Dental perspective on Sjögren’s syndrome: literature review

Abstract: The human body releases around 500-600mL of saliva daily, however when values of unstimulated whole saliva range from 0.1 to 0.2mL/min, there is a condition called Hyposalivation or hyposialia. Hyposalia is characterized by a large number of systemic conditions, including Sjögren’s syndrome, a chronic autoimmune disease that affects between 0.1 and 3% of the world population and is characterized by exocrinopathy of the salivary glands leading to glandular hypofunction and thus decreasing the normal salivary flow. Saliva is part of innate immunity, when there is a decrease in protein secretion, numerous oral manifestations occur such as dental caries, candidiasis, gingival disease, angular cheilitis, lymphomas of the salivary glands, dysphagia, erythematous and fissured tongue, among others. Currently there is no defined dental treatment, however there are alternative treatments by sialogogues and salivary substitutes, plus non-pharmacological therapies, which seek to maintain the ecology and oral conditions stable, in addition to preventive and restorative dental treatment for lesions already established as a consequence of the disease. The aim of this study is to conduct a literature review on the characteristics, classification, oral manifestations and dental management of Sjögren’s syndrome.

Keywords: Sjögren’s Syndrome, Hiposalivation, Xerostomia, Hyposialia, dental management.

INTRODUCTION.

In dental care practice, hyposialia or hyposalivation is nowadays a common disorder that affects the physiology of the oral cavity by reducing normal levels of saliva. This condition occurs in 10% of the population with the highest prevalence in the elderly.

Unfortunately, over time there has been shown that there are multiple causes leading to hyposalivation of xerostomia, which involve dysfunction of the salivary glands, including adverse effects of pharmacological agents, external beam radiotherapy, diabetes mellitus, hepatitis C, Sjögren’s syndrome, among others.

Sjögren’s syndrome (SS) is a chronic autoimmune disease of unknown etiology, with a slow and progressive course, which affects 0.1-3.0% of the population.

SS is one of the most common autoimmune diseases, with an estimated prevalence of 300-600 per 100 000 people, being more common in adults in the fourth or fifth decade of life and in a proportion of 9 women for every man.

This condition may occur in isolation as primary SS or it may develop as secondary SS together with other autoimmune diseases, such as sclerosis, rheumatoid arthritis, lupus erythematosus, among others.

The aim of this study is to conduct a literature review on the characteristics, classification, oral manifestations
and dental management of Sjögren’s syndrome.

**PATHOGENESIS**

SS is characterized by epithelial cell destruction and peri-epithelial infiltration by T CD4 lymphocytes and a lower number of B lymphocytes with multiple target organs, particularly exocrine glands. Th2 cytokines have been found to be involved in an early stage of the disease, while Th1 cytokines appear at an advanced stage.

Salivary and lacrimal glands are usually involved in the condition, causing dry mouth (xerostomia), dry eyes (xerophthalmia), these being representative clinical features of this disease. However, despite these common factors, there may be other manifestations that complicate the initial diagnosis.

In the pathophysiology of SS, chronic immune hyperactivity plays an important role. It is characterized by a strong activation of polyclonal B cells and autoantibody production. Histopathologically, the expression of HLA-DR is present on glandular epithelial cells, there is lymphocytic infiltration of glandular tissue, as well as a sustained localized cytokine production, causing an irreversible damage of salivary and lacrimal glands, which leads a reduction in the saliva flow and inability of tear production.

**DIAGNOSIS**

A multidisciplinary team composed by a rheumatologist, ophthalmologist, pathologist and dentist should make the diagnosis of SS. For this there are classification criteria that contribute to the diagnosis of SS. The proposal commonly used was developed by the American-European Consensus Group (2002), in which 6 criteria, based on oral and ocular symptoms and signs, are postulated: the histopathology of salivary glands, glandular dysfunction and the presence of autoantibodies anti-Ro (SSA) and anti-La (SSB). At least 4 of the 6 criteria must be positive in order to diagnose SS (Table 2).

