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Title:
Assessment of salivary gland function in Sjögren’s Syndrome: the role of Salivary Gland Scintigraphy

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Abstract:
Salivary Gland Scintigraphy (SGS) is a non invasive method of salivary gland function assessment. This technique is easy to perform, reproducible and well tolerated by the patients. Additionally, an abnormal salivary gland scintigraphy result is accepted by the American-European consensus group as a criterion for the diagnosis of Sjögren’s Syndrome. Scintigraphic evaluation of salivary gland function also plays an important role in therapeutic decision and patient follow-up. Schall’s categorical classification is usually considered the standard method for salivary scintigraphy interpretation, though subjective and with limited capacity to discriminate borderline results. In order to improve the diagnostic accuracy of SGS, there has been an increasing interest in the quantification of glandular function. However, the debate on the most reliable and suitable parameters for the diagnosis of SS persists.

Keywords: Salivary gland scintigraphy, Sjögren’s syndrome, xerostomia, Schall’s classification, quantitative parameters.

Take-home messages:
- SGS is an easy to perform, reliable and non invasive method of salivary gland function assessment.
- Excretion impairment and preferential submandibular involvement are sensitive and early indicators of Sjögren’s syndrome.
- Schall’s classification into four categories is useful but observer-dependent. The development and standardization of quantitative indices that more accurately reflect glandular function may represent an important achievement for the diagnosis of SS.
1. Sicca symptoms as a typical feature of Sjögren’s syndrome

Sjögren’s syndrome (SS) is an inflammatory auto-immune disease of unknown aetiology, characterized by focal lymphocytic infiltration of the exocrine glands resulting in significant impairment of exocrine function. This is a relatively common condition that affects approximately 2-4 million individuals in the United States [1], as an isolated connective tissue disease (Primary Sjögren’s syndrome) or in association with other well defined connective tissue disease (Secondary Sjögren’s syndrome). SS occurs more frequently in peri-menopausal women, with a female-to-male ratio of 9:1, yet it can arise at any age. The female predominance seems to be related to the immunoregulatory properties of the sexual hormones, although the role of genetic and environmental factors is not fully elucidated [2, 3]. Lymphocytes infiltrating salivary glands play an important role in the disease process. Both T and B cells-derived cytokines are likely to contribute to glandular tissue destruction in a coordinated manner [4].

Over the last decades, different classification criteria sets for this condition have been suggested, but none has been universally accepted. Recently, the European Study Group on Classification Criteria for SS in collaboration with a group of American experts developed the International Classification Criteria for SS that are largely accepted by the rheumatology community [5]. The application of these criteria allows the standardisation of the diagnosis in patients taking part in clinical studies, facilitates the analysis of the results and the comparison of patients between different institutions.

Salivary and lachrymal gland involvement is almost universal in SS, resulting in the typical clinical features of dry mouth (xerostomia) and dry eyes (xerophthalmia). Though very frequent, sicca symptoms are not exclusive of this condition and other diseases must be taken in account in the differential diagnosis. Chronic sialadenitis must be ruled
out in patients complaining of isolated xerostomia and other causes of dry mouth, such as anti-cholinergic drugs use, disregulation of autonomic pathways, fibromyalgia, sarcoid or lymphoma infiltration, certain viral infections, radiation sequelae and diseases affecting fluid and electrolyte balance must be considered [6].

Since patients complaints do not necessarily reflect the severity of salivary gland disease [7-10] an objective method to measure glandular function is necessary. From the various available methods [11], contrast sialography is considered the gold standard for the assessment of oral component in SS patients. However, this is an invasive procedure, not always available and that needs ductal cannulation. Besides some technical difficulties, various complications of sialography have been reported, namely painful overfilling, ductal perforation, fistula formation and glandular infection [12]. Moreover, it is a morphologic exam that does not provide sufficient information about glandular function.

Salivary gland scintigraphy (SGS) has been proposed as a valid and non invasive alternative approach to functional evaluation of salivary gland involvement in xerostomic patients [13-15]. The main advantage of this method, comparing with the other methods of salivary glands assessment, is that it provides information on both parenchyma and excretion of all major salivary glands after a single intravenous injection. Also, this is a non invasive technique, easy to perform, reproducible and well tolerated by patients [13]. In addition, an abnormal salivary gland scintigram is accepted by the American-European classification criteria as an objective assessment of salivary gland function for the diagnosis of Sjögren’s syndrome [5]. Interestingly, SGS results correlate with saliva production, sialography and with focus score in minor salivary gland biopsy, the most specific diagnostic test for SS diagnosis [7, 9, 16, 17].
2. Salivary Gland Scintigraphy in the evaluation of xerostomia

The main indication of SGS is the assessment of salivary gland function in patients with dry mouth complaints. This is a functional method that allows the simultaneous evaluation of major salivary gland parenchyma and function.

