



## Sjögren's syndrome – a complete literature preview

<b>Dr. Hima Desai</b>	BDS, Junior Resident College of Dental Sciences & Research Center, Bopal, Ahmedabad
<b>Dr. Ankit Shah</b>	Post Graduate Student, Department of Conservative Dentistry and Endodontics, College of Dental Sciences and Research Center, Bopal, Ahmedabad.
<b>Dr Peshal patel</b>	<b>BDS, Pacific Dental college and Hospital, Rajasthan</b>

### ABSTRACT

Sjögren's syndrome (SS) is a complex, chronic, systemic, autoimmune disease that mainly affects the exocrine glands, especially the salivary and lacrimal glands, leading to dryness of the oral and ocular mucosae. Several factors have been studied that could explain the glandular hypofunction primarily related to water transport. Sjögren's syndrome (SS) is characterized by keratoconjunctivitis sicca, xerostomia and rheumatoid arthritis. Salivary gland dysfunction is one of the key manifestations of this disease and thus it seems logical to use the dysfunction of these glands for its diagnosis. A growing number of researchers from various fields including dentistry are finding saliva as a useful diagnostic tool due to easy and noninvasive collection methods. Recent reports have shown alterations in secretory route and trafficking in labial salivary glands, explaining alterations in the saliva quality. The decrease in salivary flow and qualitative alterations in saliva could explain many of the oral manifestations. The exocrine manifestations and systemic involvement significantly impact the patient's perception of health-related quality of life. The non-invasive nature of saliva makes it the most reliable and favored tool for diagnosis of SS. The ability to measure a wide range of molecular components in saliva and compare them with serum has made it feasible to study microbes, chemicals and immunological markers. This review article aims at summarizing the variable use of saliva as a diagnostic aid on a daily basis while treating patients with SS.

### KEYWORDS

Keratoconjunctivitis, Saliva, Sjögren's syndrome, Xerostomia

### Introduction

Sjögren's syndrome (SS) is a condition originally described by Henrik Sjögren in 1933 as a triad consisting of keratoconjunctivitis sicca, xerostomia and rheumatoid arthritis. The main etiologic factor for this disease is considered to be altered immunological response. Since, the etiopathogenesis of the diseases unclear, its diagnosis is still based on characteristics signs and symptoms. As a single diagnostic test does not detect changes pathognomic of SS, combinations of different tests are used. Salivary gland dysfunction in one of the key manifestations of this disease and thus it seems logical to use the dysfunction of these glands for its diagnosis.

Primary Sjögren's syndrome (PSS) is a systemic autoimmune disorder characterized by inflammation of the exocrine glands, such as lacrimal and salivary glands without any associated connective tissue disease. PSS ultimately results in hypofunction and dryness of the mucosal surfaces, particularly of the eyes and mouth. Secondary Sjögren's syndrome (SSS) has similar pathophysiology, signs and symptoms as PSS, but is associated with some forms of connective tissue disease such as PAPER rheumatoid arthritis and systemic lupus erythematosus. Primary biliary cirrhosis and other autoimmune conditions can also be associated with SSS.

The autoimmune features of the disease are characterized by circulating autoantibodies and lymphocytic infiltrates in exocrine glands. Both findings are considered in the diagnostic criteria. In this context, the inflammatory cells play a major role in the pathogenesis, attacking the epithelial cells. However, an important body of evidence suggests that other factors promote the loss of epithelial cell homeostasis, occurring in the pre-autoimmune phase or independent of inflammatory cells.

The SS patient presents with a variety of signs and symptoms, with ocular and oral dryness subsequent to salivary and lacrimal gland damage constituting the most common complaints. Several factors related to water transport could explain the glandular hypofunction<sup>8</sup>. Recent reports have also shown alterations in

secretory route and trafficking of secretory products in labial salivary glands (LSG). Additionally, changes in protein expression involved in maintaining cell-cell and cell-extracellular matrix relationships have been described in murine models and SS patients. These alterations would produce changes in quality of secretion and may even contribute to inflammatory process.

