

Salivary Gland Ultrasonography in Sjögren's Syndrome: Clinical Usefulness and Future Perspectives

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ABSTRACT: In recent years, salivary gland ultrasonography (SGUS) has emerged as a promising tool for the diagnosis and prognostic stratification of patients with primary and secondary Sjögren's syndrome. Several studies have emphasized that salivary ultrasonography could be a highly specific tool for the diagnosis of the disease. However, before it can be used in daily clinical practice the SGUS procedure needs standardization and validation in larger disease-control groups. In this review we provide an update on the role of SGUS in the diagnostic algorithm of primary Sjögren's syndrome.

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Sjögren's syndrome (SS) is a complex heterogeneous disease primarily affecting salivary and lachrymal glands. The full spectrum of the disease encompasses a myriad of systemic features, including non-Hodgkin's lymphoma [1-4]. The pathophysiology of the disease comprises concurrent dysregulation of innate and adaptive immune responses involving both cell-mediated and humoral disease processes [5-8]. The diagnosis of primary SS is therefore currently based on a combination of clinical, serologic, histologic, functional and instrumental parameters able to detect both the "autoimmune exocrinopathy" in the salivary and lachrymal glands and the systemic SS autoimmune response [9,10]. The involvement of major salivary glands has been traditionally evaluated by either sialography or scintigraphy [11-13]. Recently, salivary gland ultrasonography (SGUS) has emerged as a valuable tool for the assessment of major salivary gland involvement in primary SS [14,15]. In this review we provide an update on the role of SGUS in the diagnosis and prognostic assessment of patients with SS.

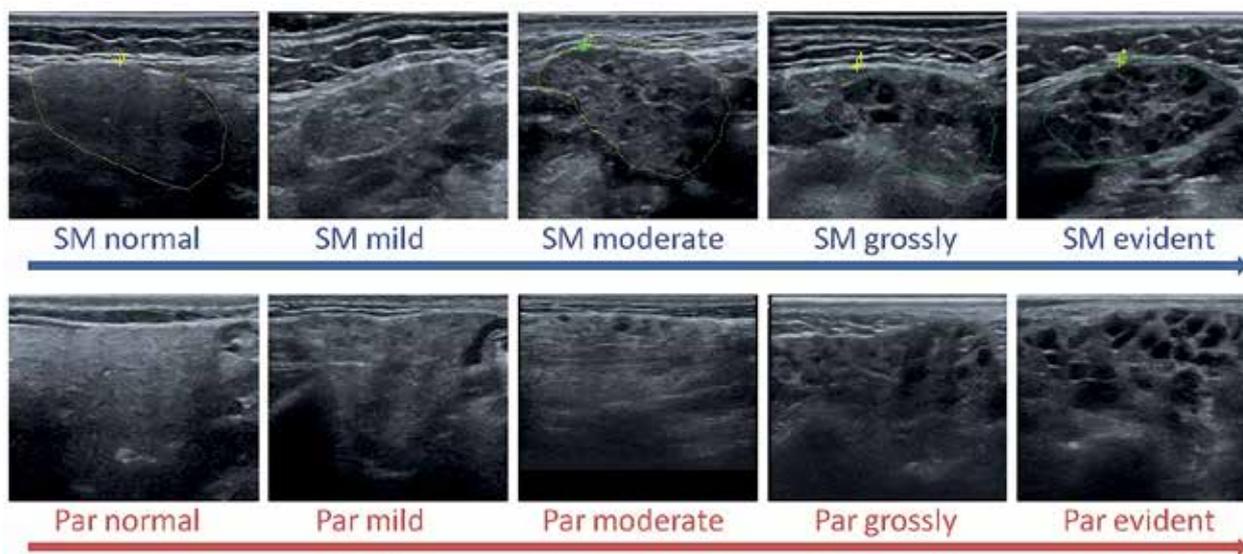
DOES SGUS HAVE A ROLE IN THE DIAGNOSIS OF PRIMARY SJÖGREN'S SYNDROME?

In 1992, De Vita et al. [16] assessed the potential value of SGUS for the diagnosis of primary and secondary SS. The authors

reported that glandular inhomogeneity was the most discriminating element able to distinguish patients with primary SS from controls, with a sensitivity of 89% and a specificity of 85%. The authors recognized mild, evident or gross inhomogeneous parenchymal patterns in the glands of SS patients based on the presence of hypoechoic or anechoic scattered areas in the glandular parenchyma. An echographic score (range 0–0.6) assigning points to the different degrees of glandular inhomogeneity was therefore proposed.