After intravenous $^{99m}$Tc-sodium pertechnetate administration, sequential images of the head, on anterior projection, are acquired during a variable time interval, usually between 20 and 40 minutes. The images are then stored and glandular regions of interest (ROI) and a background ROI, usually in the skull, are manually drawn. Computer software generates time-activity curves for each major salivary gland. Time-activity curves are divided in two phases: the uptake phase, corresponding to the accumulation of the tracer by the glandular parenchyma, which duration depends on the protocol; and the excretion phase, initiated by the administration of a salivary stimulus, usually lemon juice, which corresponds to the tracer elimination through the oral cavity, providing information on the patency of salivary ducts and the overall functional integrity of the system (Figure).

Even though widely used for the evaluation of xerostomic patients, SGS procedure is insufficiently standardized and no gold standard for the assessment of Sjögren’s syndrome has been established [7, 14]. SGS interpretation is mainly based on Schall’s classification [15], which is qualitative and observer dependent, resulting that, although simple and easy to perform, borderline results may be misclassified by the subjective judgement of the evaluator [18].

In order to refine salivary gland scintigram interpretation and improve the diagnostic accuracy, there has been an increasing interest in quantification of glandular function. A variety of parameters have been proposed over the last decade [7-9, 14, 18-20], but
there is little consensus about which are most reliable and suitable for SS diagnosis [21] and their contribution to scintigraphy accuracy improvement.

3. Qualitative evaluation and scintigraphic patterns of Sjögren’s syndrome:

The interest in SGS as a diagnostic tool in the evaluation of dry mouth symptoms began four decades ago. In the early 70’s, Schall and colleagues proposed a categorical classification scheme [15, 22] based on visual quality of glandular uptake and tracer excretion into the oral cavity. According to this classification, salivary gland functional impairment is classified into four grades, according to the intensity of uptake and of activity present at the mouth after administration of the excretory stimulus, being grade 1 the normalcy and grade 4 the total absence of uptake and mouth activity. This widely diffused classification is considered the standard method for salivary scintigram interpretation.

In the original Schall’s categorization, each gland was classified separately. For simplification purposes, many authors score the highest value of both parotids and both submandibular glands together or take into account only the maximum glandular value. Using grade 3 of Schall’s classification as the cut-off value, Coll et al, in a study including 142 patients, achieved an overall sensitivity and specificity of SGS for the diagnosis of SS of 54% and 98%, respectively [23]. Adding ocular involvement, documented by a positive Rose bengal test, the diagnostic accuracy of SGS increased to 65% sensitivity, 100% specificity and a positive predictive value of 100%. Later, Vitali et al [11], studying the diagnostic accuracy of each diagnostic test for ocular and oral involvement in SS patients, found an overall sensitivity and specificity of SGS, interpreted according to the Schall’s classification, of 87.2% and 79% respectively.
Our group, in a recent study that included 56 women with sicca symptoms (20 with primary SS defined according to the international classification criteria and the remaining 36 with sicca symptoms but not fulfilling criteria for SS) [24] and using grade 3 as the cut-off value of positivity, found the sensitivity and specificity of SGS to be 75% and 78% for the diagnosis of primary SS. Using grade 2 as the cut-off value of scintigraphy, the sensitivity improved but the specificity decreased to unacceptable values, thus greatly diminishing the test accuracy.

In 1988, Sugihara and Yoshimura proposed another qualitative approach to the evaluation of salivary gland function based on tracer accumulation and excretion. These authors classified time-activity curves into 4 stereotypes: normal, median, flat and sloped [25]. The usefulness of this classification was demonstrated later by Shizukuishi et al [16] who described the inverse linear correlation between scintigraphic scores and saliva production, measured by the Saxon test, in SS patients. Additionally, these authors describe a good reproducibility of this scoring method in the evaluation of salivary gland function in patients with SS.

The most common and early scintigraphic abnormality observed in SS is the impairment of excretion, followed by a decrease in tracer accumulation, reflecting glandular parenchyma destruction [6, 16, 20]. The preferential involvement of submandibular glands and the decrease of spontaneous, non stimulated, salivary secretion by these glands is well recognized in literature and is related to the degree of dry complaints, putting in evidence the primary role of submandibular glands secretions in oral lubrication and mucosal protection [9, 16, 17, 19-20, 26].