### ORAL MANIFESTATIONS

The predominant effects of SS on the oral cavity are mainly consequent to hyposalivation. Recent evidence indicates that over half of the patients with PSS experienced an oral symptom as their first manifestation of the condition. However, PSS can also indirectly cause oral manifestations secondary to systemic involvement. An appropriate example is that of SS-induced thrombocytopenia manifesting as oral bruising or purpura. Significant thrombocytopenia at levels below  $50 \times 10^9$  may also influence any planned dental treatment. PSS patients are 44 times more likely to develop B cell lymphomas of the salivary gland. The presence of any firm or discrete swelling involving major salivary glands or presenting intraorally should raise suspicion and may warrant further investigation. Lack of saliva causes difficulties in oral function. Patients may complain that their lips stick together and they have difficulties eating, speaking, chewing, swallowing and with denture retention.

Saliva may be of a frothy consistency with an absence of saliva pooling in the floor of mouth. It may not be possible to express saliva from the parotid and submandibular ducts. The tongue may appear erythematous, dry and fissured. Alternatively the tongue may be coated and appear brown or black, a presentation appropriately termed black hairy tongue. The oral mucosa may appear dry and stick to the dental mirror or gloved finger, have a normal appearance or appear erythematous. Such dry erythematous mucosa is often uncomfortable to touch with patients complaining of soreness even in the absence of overt clinical infection.<sup>8</sup> Patients may also complain of dysgeusia and halitosis. Oral candidosis occurs in individuals with SS more frequently than the general population. The most common clinical variant is that of chronic erythematous candidosis, although other

types such as acute pseudomembranous candidosis may complicate SS.

Patients with overt intraoral candidosis may be completely asymptomatic. They may simply seek medical attention after developing complications such as angular cheilitis, which may cause soreness on mouth opening. Angular cheilitis may be due to candidal or staphylococcal infection, however, it is important to exclude other predisposing factors such as anaemia.

Patients may present with new, recurrent and atypical patterns of dental caries, particularly cervical caries. Factors involved may be the loss of salivary buffering capacity and the imbibition of cariogenic drinks to relieve symptoms of xerostomia.<sup>11</sup> Even with excellent levels of oral hygiene, caries and premature tooth loss have been found in some studies where patients have a higher DMFT (decayed/ missing/filled teeth) score compared to control individuals. It is unclear whether patients with SS are at an increased or indeed reduced risk of periodontal attachment loss compared to a non-SS population, as current evidence is conflicting.<sup>13-15</sup>

Patients with SSS may exhibit oral manifestations related to their primary autoimmune disease. Appropriate examples include systemic lupus erythematosus (SLE), presenting with oral lichenoid lesions, which may clinically resemble oral lichen planus. Another example is scleroderma, which may present with fibrosis of the oral tissues and generalised pallor due to loss of vascularity.

## SYSTEMIC MANIFESTATIONS

SS is not only a disease of the exocrine glands but a systemic condition. Regarding extra-glandular symptoms and signs, fatigue is often a prominent and disabling symptom for SS patients. Myalgia and arthralgia are also common but severe inflammatory muscle or joint disease is relatively uncommon. Various forms of skin lesions secondary to disease such as vasculitis, discoid lupus and Raynaud's phenomenon can occur. Both the peripheral and central nervous system can be affected in SS but the prevalence of SS-associated neurological complications remains under debate. Peripheral neuropathy, especially involving sensory nerves, are thought to be common. Cranial nerves can be affected, leading to paraesthesia and discomfort of the face and tongue as previously described. Other organs that can be affected by SS include the lungs, kidneys, pancreas and the heart. Preliminary data from the UK Primary Sjögren's Syndrome Registry suggest that patients with PSS are at significantly increased risk of hypertension.

Serum levels of immunoglobulins, particularly IgG, are often elevated. Other haematological and biochemical abnormalities that may be observed include lymphopaenia, thrombocytopaenia, elevated erythrocyte sedimentation rate (ESR) and raised levels of C-reactive proteins. Anti-Ro and Anti-La antibodies are a part of the current classification criteria for PSS. These autoantibodies are found in 60-70% of patients.<sup>16</sup> The presence of these autoantibodies has been linked to increased disease severity and duration, as well as earlier onset of the disease.<sup>17</sup>

Finally, the symptom mostly associated with SS, xerostomia, may also influence general well-being. Patients will often report waking up at night, possibly repeatedly because of dry mouth, which consequently may result in a poor sleep pattern and onward impact in terms of fatigue and quality of life.

## Diagnostic criteria

Methods for assessing salivary gland dysfunction include the following:

- Sialometry—method for determining flow rate.
- Sialochemistry—chemical analysis of salivary composition.