A new classification proposed in 2012 by the Sjögren’s International Collaborative Clinical Alliance, and approved by the American College of Rheumatology, states that the diagnosis of SS can be established with the presence of two or more of the following findings: 1) positive anti-Ro/SSA and/or anti-La/SSB, or positive rheumatoid factor (RF) and positive antinuclear antibodies (ANA); 2) positive biopsy of minor salivary gland with an inflammatory focus score of ≥1/4 mm²; and 3) keratoconjunctivitis sicca with ocular staining score (OSS) of ≥3.

**Minor salivary gland biopsy:** The minor salivary gland biopsy is a simple procedure carried out by a dentist, which now is widely used in internal medicine and rheumatology for the diagnosis of SS and other infiltrative diseases of connective tissue, such as amyloidosis, hemochromatosis, and sarcoidosis. Although it is a simple procedure, some side effects and disadvantages of this diagnostic technique have been reported, such as pain, salivary duct trauma, infection, loss of sensation and development of granulomas.

**Salivary biomarkers:** Noninvasive diagnostic techniques for SS by means of biomarkers are currently being developed. Biomarkers are substances found in biological fluids such as saliva, which facilitates sample collection, and contains elements that reflect both the local and systemic condition of the patients.

These techniques are designed to detect, classify and monitor oral diseases and design a noninvasive treatment for them. Although there is not a defined proteomic pattern characterizing salivary gland dysfunction, kallikrein, as well as lactoferrin and albumin, have been linked to damage in salivary ductal cells.

Many of the antimicrobial defenses found in saliva are proteins, which are responsible for cleaving the chemical bonds of bacteria. However, they are not used as definitive diagnostic tools and are still under research as potential biomarkers for the diagnosis of SS.

Lysozyme, an enzyme found in saliva and gingival elastic fibers, is among the most common antimicrobial proteins. Low levels of lysozyme in the saliva imply increased plaque index in SS, which is considered a risk factor for periodontal disease. Salivary peroxidase is another enzyme produced by the acinar cells of the parotid and submandibular glands and exerts its anti-
Table 1. Main systemic manifestations in Sjögren’s syndrome.

| System       | Manifestations                                                                 |
|--------------|--------------------------------------------------------------------------------|
| Eyes         | Xeroftalmia\(^{17}\), keratitis sicca, conjunctivitis sicca\(^{18}\) dacryoadenitis, photosensitivity\(^{19}\) |
| Oral cavity  | Hyposalivation\(^{20}\), xerostomia\(^{21,22}\), sialadenitis, stomatitis, halitosis\(^{5}\), dental caries, oral candidiasis\(^{23,24}\), periodontal disease\(^{26,26}\), angular cheilitis, dysphonia, dysphagia\(^{27}\), erythematous and fissured tongue, mucositis\(^{28}\) |
| Gastrointestinal | Sialadenitis, stomatitis sicca, lymphoma\(^{29}\), atrophic gastritis, esophagitis sicca\(^{30}\) |
| Respiratory tract | Rhinitis sicca, sinusitis, bronchitis, pleuritis, pneumonitis\(^{31}\) |
| Vascular system | Vasculitis, Raynaud’s phenomenon, purpura\(^{30}\) |
| Cardiological | Cardiovascular autonomic neuropathy, congenital heart block, pericarditis, pulmonary hypertension\(^{6}\) |
| Rheumatologic | Peripheral synovitis, fatigue\(^{32}\), arthralgia\(^{39}\). |
| Dermatological | Dermatitis sicca, photosensitive lesions, xeroderma, urticaria\(^{34,35}\). |
| Nervous system | Fatigue\(^{32}\), polyneuritis, mononeuritis, encephalopathy, cerebellar syndrome, cranial nerve deficits\(^{10}\). |
| Urogenital | Vaginitis sicca\(^{10}\), glomerulonephritis, interstitial nephritis\(^{6}\). |
| Hematological | Anemia, lymphoma, thrombocytopenia, lymphopenia\(^{32}\). |

Table 2. Criteria of American-European Consensus Group (Adapted from Vitali et al., 2002\(^{13}\)).

