). Using SGUS scoring method of Salaffi showed better diagnostic performance than sialography or scintigraphy (AUC-ROC = 0.863 for SGUS, 0.804 for sialography, and 0.783 for scintigraphy) (57). Additionally, another study similarly showed that diagnostic performance (AUC-ROC) using the Salaffi's method for SGUS was 0.99, whereas for salivary gland scintigraphy and minor salivary gland biopsy, it was 0.98 and 0.97, respectively (58). Adding the De Vita's method of SGUS to the 2002 AECG classification criteria improved diagnostic value than only using the 2002 AECG classification criteria by increasing sensitivity from 77.9% to 87.0%, whereas specificities were similar (98.7% and 96.1%) (20). The 2012 ACR classification criteria only included objective features, such as anti-Ro/SSA antibody

or anti-nuclear antibody titre ≥1:320 with rheumatoid factor positivity, minor salivary gland biopsy (focus score ≥1), and ocular staining score ≥3 (59). Applying the 2012 ACR classification criteria for SjS and SGUS of the De Vita method increased the diagnostic sensitivity from 64.4% to 84.4%, combined with a slight decrease in specificity from 91.1% to 89.3% (60). Similarly, adding the SGUS score of the OMERACT method to the 2016 ACR/EULAR classification criteria for SjS improved the diagnostic value by increasing the sensitivity from 90.2% to 95.6% with comparable specificity (11, 61). Therefore, SGUS findings may improve the diagnostic performance of the existing SjS classification system, especially with respect to sensitivity.

Several studies have evaluated the association between ultrasonographic findings with salivary gland dysfunction, disease activity, damage index, SjS-related autoantibodies, or minor salivary gland biopsy findings. Decreased sialometry, assessed using unstimulated whole saliva flow, was significantly associated with the severity of hyperechoic bands in the parotid and submandibular glands (62). Unstimulated whole saliva flow (mL/min) showed a significant negative correlation with SGUS score (63-65). Although salivary scintigraphy was excluded from the 2012 ACR and 2016 ACR/EULAR classification criteria for SjS (7, 59), it is advantageous because both salivary gland function, saliva uptake and excretion, can be evaluated using salivary scintigraphy (66). One study showed a correlation between the SGUS scores obtained using the Hocevar method and salivary scintigraphy findings (67). Patients with SjS and higher SGUS scores, which imply more severe morphological abnormalities on ultrasonography, had lower saliva uptake and excretion (67). Anormal Schirmer's test finding was not different between SjS patients with positive and negative LGUS findings (detectable intraglandular branch of the lacrimal artery and inhomogeneity) (38). However, another study using the LGUS score to adopted the SGUS scores obtained by the OMERACT ultrasound working group (assessing the severity of an an/hypoechoic lesion of the lacrimal glands) showed a significant correlation with the Schirmer's test (39). The association between SGUS score and disease activity or damage index of SjS has yielded inconsistent results (68, 69). A study by Milic *et al*. showed that the SGUS score of the De Vita method was significantly associated with the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI), Sjögren's Syndrome Disease Activity Index, and Sjögren's Syndrome Disease Damage Index (SSDDI) (68). Additionally, the SGUS score of hyperechoic bands was significantly associated with oral dryness on the visual analog scale (62). One study showed that the SGUS score only showed a significant association with the dryness component of the EULAR Sjögren's Patient-Reported Index, whereas the ESSDAI did not (64). However, another study demonstrated that disease activities (ESSDAI and SSDDI) were comparable between patients with SjS having SGUS scores higher and lower than the cut-off values (69). Anti-Ro/SSA and anti-La/SSB were more frequent in patients with SjS having higher SGUS scores than those in patients with lower SGUS scores (30, 64, 69). Patients with anti-centromere Antibody-positive SjS are assumed to be a specific subgroup of SjS, which possess typical characteristics, such as the Raynaud's phenomenon and liver involvement (70). The SGUS score using the Hocevar method was significantly lower in patients with SjS positive for anti-centromere antibody than in anti-centromere antibody-negative patients with SjS (71). The SGUS score measured by the De Vita and Hocevar methods showed a significant correlation with the focus score of the minor salivary gland biopsy (r=0.61 and p<0.01 for the De Vita method; r=0.22 and p<0.05 for the Hocevar method) (63, 65). Additionally, the LGUS score was significantly correlated with minor salivary gland biopsy results (r=0.475, p<0.01) (39).

Some studies have evaluated changes in SGUS findings in SjS. A two-year follow-up period of the SGUS score in patients with SjS did not show a significant change from the baseline SGUS score (p=0.54) (72). Another study also showed that SGUS score did not increase in 78.6% of patients with SjS, and only 18.6% of them showed a significant increase in SGUS score for 2-year duration (34). In a cross-sectional study, Zhang *et al*. showed that the SGUS score of patients with SjS with longer disease duration (disease duration >5 years) was higher than that of SjS patients with disease duration <5 years (30). The changes in SGUS findings according to disease duration of SjS and their clinical significance should be further studied in the future. The clinical significances of SGUS and LGUS are summarised in Table II.

