Review Article

Evaluation of the oral component of Sjögren's syndrome: An overview

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Abstract

Sjögren's syndrome is a chronic autoimmune disorder characterized by lymphocytic infiltration, and consequently hypofunction of lacrimal and salivary glands. The loss of salivary function induces oral dryness (xerostomia). This review focuses on methods for determining salivary gland function including clinical signs, salivary flow rate measurements (sialometry), analysis of salivary composition (sialochemistry), histopathological and radiologic examinations, and other recent advanced techniques.

Key words: *Biopsy, labial salivary gland, sialochemistry, sialography, sialometry, Sjögren's syndrome, xerostomia*

INTRODUCTION

Sjögren's syndrome (SS) is a chronic autoimmune disease, which was first described in 1933 by the Swedish ophthalmologist Henrik Sjögren. It is characterized by lymphocytic infiltration causing progressive destruction of exocrine glands, specifically the salivary and lacrimal glands, leading eventually to xerostomia and keratoconjunctivitis sicca.[1,2]

SS is the second most common chronic systemic autoimmune disease affecting between 0.05 and 0.4% of the world population.[3-5]

Although being relatively common, it is still difficult to be diagnosed because of the variability of its clinical presentations that range from mild cases of dryness, fatigue, and pain to severe systemic conditions involving multiple organs.[6]

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SS can occur alone (primary SS) or associated with other underlying autoimmune diseases (secondary SS) such as rheumatoid arthritis, scleroderma, and polymyositis.[6-8]

Xerostomia is not pathognomonic to SS; it can be a symptom of other diseases (sarcoidosis, poorly controlled diabetes, systemic lupus erythematosus, etc.), an adverse effect of certain medications (antidepressants, antihistamines, diuretics, etc.) or previous treatment (radiation of the head and neck).

Thus, the evaluation of xerostomia in SS is as varied as variable. Indeed, the diagnosis based on clinical examination needs to be made by more specific tests studying the function of salivary glands. The main objective of this article was to review the different methods of exploration of the salivary glands and to clarify their diagnostic value.

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METHODS

Clinical signs

Xerostomia, frequently encountered in dental practice, is associated with:

- Increased risk of developing dental caries: The deficiency of the anticariogenic actions of saliva induce more aggressive tooth decay progress than normal. Caries may affect all teeth surfaces including the ones that are usually spared such as the cervical margins of the anterior mandibular and maxillary teeth[9]
- Dental erosion: The normal saliva prevents demineralization of teeth[10]
- Fungal infections especially oral candidiasis: The lack of antimicrobial agents contained in saliva leads to an opportunistic infection with *Candida* species[11]
- Suppurative sialadenitis: Hyposalivation may result in bacterial entrance into the duct of the gland and consequently infection and swelling. The parotid is the mostly concerned[12]
- Oral discomfort while chewing, swallowing, tasting, or speaking[13]
- Problems for denture wearers such as denture instability, generalized mucosal soreness, and ulceration of the areas covered by the denture[14]
- Oral mucosa alterations, among others, angular cheilitis, burning or tingling sensation[15]
- Fissured, sticky, depapillated, and erythematous tongue[15]
- Dysgeusia and intraoral halitosis possibly due to increased activity of halitogenic biofilm.[15]

Measurement of salivary flow

Major and minor salivary glands generate saliva in different ways and flow rates. While the parotid gland produces saliva under stimulation (eating, sucking, chewing, or smelling a tasty meal), the submandibular secretes saliva continuously (without stimulation) keeping the mouth moist.

Salivary flow measurement (sialometry) is widely applied in diagnosing xerostomia. Several methods for collecting saliva have been reported, yet none is perfect. These methods are divided into two types: (1) Collection of the saliva present in the mouth known as the whole saliva technique (combined secretions of all salivary glands) and (2) collection directly from a specific salivary gland.[16]

The collection of the whole saliva is commonly used. It is easy to perform, is quickly accomplished, and does not require any collection device.[17] However, in this technique, the collected saliva may be subject to the interference of nonsalivary elements such as epithelial cells and food debris.[18]

Normally, unstimulated whole saliva flow rate is 0.3–0.4 ml/min; below 0.1 ml/min rate is considered abnormal.[12] For the stimulated one, a rate less than 0.5 ml/gland in 5 min or less than 1 ml/gland in 10 min is significantly low.[15]

For many researchers, the diagnostic value in SS is defined only by a reduced rate of secretion of unstimulated whole saliva.[19-22] For others, many alterations in flow rate, not seen or less obvious when using the whole saliva, have been reported in patients with SS tested with the separate glandular saliva technique.[23-25]