I. Ocular symptoms: a positive response in at least one of the following questions:
   a) Have you had daily, persistent, troublesome dry eyes for more than 3 months?
   b) Do you have a recurrent sensation of having sand or gravel in your eyes?
   c) Do you use tear substitutes more than 3 times a day?

II. Oral symptoms: a positive response to at least one of the following questions:
   a) Have you had a daily feeling of dry mouth for more than 3 months?
   b) Have you had recurrently or persistently swollen salivary glands as an adult?
   c) Do you frequently drink liquids to aid in swallowing dry food?

III. Ocular signs—that is, objective evidence of ocular involvement defined as a positive result for at least one of the following two tests:
   a) Schirmer’s test I, performed without anesthesia (≤ 5 mm in 5 minutes).
   b) Rose bengal score or other ocular dye score (≥4 according to van Bijsterveld’s scoring system)

IV. Histopathology:
   In minor salivary glands (obtained through normal-appearing mucosa), focal lymphocytic sialadenitis, assessed by an expert in histopathology, with a score of ≥1, defined as a number of lymphocytic foci (which have a normal appearance of mucus acini and contain more than 50 lymphocytes) per 4 mm\(^2\) of glandular tissue.

V. Salivary gland involvement: objective evidence of salivary gland involvement defined by a positive result for at least one of the following diagnostic tests:
   a) Unstimulated whole salivary flow (<1.5 ml in 15 minutes)
   b) Parotid sialography showing the presence of diffuse sialectasias (punctate, cavitary or destructive pattern), without evidence of obstruction in the major ducts
   c) Salivary scintigraphy showing delayed uptake, reduced concentration and/or delayed excretion of tracer.

VI. Autoantibodies: presence in serum of the following autoantibodies:
   a) Antibodies to Ro (SSA) or La (SSB) antigen, or both.
microbial action by consuming $\text{H}_2\text{O}_2$. It has been demonstrated that peroxidase can reduce the adhesiveness of Streptococcus mutans and Porphyromonas gingivalis to the hydroxyapatite surface. These microorganisms have been linked to periodontal disease when their levels are elevated in the saliva.

**ORAL MANIFESTATIONS OF SJÖGREN’S SYNDROME**

**Hyposalivation:** Saliva is an exocrine fluid secreted by the major salivary glands (parotid, submandibular and sublingual) and minor salivary glands located on the lower lip, tongue, palate, and upper part of the pharynx. Saliva plays a pivotal role in the homeostasis of the oral cavity. Because of its functional properties it helps to protect teeth and mucous membranes, phonation, dental remineralization, bolus swallowing and maintenance of pH. It also helps to maintain a good digestion, and to prevent oral colonization by pathogens through its enzymatic processes.

The human body secretes about 500 to 600mL of serous and mucous saliva each day. This saliva contains minerals, electrolytes, enzymes, cytokines, growth factors, buffers, immunoglobulins (IgA), mucins, among other glycoproteins. However, when there is a decrease in normal salivary flow, with values below 0.1-0.2mL/min of unstimulated whole saliva or below 0.4 to 0.7mL/min of stimulated total saliva, we talk of hyposalivation, a condition that contributes to the development of opportunistic infections in the oral cavity; unlike xerostomia, which is the subjective sensation of dry mouth without a decrease in salivary flow.

It is known that multiple causes may lead to xerostomia, also referred to as burning mouth syndrome. This condition may or may not include hyposalivation. Among the causes of xerostomia, which do not involve a decrease in salivary secretion, are dehydration, cognitive and neurological disorders, oral sensory dysfunction, and oral breathing.

There are many causes that can induce hyposalivation, the most common are the adverse effects of pharmacological agents, considered as an iatrogenic consequence, the most prevalent being SS, external beam radiotherapy, and diabetes mellitus (more than half of the patients with diabetes mellitus have SS).
betes type I and II have hyposalivation), among others\(^63-69\) (Table 3).