Treatment response prediction using SGUS in patients with SjS

Two clinical trials of rituximab in patients with SjS, Tolerance and Efficacy of Rituximab in Primary Sjögren's Syndrome (TEARS) and TRial for Anti-B-Cell Therapy in patients with pSS (TRACTISS), included SGUS as an outcome parameter (73, 74). In the TEARS study, 50% of a rituximab treated group showed improvement in SGUS score measured using the De Vita method, whereas only 7% of a placebo group showed improvement at week 24 (p=0.03) (73). Additionally, a lower baseline SGUS score could predict better sicca-related outcomes (Sjögren's Syndrome Responder Index-30) after the rituximab treatment (63). The SGUS scores of rituximab-treated patients with SjS were significantly lower than those of a placebo-treated group after weeks 16 and 48 (74). Another pilot study showed that the size of the parotid and submandibular glands was reduced in patients with SjS between baseline and 12 weeks after rituximab treatment, and the Doppler resistive index after lemon stimulation also increased at week 12 (75). The baseline SGUS score was negatively associated with whole saliva flow rate after saliva stimulant treatment, such as pilocarpine or cevimeline (β=-0.523, p<0.001), which indicates that patients with SjS with lower baseline SGUS scores have better saliva flow improvement after saliva stimulant treatment (76).

Table II. Clinical usefulness of salivary glands ultrasonography (SGUS) and lacrimal glands ultrasonography (LGUS).

Clinical parameters	Compared items	Findings
Diagnosis performance	The 2002 AECG criteria for SjS	Improved diagnostic performance with SGUS than sialography or salivary gland scintigraphy (57) AUC-ROC: SGUS, 0.863±0.030; sialography, 0.804±0.035, and salivary gland scintigraphy, 0.783±0.037
		Comparable diagnostic performance of SGUS with salivary gland scintigraphy and minor salivary gland biopsy (58) AUC-ROC: SGUS, 0.99; salivary gland scintigraphy, 0.98; and minor salivary gland biopsy 0.97
		Improved diagnostic performance by adding SGUS finding to the 2002 AECG criteria (20) The 2002 AECG criteria only – sensitivity 77.9%/specificity 98.7% The 2002 AECG criteria + SGUS – sensitivity 87.0%/specificity 96.1% Best combination ([salivary flow × 1.5] + [Schirmer's test × 1.5] + [salivary gland biopsy × 3] + [anti-SSA/SSB Ab × 4.5] + [SGUS × 2]) – sensitivity 85.7%/specificity 94.9%
	2012 ACR criteria for SjS	Improved diagnostic performance by adding SGUS (60) The 2012 ACR criteria only – sensitivity 64.4%/specificity 91.1% The 2012 ACR criteria + SGUS – sensitivity 84.4%/specificity 89.3%
	2016 ACR/EULAR criteria for SjS	Improved diagnostic performance by adding SGUS(61) The 2016 ACR/EULAR criteria only – sensitivity 90.2% / specificity 84.1% The 2016 ACR/EULAR criteria + SGUS – sensitivity 95.6%/specificity 82.6%
Oral and ocular dryness	Unstimulated saliva flow rate (UWSF)	Negative correlation between unstimulated whole saliva flow rate and SGUS score UWSF (mL/min) vs SGUS score: r = - 0.68, p<0.01(63)
		UWSF (mL/min) was lower in SjS patients with higher SGUS score (above cut-off) than lower SGUS score: 0.62±0.71 (SGUS score ≥17 by the Hocevar method) *vs*. 1.05±0.80 mL/min (SGUS score <17), p=0.005 (64) 0.8 (SGUS score ≥2 by the Theander method) *vs*. 1.9 mL/15min (SGUS score <2), p<0.01 (65)
		Predictors for abnormal UWSF findings (<0.1 mL/min) Parotid gland hyperechoic band grade: odds ratio (OR) = 2.51, 95% confidence interval (CI) 1.01–6.23 Submandibular gland hyperechoic band grade: OR = 2.57; 95% CI = 1.05–6.27
	Salivary gland scintigraphy	Negative correlation between salivary gland scintigraphy findings and SGUS score (the Hocevar method)(67) Parotid saliva uptake ratio: r = -0.36, p=0.03 Submandibular saliva uptake ratio: r = -0.42, p=0.01 Percentage parotid saliva excretion: r = -0.35, p=0.04 Percentage submandibular saliva excretion: r = -0.39, p=0.02
	Schirmer's test	Negative correlation between the Schirmer's test and LGUS score (scoring method adopted from the OMERACT ultrasound working group) Schirmer's test (mm/min) vs. LGUS score: r = - 0.47, p<0.01 (39)
Minor salivary gland biopsy	Focus score *vs*. SGUS	Positive correlation between focus score and SGUS Focus score vs. SGUS score (the De Vita method): r = 0.61, p<0.01 (63) Focus score vs. SGUS score (the Hocevar method): r = 0.22, p<0.05 (65)
	Focus score *vs*. LGUS	Positive correlation between focus score and LGUS Focus score vs. LGUS score (adopted from the OMERACT ultrasound working group): r = 0.475, p<0.01
Autoantibody	Anti-Ro/SSA & anti-La/SSB Ab	SjS patients with either anti Ro/SSA or anti La/SSB Ab positive have higher SGUS score than patients with autoantibody negative SjS (p<0.001) (30, 64)
		SGUS (the Hocevar method) above cut-off value vs. SGUS lower than cut-off value (69) Double positive for anti-Ro/SSA and anti-La/SSB positivity: 52.6% *vs*. 16.7% (p=0.001) Anti-La/SSB positivity: 55.3% *vs*. 27.8% (p=0.036)
	Anti-centromere Ab	Patients with anti-centromere Ab (+) SjS have lower SGUS score (the Hocevar method) than those with anti-centromere Ab (-) SjS (71) SGUS score: 16.0 *vs*. 23.0, p=0.027
Treatment response predict	Rituximab	Rituximab responders have lower SGUS scores than non-responder(63) SGUS score (Cornec method): 9 *vs*. 16, p=0.04
	Saliva stimulant	SjS patients with lower SGUS score achieved greater net increase of saliva flow rate after treatment with saliva stimulants (76)