From that point on, a large amount of data have encouraged the use of SGUS in primary and secondary SS, even in children with juvenile SS and recurrent parotitis [2,17]. Today, SGUS is widely considered an easy, non-invasive and highly specific imaging technique for the assessment of salivary gland involvement in primary SS. In recent years, SGUS studies adopted different ultrasonography scoring systems and included heterogeneous study populations. Several factors have been optionally analyzed in the available scoring systems, including gland size, echogenicity, visibility of the borders, calcifications, and presence of hyperechogenic bands. Nonetheless, there was general agreement among researchers that the most important sonographic sign in SS remains the presence of bilateral parenchymal inhomogeneity. Evident or gross parenchymal inhomogeneity with multiple, scattered hypoechoic areas, likely representing lymphocytic infiltration, were considered highly specific for the diagnosis of SS, suggesting that SGUS may successfully identify subjects who do not have SS. Figure 1 presents different patterns of parenchymal inhomogeneity in submandibular and parotid glands ranging from normal to gross abnormalities.

Table 1 summarizes the diagnostic accuracy of SGUS in studies comparing SGUS findings in patients with SS and in subjects initially suspected of having SS, in whom the diagnosis of SS was not confirmed [18-30]. The sensitivity ranges from 44% to 86% and the specificity from 84% to 99%. Data on diagnostic accuracy of SGUS in patients with disease duration of ≤ 5 years are also provided [26,30]. In two studies, by Cornec et al. [31] and Baldini et al. [30], the specificity for the diagnosis of SS in the early stages was relatively high, ranging from 87.5% to 98%, whereas the sensitivity was lower, 60% and 66% respectively, suggesting that the diagnostic accuracy of SGUS for the early diagnosis of SS was acceptable but not exciting.

Figure 1. Degrees of parenchymal inhomogeneity in submandibular (SM) and parotid glands (Par)**Table 1.** Salivary gland diagnostic accuracy in patients with Sjogren's syndrome (SS) compared to initially suspected non-SS syndrome controls

Authors, year [ref]	Patients	Sensitivity	Specificity
Hocevar et al., 2005 [19]	68 SS and 150 non-SS	59%	99%
Wernicke et al., 2008 [20]	57 SS, 78 non-SS	63%	99%
Salaffi et al., 2008 [21]	77 SS, 79 non-SS	75%	84%
Shimizu et al., 2008 [22]	43 SS, 29 non-SS	44%	97%
Milic et al., 2009 [23]	107 SS, 28 non-SS	65%	91%
Milic et al., 2012 [25]	140 SS, 50 non-SS	86%	94%
Cornec et al., 2013 [26]	78 SS, 45 non-SS	54%	99%
Cornec et al., 2014 [27]	45 SS, 56 non-SS	60%	87,5%
Takagi et al., 2014 [28]	102 SS, 82 non-SS	79%	90%
Theander & Mandl, 2014 [29]	105 SS, 57 non-SS	52%	98%
Baldini, 2015 [30]	50 SS, 57 non-SS	66%	98%

Two meta-analyses examining the properties of SGUS for diagnosing primary SS were recently published [32-34]. The first included six studies and compared the diagnostic performance of sialography and SGUS in SS [32]. The authors found that the pooled sensitivity and specificity for SGUS were 77.4% and 81.5%, 95% confidence interval (95%CI) 73.7-80.9 and 77.6-85.0 respectively. The diagnostic accuracy of SGUS was comparable with sialography which presented a sensitivity of 80% (95%CI 74.4-83.2) and a specificity of 89% (95%CI 85.8-91.8) respectively [32]. Delli and colleagues [34] in their meta-analysis included 29 studies with a pooled sensitivity of 69% (95%CI 67-71) and pooled specificity of 92% (95%CI 91-93) for SGUS in SS. These two meta-analyses confirmed the high specificity of

SGUS in distinguishing SS patients from controls and its good, although lower, sensitivity. From a practical point of view, this suggests that SGUS may be able in the next future to replace the more invasive sialography in the diagnostic algorithm of SS. Noteworthy, Cornec et al. [26,31] recently proposed that the adjunction of SGUS may improve the diagnostic performance of both the American European Consensus Group (AECG) and the American College of Rheumatology (ACR) classification criteria. However, despite these encouraging data, SGUS needs standardization and validation in larger disease-control groups before its use in SS diagnosis. In fact, it must be emphasized that the specificity of SGUS for SS was generally assessed in comparison with healthy controls, and in subjects with drug-induced sicca symptoms or idiopathic sicca syndrome. So far, patients with chronic salivary gland inflammatory conditions, including other rheumatic disorders, sarcoidosis, chronic hepatitis C virus infection, and IgG4-related disease have rarely been enrolled in studies [15,20,26,35]. These conditions should be included in larger disease-control studies to refine the specificity of SGUS in SS. Moreover, an international task force was created in 2012 to develop and validate a novel common scoring system according to the OMERACT filter. This novel scoring system will allow the scientific community to standardize the procedure, ultimately increasing the reproducibility of the SGUS.