Sialometry can be used as a diagnostic tool mainly in two ways:

### Sialometry

A reduced rate of secretion of unstimulated whole saliva is

currently considered to be of diagnostic value in SS. Various studies have showed reduced submandibular/ sublingual (SM/SL) flow rate in SS. A possible explanation for this appreciably reduced flow rate is early involvement of SM/SL gland. In contrast, parotid flow rate may be decreased in SS negative patients also and hence measurement of parotid flow as a single test is of no use in diagnosing SS.<sup>18</sup>

### Sialochemistry

Sjögren's syndrome patients showed elevated levels of Na<sup>+</sup> and Cl<sup>-</sup> levels. Normally Na<sup>+</sup> are extensively absorbed in the ductal system to produce hypotonic saliva, and in normal individuals, their concentrations decrease with decrease in flow rates. This phenomenon is not observed in SS patients and even patients with very low flow rates show a two fold or three fold increase in Na<sup>+</sup> and Cl<sup>-</sup> concentration.<sup>19</sup> This could be due to impaired duct function by periductal lymphocytic infiltration that is present in major salivary glands in SS. Phosphate concentration was decreased in SS patients in unstimulated whole saliva and concentration was unaltered in stimulated saliva. The unaltered levels in stimulated saliva indicate a disease independent potassium secretion by duct cells or that potassium is secreted at other sites.

### Proteins

Qualitative and quantitative changes of salivary protein content have been examined by means of electrophoresis and isoelectric focusing on stimulated parotid secretion. Increased amount of anionic proteins was observed in SS patients.

### Lipids

Salivary levels of phospholipids are increased and this may have diagnostic implications. Unsaturated fatty acids of salivary lipids were below normal, which may indicate an alteration in cell membrane function.

### Lactoferrin (LI)

Tabak et al reported an increase in lactoferrin in stimulated parotid saliva with primary SS.

### Lysozyme

In SS patients, the lysozyme levels, an antibacterial enzyme, were decreased which could be due to pronounced atrophy of epithelial cells.

### Amylase

No significant difference in saliva of SS patients and healthy controls were reported, but in a group of patients with primary SS, a significantly decreased concentration in the nonsecreting patients as compared to nearly normal secreting patients were found. Amylase may be used as a marker/or acinar function.

### Kallikreins

In SS patients, elevated levels especially in the morning were found in stimulated whole saliva compared with healthy controls. Salivary Kallikrein may serve as a marker for striated duct cell function and elevations found in SS may indicate damage to these cells.

### Albumin

In SS albumin, levels in saliva are elevated indicating a certain loss of parenchymal integrity. These elevations reflect leakage and are, therefore valuable in the assessment of extent of inflammatory changes present.

### B-2 Microglobulin (B2M)

In majority of patients, the concentrations were higher than in serum, suggesting a local B2M production. Acinar cells and majority of lymphocytes stain for B2M in SS and intensity parallels the severity of inflammation. Salivary B2M may therefore be a marker for the degree of inflammation in salivary glands in SS patients.

### Immunoglobulins

Immunoglobulin A (IgA): Increased concentration of secretory IgA

has been found in SS patients in view of the lymphocytic glandular infiltration. Decreased in flow rate may also be partly responsible. Some studies have advocated the increase in salivary IgA, as a criterion for diagnosis of SS. Immunoglobulin G (IgG): Marked elevation of IgG in SS patients were reported by several studies. The increase in salivary IgG is not influenced by diminution of salivary flow. The elevated levels are due to activated local synthesis which is supported by reports detecting increased number of IgG producing plasma cells in the lymphocytic infiltrate of minor salivary gland biopsy specimens in SS patients. Immunoglobulin M (IgM): The presence of IgM in saliva of SS patients was inconsistent.

### Salivary Auto-Antibodies

Both IgM and IgA-RF have been found in the saliva of primary SS. IgA-anti SB autoantibodies are also synthesized locally in the diseased salivary glands and secreted into saliva of SS patients. Horsfall et al reported the presence of salivary anti-La antibodies in SS patients by ELISA.<sup>19</sup> Ben-Chitrit et al detected anti-Ro and anti-La antibodies in the saliva of patients with SS. Analysis of these antibodies showed that, although the serum contained mainly IgG and IgM antibodies, saliva contained antibodies of IgG and IgA classes only. SS anti-La antibodies were primarily found in the saliva of patients whose resting and stimulated whole saliva flow rates was extremely low. In some patients, this antibody was detected in whole saliva but not in serum, which suggested that the antibody is produced in the salivary glands. The deposition of this antibody within salivary gland tissue may contribute to the pathogenesis of SS.