Comparison of SGUS with other imaging techniques

Magnetic resonance imaging (MRI) is an excellent tool for assessing soft tissue disorders. Magnetic resonance imaging of the parotid gland was semi-quantitatively scored as grade 0–3 (0: normal homogeneous parenchyma, 1: fine reticular or small nodular structure, nodule diameter <2 mm, 2: medium nodular pattern, nodule diameter 2–5 mm, and 3: coarse nodule, nodule diameter >5 mm), and SGUS of the parotid glands as grade 0–3, according to the severity of parenchymal inhomogeneity (19). Both MRI and SGUS grades of the parotid gland significantly correlated with the focus score of minor salivary gland biopsy in patients with SjS (19). Additionally, good agreement was observed between MRI grades and SGUS scores (r=0.87) (19). Takagi *et al*. graded parotid and submandibular gland MRI findings in two aspects: high-intensity spots in fat-suppressed T2-weighted images or MR sialography, and another one was fatty degeneration in T1-weighted images (77). Both MRI components were semi-quantitatively measured as grades 1-4 (77). Multiple high-intensity spots were more frequently observed in juvenile patients with SjS (aged <18 years), whereas fatty degeneration was more prominent in elderly patients with SjS (aged >69 years) (77). Additionally,

the fatty degeneration area observed on MRI was significantly associated with decreased saliva flow rate and hyperechoic bands in SGUS findings (77). One study compared the diagnostic accuracy of immunoglobulin (Ig)-G4 related disease (IgG4-RD) and SjS among four imaging modalities (SGUS, computed tomography, MRI, and 2-[18F]-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography) (78). SGUS showed the highest sensitivity and specificity for both IgG4-RD and SjS (78). Furthermore, IgG4-RD must be differentiated when diagnosing SjS (7, 59), and the reticular and nodal patterns of SGUS are distinguishable characteristics of IgG4-RD (78).

Minor salivary gland ultrasonography

Minor salivary glands (labial salivary glands [LGSs]) biopsy is included in recent ACR/EULAR classification criteria for SjS (7), and this can be visualised with ultra-high frequency ultrasonography (UHFUS) (13). LGSs are located in buccal (inner lining of the cheeks), labial (inner lining of the lips), lingual (underside of the tongue) mucosa, soft and hard plates (roof of the mouth), and floor of the mouth (13). Patients with SjS showed higher LGS ultrasonography scores than non-SjS controls when using a semi-quantitative scoring system (range 0 to 3), which is similar to the OMERACT method (79). SjS patients who were positive for anti-Ro/SSA showed higher LGS ultrasonography scores, and LGS scores significantly correlated with LGS biopsy findings (focus score and number of foci) (79, 80). In addition, UHFUS-guided biopsy of LGS enhanced the accuracy of obtaining a proper LGS sample compared to conventional blind method (80, 81).

Conclusions

Salivary gland ultrasonography and LGUS are non-invasive, inexpensive, bedside performable, and non-radiating tools that aid in the diagnosis of SjS. Both SGUS and LGUS can improve the diagnostic performance for SjS. Additionally, SGUS can predict salivary gland dysfunction and show potential as a treatment response to biologics (rituximab) and saliva stimulants. Currently, the grey-scale scoring of SGUS or LGUS aids in the diagnosis of SjS; however, the utility of Doppler ultrasound and elastography of the salivary and lacrimal glands is being actively studied and has been shown to be useful in SjS. Ultrasonography of the salivary and lacrimal glands is a useful tool for determining the diagnosis, predicting glandular function, and treatment response in patients with SjS, and is expected to be used in a variety of fields in SjS.

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