Pijpe *et al*. concluded in their study that early SS is accompanied by a reduction of all salivary glands function which becomes severe over time.[26]

For Vissink *et al*., among the salivary glands, in patients with SS, the parotid is the last one that is affected. This unclear mechanism is, in the same manner, observed in healthy elderly people in whom the capacity of saliva secretion by the parotid is not perturbed by age, whereas submandibular and sublingual glands physiologically present a decrease in their secretory capacity.[27]

Finally, it is important to note that xerostomia may also result from a change in the composition of saliva from serous to mucous.[28]

Chemical study of saliva

Chemical saliva study (sialochemistry) may show several characteristic changes in electrolytes and enzymes in SS due to the effect of an autoimmune attack on the secretory cells of the salivary glands.[29] A study conducted by van der Reijden *et al*. concluded that the absolute concentrations of albumin, cystatin C, cystatin S, total IgA, and total protein (except amylase), were increased significantly in SS.[29] In the same manner, a marked elevation in sodium and chloride in saliva is noted while phosphate concentration is reduced.[17]

Baldini *et al*. conducted a study using a proteomic approach to analyze the saliva of patients with primary SS. They concluded that the salivary profile of these patients is characterized by a decrease in many secretory proteins (α-amylases precursor, carbonic anhydrase VI,

etc.), an increase in proteins related to the autoimmune response (β-2 microglobulin, IGKC protein, and rheumatoid factor D5 light chain), as well as an increase in the inflammatory proteins (alpha-enolase, lipocalin, and S100-A7 and A9 proteins).[30]

In regards to the saliva pH, dos Anjos Corvo *et al*., in their study, compared the salivary pH of individuals with SS to healthy individuals and found no statistically significant difference both in stimulated and nonstimulated total saliva.[31]

Histopathological examination

The inflammatory cells infiltration in SS occurs in both major and minor salivary glands. The infiltrate contains, among others, T cells, B cells, macrophages, and natural killer cells. T and B cells predominate and the proportion of B cells increases with lesion severity.[32] To perform the histopathological examination, a salivary gland biopsy is needed. For most researchers, minor salivary gland biopsy remains a highly used diagnostic procedure for oral salivary component of SS.[33,34]

However, biopsy of a major salivary gland mainly the parotid is sometimes indicated when mucosa-associated lymphoid tissue (MALT) lymphoma, which can occur in SS, is suspected. MALT lymphomas mostly originate in the parotid gland.[35]

Sampling is usually performed at the lower lip where 5–7 accessory glands are excised [Figure 1].

Histopathological examination may help to diagnose SS if it reveals a mononuclear infiltration with mostly periductal and/or perivascular distribution [Figure 2a and b].

The inflammatory infiltrate is quantified and an aggregation of ≥50 lymphocytes, plasma cells, or histiocytes is considered a focus.[34,36] The number of focus in a surface of 4 mm^2 denotes the focus score.[34,36]

The classical method for scoring SS biopsies is based on the Chisholm and Mason classification composed of 5 criteria [Table 1].[36,37]

The focus score has been considered to be an index of severity of the salivary gland lesion in SS, with higher focus score related to acinar damage.[33]

According to the Revised International Classification Criteria (RICC) and the Japanese Expert Criteria (JEC), a focus score of ≥1 is considered positive for SS diagnosis.[34]

In their studies, Daniels *et al*. and Haldorsen *et al*. found that a focus score of ≥1 matches with the presence of keratoconjunctivitis sicca and low unstimulated but not stimulated salivary flow rates.[38,39] In 1974, Tarpley *et al*. developed another classification of 5 grades also based on the focus scores [Table 2].[40]

Table 1: Grading method as developed by Chisholm and Mason (1968)

Grade	Lymphocytes and plasma cells per 4 mm^2
Grade 0	No infiltrate
Grade 1	Slight infiltrate
Grade 2	Moderate infiltrate or less of 1 focus
Grade 3	1 focus
Grade 4	More than 1 focus

Table 2: Grading method as developed by Tarpley *et al*. (1974)

Grade	Infiltrate
Grade 0	No infiltrate, normal appearance
Grade 1	1 or 2 focus
Grade 2	Over 2 focus
Grade 3	Diffuse mononuclear infiltrate with partial acinar destruction
Grade 4	Diffuse infiltration with total acinar destruction