**Oral conditions with hyposalivation:** Because of the exocrinopathy in SS, hyposalivation contributes to the ideal environmental conditions for the colonization by opportunistic pathogens such as *Streptococcus mutans* and *Candida albicans*\(^70\). The lack of self-cleansing processes and the absence of enzyme systems commonly found in saliva contribute to specific clinical features such as salivary candidiasis, stomatitis, dry mouth and dry mucous membranes, halitosis\(^1\), dental caries (with rapid evolution and prevalence in the cervical area), oral candidiasis\(^23\) (a prevalence of chronic atrophic candidiasis of 37% in SS have been reported\(^23\)); periodontal disease\(^24,25\), angular cheilitis, tongue depapilation, dysphonia, dysphagia\(^26\), erythematous and cracked tongue and atrophic fissured mucosa, burning mouth\(^27\), among others\(^20-28\) (Table 1).

**Periodontal disease in Sjögren’s syndrome:** There is discrepancy in some of the reviewed studies. A number of them show that the plaque index is lower in patients with primary SS than in patients with xerostomia, and that there are no differences between the gingival index, bleeding on probing index and pocket depth between both groups\(^71\).

These findings coincided with a study of periodontal conditions in patients with primary and secondary SS compared to healthy subjects, in which researchers found no difference in relation to the presence of microorganisms in the gingival sulcus, such as *Aggregatibacter actinomycetemcomitans*, *Streptococcus oralis*, *Fusobacterium nucleatum*, *Prevotella intermedia*, *denticola Treponema*, *Porphyromonas gingivalis*, *Eikenella corrodens*, *Campylobacter rectus* and *Bacteroides forsythus*\(^25\).

However, a study carried out by Antoniazzi *et al.* (2009) showed that a larger number of missing teeth were found in patients with primary and secondary SS in comparison to healthy subjects. They also found an increase in the gingival index (65%) and plaque index (75%), pocket depth, clinical attachment level and bleeding on probing compared to healthy subjects. Until the date of this research, no study has identified a periodontal condition in patients with SS\(^26\).

**Development of neoplasia:** A large number of autoimmune diseases predispose to the development of neoplasia\(^72\). In the case of SS the risk has been estimated to be 44 times that of the general population\(^73\). It has been reported that stimulation of cytokines, parotidomegaly\(^74\), environmental factors, viral infections\(^75\) and vitamin deficiencies predispose to the development of these lesions\(^76\).

Although there is a high prevalence of monoclonal B-cells non-Hodgkin lymphoma in salivary glands (4.3%)\(^77\), the factor for the development of lymphoma in patients with SS has not been discovered. However, one study has reported that patients with SS show a higher prevalence of monoclonality of the heavy chain of immunoglobulins in labial salivary gland biopsies, which may be the etiology of origin of the neoplasia in SS\(^78\).

**DENTAL MANAGEMENT OF SJÖGREN’S SYNDROME**

SS is a condition that requires a multidisciplinary approach. Patients are usually under a systemic management with hydroxychloroquine, nandrolone, and cyclosporine, drugs that have improved the systemic symptoms of SS\(^80\).

Although there is no definite treatment for SS\(^79\), preventive measures must be applied, together with the treatment of established oral lesions. The use of combined therapies to treat the signs and symptoms of hyposalivation is also recommended\(^62\):

**Preventive measures and treatment of established lesions:** When there is a decrease in salivary flow and innate barriers are depressed, good oral hygiene is required to maintain stable conditions preventing caries and gingivitis. Patients should visit the dentist periodically every 4 or 6 months to control plaque and to receive mechanical preventive therapy\(^82\). The application of pH-neutral sodium fluoride and yearly radiographs taken for caries prevention and control, together with sialometries in each medical checkup are also recommended\(^4\).