In a study aimed to compare scintigraphic features of chronic sialadenitis and SS, Hermann et al demonstrated that SS patients have multi-glandular involvement more frequently, more biphasic kinetics defects and more severe dysfunction than chronic
sialadenitis patients [6]. However, both conditions shared similar features, namely less frequent single gland dysfunction, preferential submandibular involvement and a tendency to slow isolated discharge failure over uptake failure.

Even if qualitative methods are useful and easy to perform, their discriminatory capacity is an important drawback. The distinction between normal results and minor dysfunction is not always easy and mild glandular impairment and borderline results may be misclassified by the subjective judgement. Cortes-Blanco et al [27] evaluated intra and inter-observer agreement of qualitative classification of dynamic SGS and detected a moderate intra and inter-observer concordance of SGS interpretation in patients with sicca complaints (0.63 for intra-observer evaluation and 0.36 – 0.51 between observers), thus confirming the subjectivity of these classifications.

4. The development of quantitative scores in salivary gland scintigraphy

The development of powerful gamma cameras, together with the evolution of software, lead to a great interest in the quantitative evaluation of SGS, with the goal of refining its interpretation. Data supports that quantitative SGS is sensitive enough to detect abnormalities of merely 25% gland parenchyma destruction [9, 28, 29] allowing to identify mild glandular dysfunction in early SS [30].

Over the past decade, a variety of different parameters obtained from time-activity curves have been proposed (Table) [8, 9, 14, 18, 19, 21, 30] as sensitive measures for SS diagnosis. These computer-assisted quantitative indices are numeric and objective measures that reflect glandular function more accurately than qualitative evaluation.

In order to improve the diagnostic performance of the quantitative evaluation in SS, some authors recommend a coordinated analysis of the parameters related to oral and salivary gland activity [9, 10, 31].
The main objective of obtaining quantitative scores is the differentiation of slightly abnormal from normal results, where qualitative analysis has limitations and becomes subjective. However, some authors [20, 26] found a wide dispersion of most quantitative indices. Hermann et al [26] verified that, to accommodate the wide range of normal values, the setting of cut-off limits to maintain the desired specificity and negative predictive values would severely compromise the sensitivity and positive predictive values.

At present, there is no consensus about which quantitative indices are more trustworthy and suitable for the diagnosis of SS. The evident disagreement in literature about the true value and reliability of these parameters results from the wide dispersion of normalcy values, possibly as a consequence of the heterogeneity of studied populations, the inclusion of patients in different stages of the disease and the lack of a standard protocol of salivary scintigraphy, both in terms of acquisition as in processing parameters [21]. Therefore, in order to accept these indices and include them in SGS interpretation, an effort should be made not only in terms of standardizing SGS procedure, but also in performing multicenter studies. This would allow the determination of universal normalcy and cut-off values, as well as the evaluation of its sensitivity, specificity and consequent incremental value for SS diagnosis.

In parallel to its relevance as a diagnostic tool, SGS may be helpful for therapeutic decision, as the demonstration of potentially functioning glandular tissue is decisive for the use of secretagogues. In patients’ follow-up SGS allows the evaluation of therapeutic response and disease evolution over time [32, 33].

5. Conclusion
Salivary gland scintigraphy is a non invasive, reliable and broadly accepted method for the evaluation of salivary glands function in xerostomic patients. Moreover, SGS is accepted by the international classification criteria for SS as an objective assessment method of salivary gland involvement.

SGS is sensitive enough to detect mild abnormalities such as 25% destruction of glandular parenchyma and its results correlate with clinico-pathological features of SS, namely with non-stimulated saliva production, sialography and focus scores in minor salivary gland biopsy.

The qualitative evaluation employing Schall’s classification, despite being subjective and having a limited ability to discriminate borderline results, is still the most widely used method for salivary scintigraphy interpretation. The use of quantitative indices may refine the interpretation of SGS and might increase the accuracy of this procedure for SS diagnosis, but the standardization of this technique is necessary in order to allow its inclusion into daily practice. Additionally, SGS is also useful for therapeutic decisions and patients’ follow-up.