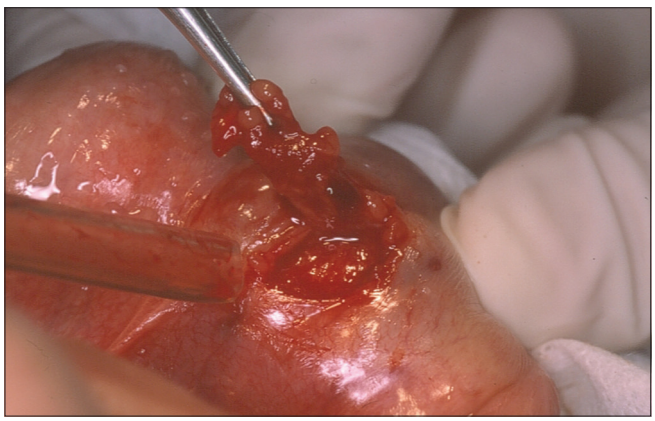

Figure 1: Minor salivary glands biopsy through an incision in the lower lip

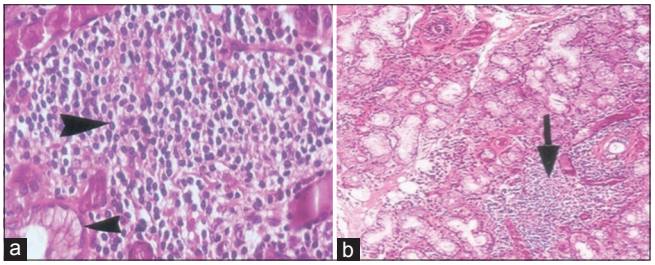

Figure 2: (a and b): Hematoxylin and eosin colored sections of minor salivary gland biopsy specimens showing lymphocytes infiltration

Although focus score may give some idea of the extent of the glandular infiltration, dealing with it to elaborate a final diagnostic in SS must be done carefully. False negative and positive results have been found, respectively, in 20–40% and 10% of healthy individuals.[41]

Similarly, Radfar *et al*. reported in their study[42] that salivary gland biopsies with 2 to 6 focus score have been found in 15% of healthy individuals, with no clinical signs of xerostomia or keratoconjunctivitis sicca.[42]

Furthermore, patients affected by some autoimmune disorders not associated with dryness symptoms may also reveal minor salivary gland infiltration.[43]

Sialography

Sialography is a radiographic study of the salivary glands. Usually, it targets the parotid gland; however, it can also be applicable to the submandibular. It consists of obtaining an X-ray after injecting a contrast medium into the salivary duct [Figure 3a and b]. In SS patients, sialography shows a twisted and dilated duct associated with an uneven distribution of the contrast medium inside the gland [Figure 4 a and b].[34]

Rubin and Holt[44] developed a classification for SS diagnosis based on sialography imaging composed of 5 stages [Table 3].

For the RICC, the JEC, as well as the American-European consensus group (AECG), a positive result in the sialography study is included among the SS diagnosis criteria.[34] However, this technique is less frequently used because it may present false positive and negative results.[45] Furthermore, it is not indicated when a gland is highly damaged due to the risk of the contrast medium retaining.[46,47]

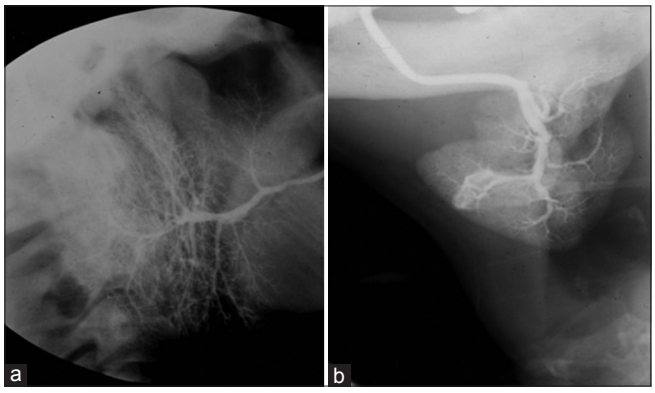

Figure 3: (a) Normal sialogram of the parotid gland; (b) Normal sialogram of the submandibular gland.