It is very important that the dentist instructs and motivates the patient about the importance of following a good oral hygiene regimen. This can be carried out using the...
modified Stillman method or the modified Bass technique that facilitates intrasurcular cleaning in cases of periodontal disease. These techniques should be performed using a soft-bristle toothbrush, fluoride toothpaste with little flavor, a proper interdental cleaning technique with dental floss or interdental brushes and non-alcohol mouthwash. When established carious lesions are already present, they must be removed and sealed with materials such as glass ionomer cement in class V lesions. The use of glass ionomer cement is indicated in SS because of its prolonged-release fluoride properties and low dimensional change. The use of amalgams and composite resins has also been recommended in anterior and posterior zones where the periodontal area is not affected.

Recurrent oral candidiasis can be treated with topical antifungal or a systematic administration of a sugar-free nystatin mixture. Also prostheses should be cleaned separately with topical antifungal or chlorhexidine, and the use of nystatin or clotrimazole cream 4 times a day in cases of angular cheilitis is recommended. Palliative recommendations and salivary substitutes: In order to prevent further oral lesions as dental caries, candidiasis, mucositis or gingival disease, substances that increase dryness or irritate oral tissues should avoided, such as alcohol and tobacco. The use of a humidifier is recommended at night, to chew sugar-free gum and healthy products containing xylitol, lactoperoxidase, or glucose oxidase, as they reduce the level of cariogenicity.

Patients with SS should be encouraged to drink water continuously as hydration reduces dry mouth, however, excessive water intake could lead to loss or electrolyte imbalance. There are plenty of salivary substitutes available: mouthwash solution, gels, sprays and toothpastes, which are based on mucopolysaccharides, mucins and sodium carboxymethylcellulose. Biotine is a saliva substitute based on poliglucosilmetacrilate, lactoperoxidase and glucose oxidase, with antimicrobial activity and available in toothpaste, chewing gum and mouthwash.

Artificial saliva substitutes do not replace the antibacterial and immune protective functions of natural saliva and, therefore, do not leave out the need for regular dental care and proper oral hygiene. However it has been shown that the use of these products does mitigate symptoms of severe xerostomia produced by glandular dysfunction. Xialine improves problems with speech and senses. However it has been shown that the use of Buccotherm in spray is not more effective than a placebo in patients with xerostomia.

Sialogogue drugs: Pilocarpine is a cholinergic agonist that stimulates muscarinic receptors of the salivary glands and increases salivary flow. This drug, approved by the FDA, is used to treat the impairment of salivary glands, however its use may have adverse effects such as sweating, rhinitis, nausea, increased urinary frequency, as well as increased gastrointestinal secretion of hydrochloric acid. Pilocarpine is also contraindicated in asthma, acute rhinitis, glaucoma, obstructive lung diseases, uncontrolled peptic ulcer, high blood pressure and interaction with β-adrenergic blockers. The recommended dose to treat hyposalivation in primary SS is 5mg 3 times a day.

Cevimeline is another muscarinic agonist for the treatment of hyposalivation caused by SS. The usual dose is 30mg 3 times a day. However it has been found that the administration of 5mg of pilocarpine largely increases salivary flow (8.96mL / 5min), however, it produces more side effects compared to a dose of 30mg of cevimeline (7.05mL / 5min). Rates of discontinuation of therapy found in patients with primary Sjögren’s syndrome due to adverse effects of pilocarpine reached 61%, compared to those of cevimeline that reached 32%. Other drugs to treat hyposalivation are bethanechol, methacholine, carbachol and pyridostigmine, but their use has been decreasing due to their lower pharmacological potency.

Prolonged-release films of pilocarpine: Because of the wide variety of adverse effects that sialogogue drugs can produce, researchers have looked for different ways to administer these drugs in order to mitigate their adverse effects.
Locally applied drugs for prolonged periods provide many advantages, such as an increasing desirable pharmacological action in the local site, reduction of the usual dose and decreased side effects. Currently there are biopolymers such as chitosan and hydroxypropylmethylcellulose, which are used for a prolonged-release of drugs. Recently there have been attempts to find an alternative for local treatment by means of prolonged-release biofilms of pilocarpine, that have shown a substantial increase in normal salivary flow in diabetic rats. Pilocarpine is controllably released for 4 hours and is biocompatible with adherent fibroblast cell line, however its effects have not been tested in humans.