### Other Markers of Inflammation

Levels of salivary eicosanoids (PGE2 and TXB2), interleukin-6 and hyaluronic acid were elevated in SS patients compared with healthy controls.

### Prevalence

Sjögren's syndrome occurs worldwide and in all ages. The peak incidence is in the fourth and fifth decades of life, with a female : male ratio of 9:1.<sup>20</sup> A number of studies have shown great variation in the frequency of Sjögren's syndrome.<sup>15</sup> Prevalence studies have demonstrated that sicca symptoms and primary Sjögren's syndrome affects a considerable percentage of the population, with precise numbers dependent on the age group studied and on the criteria used. A cautious but realistic estimate from the studies presented thus far is that primary Sjögren's syndrome is a disease with a prevalence not exceeding 0.6% of the general population.

### Management

Sicca symptoms of the disease could be treated by using topical agents whereas extraglandular features are managed with glucocorticoids and immunosuppressive drugs. But, literature search revealed no evidence based therapeutic guidelines for the management of primary Sjögren syndrome which is also universally accepted.<sup>22</sup> The results of one excellent systematic review about the treatment of SS shows that B cell targeted agents seem to be the most promising future therapy, especially rituximab, which has been used in more than 100 reported cases. Agents that block B cell-activating factor of the tumor necrosis factor family may also be a promising therapy. Advances in knowledge of the molecular mechanisms involved in the etiopathogenesis of Sjögren's syndrome may allow the development of more effective, highly selective therapies without the adverse effects often associated with standard, less-selective drugs (41). Today, current treatment options are decided upon a mix of personal experience, expert opinion, and reported studies.

### Oral aspects of treatment

The management of SS from the perspective of the dental practitioner is that of symptomatic control, the prevention and treatment of oral complications of dry mouth. SS patients will require multidisciplinary care including early referral to oral medicine specialists to ensure delivery of oral and maxillofacial aspects of their care. other factors such as poorly controlled

diabetes mellitus, smoking and certain drugs that may contribute towards hyposalivation should not be overlooked. Symptom management is particularly influenced by patient preference, with some patients preferring to take frequent sips of water or chew sugar-free chewing gum. Other patients supplement such measures with a range of proprietary topical products ranging from artificial saliva to salivary stimulating products. Saliva replacement therapy helps to lubricate the oral mucosa and aid oral clearance of food.

Examples of the more commonly prescribed artificial saliva products are Glandosane and Saliva Orthana. Glandosane artificial saliva spray is acidic and repeated use can result in non-carious tooth surface loss in dentate patients. Saliva Orthana spray is not acidic, contains fluoride and is preferred to Glandosane for use in dentate patients. The effectiveness of artificial saliva may be limited by the fact that swallowing may rapidly deplete the applied product, hence frequent application is necessary, which may be time consuming and socially unacceptable. Other products described as oral lubricants are gel-based such as Biotene Oralbalance gel, which also contains fluoride. Topical sialogogues such as Salivix pastilles are designed to stimulate salivary flow when sucked. As they are acidic, repeated use can result in non-carious tooth surface loss in dentate patients. The evidence base and limitations of the effectiveness of such products has been the subject of a recent Cochrane review.<sup>23</sup>

Cevimeline is a selective muscarinic agonist with similar mode of action and side effects to pilocarpine, however, it is not licensed for use in the UK. The use of fluoride regimens, together with regular oral hygiene reinforcement and dietary advice are also useful measures for caries prevention. Denture wear in patients with SS may result in accelerated dental caries and periodontal disease in the dentate patient and may represent an added risk factor. Appropriate advice for patients who are partially dentate and wearing dentures would be centred upon preserving their natural dentition, as outlined below. Patients with dentures may feel that their mouth is very dry and the lack of saliva prevents adequate retention of the prosthesis.

### CONCLUSION

Dental practitioners play a crucial role in the early diagnosis and management of the oral manifestations of patients with SS. It is therefore reasonable for dental practitioners to be aware of the syndrome, including an increased awareness of systemic symptoms. Indeed, as the dental practitioner will be in regular contact with this patient group as part of their routine recall for their dental needs, they are appropriately placed to refer this patient group to a specialist care pathway.