Despite being considered among the AECG criteria, sialography is not included in the American college of rheumatology (ACR) classification criteria for SS.[48]

Scintigraphy

Scintigraphy is a noninvasive technique which can be used to assess the function of salivary glands.[49] Its main advantage compared to other methods is by providing information regarding both salivary gland parenchyma and function.[50]

Scintigraphy consists on capturing by a detector-type gamma scintillation camera and the emitted radiation of radioisotopes such as Technetium-99m pertechnetate administered intravenously.[49,50]

Normally, the radioactive tracer is progressively accumulated in the glands (within 10 min of the substance administration), and after 20 to 30 min it is secreted into the mouth.[49,50] In SS, both the concentration inside the gland and the secretion into the mouth are lower.[34]

Schall *et al*. proposed a classification for salivary scintigraphy based on the visual evaluation of the uptake

Table 3: Sjögren's syndrome classification based on sialography imaging as developed by Rubin and Holt

Stage	Description
Stage 0	Normal image (without contrast media collection)
Stage 1	Punctuate image (refers to contrast media collection ≤1 mm in diameter)
Stage 2	Globular image (contrast media collection between 1 and 2 mm in diameter)
Stage 3	Cavitary image (contrast media collection ≥2 mm in diameter)
Stage 4	Destructive image (complete destruction of the gland parenchyma)

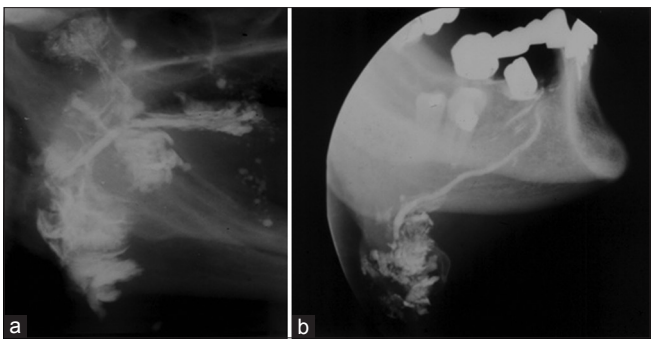

Figure 4: Sialogram of Sjögren's syndrome-affected parotid gland (a) and submandibular gland (b) showing a stage 4 according to Rubin and Holt classification

and discharge of the radioactive substance. The glands are consequently graded from 1 (normal) to 4 (severe affection).[51,52]

Abnormal salivary gland scintigram is included by the AECG among the diagnostic criteria of SS.[34] However, being rejected by most patients due to its high cost and their fear of a potential subjective risk of radiation damage, this technique is rarely performed. Interestingly, many authors found a correlation between salivary gland scintigraphy, sialography, and positive focus score in a minor salivary gland. The latter being one of the most specific tests in diagnosing SS.[53-55]

Magnetic resonance and ultrasonography

Magnetic resonance (MR) imaging, MR sialography, and ultrasonography (US) are noninvasive techniques providing precise imaging of salivary glands without the need of contrast media or biopsy procedures.

By allowing multiplanar images with high contrast tissue resolution, MR imaging is widely considered to evaluate the structural alterations of the salivary glands.[34] In SS, the glandular tissue appears inhomogeneous and speckled with multiple nodules of different sizes.[56]

In the latter years, MR sialography has widely replaced classical sialography. It has shown highly precise salivary gland assessment, and consequently a reliable SS diagnosis.[57]

In regards to US, the ability to evaluate all salivary glands at the same time added to the benefit of being cheaper and more available than MR makes it most advantageous. However, due to its delicacy, it should only be performed by proficient and qualified personnel.[58]

Although these techniques are promising, none of them is considered among the criteria of the AECG.

Raman spectroscopy

Raman spectroscopy (RS) is a spectroscopic technique used to observe the changes of chemical components and the alterations of molecular substructures in the biological tissues, referred to as "molecular fingerprint."[59] Xue *et al*. reported that RS can replace the lip biopsy, sometimes invasive, to diagnose pathological minor salivary glands in primary SS.[60]

According to the authors, lymphocytic infiltration leading to the destruction of the minor salivary glands is accompanied by a change of the "molecular fingerprint" from the early stages of primary SS.[60]

Consequently, the content of proteins, nucleic acids, and keratin increases because of inflammatory cells' infiltration and glandular foci formation while the content of lipids decreases as a result of the inflammation and the glandular destruction.[60]

CONCLUSION

The oral component of SS is characterized by xerostomia resulting from the loss of salivary function due to lymphocytic infiltration of the salivary glands. To evaluate this component, different methods have been used. These methods and their diagnostic value in SS have been reviewed. Assessment of clinical signs and symptoms, salivary flow rate measurement, salivary composition analysis, histopathological and radiologic examinations, and other new advanced techniques are key diagnostic factors to be considered.

Although different conclusions have been presented, every mean should be used for adequately determining the real status of the salivary glands.

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Conflicts of interest

There are no conflicts of interest.

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