Non-pharmacological salivary stimulation: A research carried out by the Cochrane group in 2013 about non-pharmacological treatment of dry mouth includes interventional therapies like acupuncture, neuroelectrostimulation and the use of low-level laser therapy:

1. Acupuncture: Acupuncture therapy for treating dry mouth produces a stimulation of the autonomic nervous system by increasing blood flow and in turn stimulating salivary flow. Researchers have studied the use of acupuncture in patients with xerostomia induced by external beam radiotherapy applied twice a week for 6 weeks, and they managed to obtain satisfactory results in total unstimulated salivary flow. Regarding adverse effects, some studies have shown patients experiencing slight pain in the eyes, bruising, bleeding and slight pain in the area of application, while in other studies no adverse effects were reported. Still improvements were found in relation to the symptoms of xerostomia in patients with SS.

2. Neuroelectrostimulation: Despite the efforts made to improve the signs and symptoms of hyposalivation, researchers have not found a satisfactory treatment for patients suffering from this condition. It has been shown that by applying electrical pulses to lingual nerve efferent fibers stimulate saliva secretion of the submandibular and sublingual salivary glands. In recent years there have been advances in neuroelectrostimulation, and by using devices from different generations, researchers have been able to stimulate the salivary glands:

   a) First generation: Salitron, Biosonics®: It consists of a probe with an external control device that generates an electric charge on the back of the tongue and palate. This device, approved by the Food and Drug Administration (FDA) in 1988, showed good clinical results and no adverse effects. However due to its high cost, large size and little comfort for patients it turned out commercially unsuccessful.

   b) Second generation: Removable intraoral splint-based stimulator (Saliwell, GenNarino®): With the aim of improving the flaws of the previously developed device an intraoral apparatus consisting of a dental guard made of thermoplastic polyurethane was designed. The device has signal generators that transmit electrical impulses, which are activated with a remote control operated by the patient. These generators are embedded within the plastic splint and located in such a way that they can be in contact with the mucosa of the third molar area; this in order to stimulate the buccal and lingual nerves. Some studies have shown that using the device for 10 minutes can reduce dry mouth. This machine has been well accepted by patients and no local or systemic adverse effects have been reported.

   c) Third generation: Device in dental implant (Saliwell Crown®): Some patients require more frequent stimulation of salivary glands. This is the case of patients with secondary SS, who suffer a more severe degree of hyposalivation. To help these patients a miniature neuroelectrostimulation device was developed and designed to be adapted into a dental implant, which avoids using removable parts. This device, placed on the third molar area, regulates the intensity and frequency of the stimulus due to its ability to detect the level of humidity in the oral cavity. It can also be activated with a remote control operated by the patient.

3. Laser therapy: Although low-level laser therapy has been scarcely studied and described, it has been reported that this therapy does increase salivary secretion stimulating mitotic production in epithelial tissue of the salivary glands.
CONCLUSION.

Sjögren's syndrome is one of the most common chronic autoimmune diseases. Its study has aroused considerable interest among dentists and researchers because its signs and symptoms not only occur systemically but also show various oral manifestations due to the autoimmune exocrinopathy that causes hypofunction of salivary glands. This offers an ideal environment for opportunistic organisms to thrive in. They are responsible for dental caries and candidiasis, among other diseases. Currently there is no dental treatment defined for SS, but there are treatment options such as sialogogue drugs, palliative measures, saliva substitutes, as well as preventive and restorative treatment of oral diseases. It is also important to provide periodic evaluations of patients with SS, through programs of disease control. Constant communication between dentist, rheumatologist and ophthalmologist is the key to optimal care for patients with Sjögren's syndrome.

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