### References

1. Kaufman, Lamster BI. The diagnostic applications of saliva: a review. *Crit Review Oral Bio Med* 2002; 13(2): 197-212.
2. Mandel ID. The diagnostic uses of saliva. *J Oral Pathol Med* 1990; 19(3): 119-125.
3. Steckfus CF, Bigler LR. Saliva as a diagnostic fluid. *Oral Diseases* 2002; 8: 69-76.
4. Kalk WWI, Vissink A, Bootsma H, Kallenberg CGM. Sialometry and sialochemistry: diagnostics tool of Sjogren's syndrome. *Ann Rheum Dis* 2001; 60: 1110-1116.
5. Fox PC, Bowman SJ, Segal B et al. Oral involvement in primary Sjögren syndrome. *J Am Dent Assoc* 2008; 139: 1592-1601.
6. Vitali C, Bombardieri S, Jonsson R et al (2002). Classification criteria for Sjogren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheum Dis* 61: 554-558.
7. Manoussakis MN, Kapsogeorgou EK (2010). The role of intrinsic epithelial activation in the pathogenesis of Sjogren's syndrome. *J Autoimmun* 35: 219-224.
8. Castro I, Sepulveda D, Cortes J et al (2012). Oral dryness in Sjogren's syndrome patients. Not just a question of water. *Autoimmun Rev* 12: 567-574.
9. Barrera MJ, Sanchez M, Aguilera S et al (2012). Aberrant localization of fusion receptors involved in regulated exocytosis in salivary glands of Sjogren's syndrome patients is linked to ectopic mucin secretion. *J Autoimmun* 39: 83-92.
10. Kassar S S, Thomas T L, Moutsopoulos H M et al. Increased risk of lymphoma in sicca syndrome. *Ann Intern Med* 1978; 89: 888-892.
11. Turner M, Jahangiri L, Ship J A. Hyposalivation, xerostomia and the complete denture: a systematic review. *J Am Dent Assoc* 2008; 139: 146-150.
12. Glore R J, Spiteri-Staines S, Paleri V. A patient with a dry mouth. *Clin Otolaryngol* 2009; 34: 358-363.
13. Antoniazzi R, Miranda L A, Zanatta F B et al. Periodontal conditions of individuals with Sjögren's syndrome. *J Periodontol* 2009; 80: 429-435.
14. Scardina G A, Ruggieri A, Messina P. Periodontal disease and Sjögren syndrome; a possible correlation? *Angiology* 2009; 61: 289-293.
15. Kuru B, McCullough M J, Yilmaz S, Porter S R. Clinical and microbiological studies of periodontal disease in Sjögren syndrome patients. *J Clin Periodontol* 2002; 29: 92-102.

16. Hernández-Molina G, Leal-Alegre G, Michel- Peregrina M. The meaning of anti-Ro and anti La antibodies in primary Sjögren's syndrome. *Autoimmun Rev* 2011; 10: 123–125.
17. Bayetto K, Logan R M. Sjögren's syndrome: a review of aetiology, pathogenesis, diagnosis and management. *Aust Dent J* 2010; 55: 39–47.
18. Kalk WWI, Vissink A, Stegenga B, Bootsma H, Amerongen AVN, Kallenberg CGM. Sialometry and sialochemistry: a non-invasive approach for diagnosing Sjögren's syndrome. *Ann Rheum Dis* 2002;61(2):137-144.
19. Tishler M, Yaron I, Shirazi I, Yaron M. Saliva: an additional diagnostic tool in Sjögren's syndrome. *Semin Arthritis Rheum* 1997;27(3):173-179.
20. Bolstad AI, Jonsson R. (2002) Genetic aspects of Sjögren's syndrome. *Arthritis Res.* 4(6):353-9.
21. Jonsson R, Haga H-J, Gordon T. (2001) Sjögren's syndrome. In: *Arthritis and Allied Conditions: a Textbook of Rheumatology*, 14th ed. Edited by Koopman WJ. Philadelphia: Lippincott, Williams & Wilkins;:1736-1759.
22. Ramos-Casals M, Font J. (2007) Primary Sjögren syndrome. In: Imboden J, Hellman D, Stone JH, eds. *Current Diagnosis and Treatment in Rheumatology*. New York, NY: McGraw-Hill;:237-245.
23. Oslain S, Pramanik R, Shirodaria S, Challacombe S J, Proctor G B. Investigating the relationship between hyposalivation and mucosal wetness. *Oral Dis* 2011; 17: 109–114.