References:


**Figure legend**

Figure 1 – Example of a normal salivary gland scintigraphy with normal tracer uptake and good definition of accumulation and excretion phases in time-activity curves. Parot-Dta (right parotid gland); Parot-Esq (left parotid gland); Submxlar-Dta (right submandibular gland); Submxlar-Esq (left submandibular gland); Boca (mouth); Fundo (background); Captação Máxima (maximum accumulation); sec (time in seconds); counts (tracer accumulation).
Fig 1

Captação Máxima (counts/sec)

<p>| Parot-Dir  | 177,30 |
| Parot-Esq | 156,83 |
| Subnxlar-Dir | 84,10 |
| Subnxlar-Esq | 88,07 |</p>
<table>
<thead>
<tr>
<th>Authors</th>
<th>Patients and Methods</th>
<th>Results</th>
<th>Limitations</th>
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<tr>
<td></td>
<td>39 pSS; 11 controls</td>
<td>SM preferential involvement</td>
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<td></td>
<td>Quantitative SGS</td>
<td>Histopathology correlation</td>
<td></td>
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<td></td>
<td>UR, MA, MS, Tmax, Tmin MSGB</td>
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<tr>
<td>Henriksen AM, Nossent HC Clin Rheumatol 2007</td>
<td>32 participants</td>
<td>↑ Tmax in SS patients</td>
<td>Small number of SS patients (8); no differentiation between primary and secondary SS.</td>
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<tr>
<td></td>
<td>8 SS; 16 ISC;</td>
<td>↓ Parotid C% in SS and ISC patients</td>
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<td></td>
<td>8 healthy controls</td>
<td>↓ E% in SS patients</td>
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<td></td>
<td>Quantitative SGS</td>
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<td></td>
<td>Tmax, C%, E%</td>
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<tr>
<td>Adams BK, et al. Nucl Med Commun 2003</td>
<td>50 participants</td>
<td>↓ URs of both parotid and left submandibular glands in SS patients</td>
<td>Group A constituted by patients with primary and secondary SS. Small number of patients with primary SS(6 pSS).</td>
</tr>
<tr>
<td></td>
<td>17 SS, 18 other</td>
<td>↓ U4 in SS patients</td>
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<td></td>
<td>autoimmune diseases without SC;</td>
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<td></td>
<td>15 healthy controls</td>
<td>↓ oral Tmax in SS patients compared to healthy controls</td>
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<td></td>
<td>Quantitative SGS</td>
<td>SM preferential involvement</td>
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<td></td>
<td>U4(%),U14 (%),Tmax, UR, MA(%), MS(%), PRI(%)</td>
<td>Considerable overlap of all quantitative indices between groups.</td>
<td></td>
</tr>
<tr>
<td>Nishiyama S, et al J Rheumatol 2006</td>
<td>68 participants</td>
<td>↓ Peak count and ES in SS patients. Correlation of peak count ↓ with focus score on MSGB and of ES ↓ with Saxon test.</td>
<td>No healthy individuals were included as control group</td>
</tr>
<tr>
<td></td>
<td>34 pSS; 11 ssSS;</td>
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<tr>
<td></td>
<td>23 autoimmune disease without SS</td>
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<td>Quantitative SGS</td>
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<td></td>
<td>Peak count, US, ES, EF MSGB Saxon Test</td>
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<tr>
<td>Aung W, et al. J Nucl Med 2001</td>
<td>91 participants</td>
<td>↓ POI, PRI, TI, MA and UR of the SM glands with disease progression</td>
<td>Groups (early and advanced SS) were classified according to the result of MSGB thus not reflecting truly SS according to classification criteria.</td>
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<tr>
<td></td>
<td>29 early stage SS,</td>
<td>Correlation of the oral indices with MSGB focus scores.</td>
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<td>41 advanced stage SS,</td>
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<td>21 healthy controls</td>
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<td>Quantitative SGC</td>
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<td></td>
<td>PRI, POI, TI, MA, MS, SV, Tmax, Tmin, UR MSGB</td>
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Table – Quantitative Salivary Gland Scintigraphy  Published studies evaluated different scintigraphic parameters and included heterogeneous patient populations and controls. SS (Sjögren’s syndrome); pSS (primary Sjögren’s syndrome); sSS (secondary Sjögren’s syndrome); ISC (isolated sicca complaints); SGS (salivary gland scintigraphy); MSGB (minor salivary gland biopsy); UR (uptake ratio); MA (maximum accumulation); MS (maximum secretion); TI (time interval, in minutes, between vascular perfusion peak and the prestimulated maximum oral activity point; Tmax (time interval, in minutes, needed to achieve peak uptake); Tmin (time interval, in minutes, from stimulation to minimum count); C% (peak tracer distribution in percentage); E% (stimulated excretion in percentage); PRI (pre-stimulatory oral index); POI (poststimulatory oral activity index); U4 and U14 (background corrected counts at four and 14 minutes in percentage); US (uptake speed); ES (excretion speed); EF (excretion fraction); SV (secretion velocity).