SGUS VERSUS MINOR SALIVARY GLAND BIOPSY IN SJÖGREN'S SYNDROME

In recent years, SGUS has gained increasing attention as a non-invasive tool able to detect abnormalities in parotid and submandibular glands of patients with SS. By contrast, minor salivary gland biopsy (MSGB) is generally considered an invasive procedure and its reliability has not been fully addressed

[36-38]. A number of studies have explored the diagnostic value of SGUS in comparison with the biopsy in order to assess whether SGUS could replace MSGB at least in selected cases. The vast majority of studies concluded that SGUS and MSGB were not interchangeable [18,23,26,30]. SGUS showed a lower sensitivity and similar specificity when compared with the MSGB. Agreement between the two tests has been reported as modest.

Cornec et al. [26] found a Cohen's kappa of 0.474 between SGUS and MSGB. In other words, in daily practice SGUS can be regarded as a warning sign of the possibility of SS; in cases with evident or gross parenchymal inhomogeneity the diagnostic value of SGUS is generally high and MSGB is often confirmatory, providing also complementary information on the composition of the lymphocytic infiltrate and on the presence/absence of germinal center (GC)-like structures. On the other hand, when the SGUS results are negative, we feel that MSGB should remain mandatory in order to avoid patient misclassification.

ROLE OF SGUS IN THE ASSESSMENT OF SJÖGREN'S SYNDROME

An increasing number of publications have presented convincing data on the usefulness of SGUS for prognostic stratification of patients with primary SS [29,39]. Patients with pathologic SGUS present positive serology, higher disease activity and several risk factors for lymphoma significantly more often when compared to patients with normal SGUS findings. Theander et al. [29] recruited 105 patients with primary SS, and by using a simplified scoring system demonstrated that patients with a more severe SGUS score presented a higher frequency of autoantibodies anti-Ro/SSA and anti-La/SSB, antinuclear antibodies, rheumatoid arthritis and significantly higher levels of IgG with respect to patients with normal SGUS findings. More interestingly, they found that SS disease activity as measured by the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) was significantly higher in these patients and there was a significant association between the SGUS score and lymphoma risk factors including GC-like structures in the minor salivary gland, CD4+T cell lymphopenia, reduced number of memory cells in the circulation, immunoglobulin monoclonality in serum, the presence of salivary gland swelling, purpura and skin vasculitis. Similar data were described by Hammenfors and team [39] in a cohort of 97 patients with primary SS. They found in particular that lymphoid organization in the form of GC-like structures were significantly more common in patients with severe abnormalities on SGUS. The possibility of using SGUS to identify patients at risk for lymphoma and to monitor patients non-invasively over the follow-up seems particularly interesting. However, the stability of SGUS findings over time must be investigated carefully, as should the correlation between pathological changes of the salivary glands and ultrasonographic patterns. With regard to the first point, few

studies to date have explored the value of SGUS in monitoring response to therapy in patients with SS. Intriguingly, Jousse-Joulin et al. [40] recently reported that 28 patients treated with rituximab ultrasonography showed improvement in both sub-mandibular and parotid echostructure, whereas gland size and vascularization remained unchanged. As far as the correlation between pathologic changes of the salivary glands and SGUS patterns is concerned, it is still a matter of debate whether the hypoechoic areas themselves reflect areas of lymphocytic infiltration or dilated ducts and progressive glandular destruction. In conclusion, further studies in a larger cohort are necessary to verify whether SGUS could be used to monitor primary SS patients over the follow-up.

CONCLUSIONS

SGUS appears to be a promising tool for the diagnosis and prognostic stratification of primary SS patients. Before its implementation in daily clinical practice, however, some issues should be addressed. First, the development of an international consensual scoring system seems to be mandatory to standardize the procedure and to increase the intra- and inter-observer reproducibility. Second, larger disease-control groups should be included in the studies to refine the specificity of this technique. Third, longitudinal studies are warranted to better correlate glandular inflammation and damage with the SGUS patterns and assess the value of SGUS in monitoring patient response to therapy over time.

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