



REVIEW

Dental perspective on Sjögren's syndrome: literature review

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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. Hyposialia 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, Hyposalivation, Xerostomia, Hyposialia, dental management.*

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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 saliva¹. This condition occurs in 10% of the population with the highest prevalence in the elderly².

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 agents³, external beam radiotherapy, diabetes mellitus, hepatitis C, Sjögren's syndrome, among others⁴.

Sjögren's syndrome (SS) is a chronic autoimmune di-

sease of unknown etiology, with a slow and progressive course⁵, which affects 0.1-3.0% of the population⁶.

SS is one of the most common autoimmune diseases, with an estimated prevalence of 300-600 per 100 000 people⁷, being more common in adults in the fourth or fifth decade of life and in a proportion of 9 women for every man⁸.

This condition may occur in isolation as primary SS⁹ or it may develop as secondary SS together with other autoimmune diseases, such as sclerosis¹⁰, rheumatoid arthritis, lupus erythematosus^{11,12}, among others¹³.

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 lymphocytes¹⁴ 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 stage¹⁵.

Salivary and lacrimal glands are usually involved in the condition, causing dry mouth (xerostomia)¹, dry eyes (xerophthalmia), these being representative clinical features of this disease¹⁶. However, despite these common factors, there may be other manifestations that complicate the initial diagnosis¹⁷⁻³⁵ (Table 1).

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 production³⁶. 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 production³⁷.

DIAGNOSIS

A multidisciplinary team composed by a rheumatologist, ophthalmologist, pathologist and dentist³⁸ 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 SS¹³ (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 pre-

sence 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 $\geq 1/4 \text{ mm}^2$; and 3) keratoconjunctivitis sicca with ocular staining score (OSS) of ≥ 3 ³⁹.

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 SS⁴⁰ and other infiltrative diseases of connective tissue, such as amyloidosis, hemochromatosis, and sarcoidosis⁴¹. Although it is a simple procedure, some side effects and disadvantages of this diagnostic technique have been reported, such as pain, salivary duct trauma¹⁴, infection, loss of sensation and development of granulomas⁴².

Salivary biomarkers: Noninvasive diagnostic techniques for SS by means of biomarkers are currently being developed. Biomarkers are substances found in biological fluids such as saliva⁴³, which facilitates sample collection, and contains elements that reflect both the local and systemic condition of the patients⁴⁴.

These techniques are designed to detect, classify and monitor oral diseases and design a noninvasive⁴⁵ treatment⁴⁶ for them. Although there is not a defined proteomic pattern characterizing salivary gland dysfunction, kallikrein, as well as lactoferrin and albumin⁴⁷, have been linked to damage in salivary ductal cells¹⁶.

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 SS⁴⁸.

Lysozyme, an enzyme found in saliva and gingival elastic fibers⁴⁹, is among the most common antimicrobial proteins. Low levels of lysozyme in the saliva imply increased plaque index in SS⁵⁰, which is considered a risk factor for periodontal disease⁵¹. Salivary peroxidase is another enzyme produced by the acinar cells of the parotid and submandibular glands⁵² and exerts its anti-

Table 1. Main systemic manifestations in Sjögren's syndrome.

Eyes	Xeroftalmia ¹⁷ , keratitis sicca, conjunctivitis sicca ¹⁸ dacryoadenitis, photosensitivity ¹⁹
Oral cavity	Hyposalivation ²⁰ , xerostomia ^{21,22} , sialadenitis, stomatitis, halitosis ³ , dental caries, oral candidiasis ^{23,24} , periodontal disease ^{25,26} , 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 ³³ .
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 ³⁰ , glomerulonephritis, interstitial nephritis ⁶ .
Hematological	Anemia, lymphoma, thrombocytopenia, lymphopenia ³⁰ .

Table 2. Criteria of American-European Consensus Group (Adapted from Vitali *et al.*, 2002¹³).

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, cavitory 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.

Table 3. Main causes of hyposalivation and xerostomia.

Hyposalivation	
Sjögren syndrome ⁶³ .	
Diabetes mellitus ⁶⁴ .	
HIV	(antiretroviral drugs) ⁶⁵ .
Sarcoidosis ⁶⁶ .	
Hepatitis C ⁶⁷ .	
Renal insufficiency.	
Amyloidosis ⁶⁸ .	
Adverse effects of pharmacological agents	(tramadol, antihypertensives, cholinergic agonists, antidepressants, barbiturates ⁶⁹ , diuretics, antihistamines) ³ .
External beam radiotherapy	(Doses greater than 30G) ⁶⁰ .
Tumors of the salivary glands.	
Nutritional deficiencies	(anorexia, bulimia) ⁴ .
Xerostomia	
Dehydration.	
Cognitive and neurological disorders.	
Oral sensory dysfunction.	
Oral breathing.	
Psychological factors ⁴ .	

microbial action by consuming H₂O₂. It has been demonstrated that peroxidase can reduce the adhesiveness of *Streptococcus mutans* and *Porphyromonas gingivalis*⁵³ to the hydroxyapatite surface^{45,53}. These microorganisms have been linked to periodontal disease when their levels are elevated in the saliva⁵⁰.

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 glands⁵⁴ located on the lower lip, tongue, palate, and upper part of the pharynx^{55,56}. Saliva plays a pivotal role in the homeostasis of the oral cavity⁵⁷. Because of its functional properties it helps to protect teeth and mucous membranes, phonation, dental remineralization, bolus swallowing and maintenance of pH⁵⁸. It also helps to maintain a good digestion, and to prevent oral colonization by pathogens through its enzymatic processes⁵⁹.

The human body secretes about 500 to 600mL of serous and mucous saliva each day⁶⁰. This saliva contains

minerals, electrolytes, enzymes, cytokines, growth factors, buffers, immunoglobulins (IgA), mucins, among other glycoproteins⁴³, 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 or hyposialia⁶¹, a condition that contributes to the development of opportunistic infections in the oral cavity⁴; unlike xerostomia, which is the subjective sensation of dry mouth without a decrease in salivary flow⁶².

It is known that multiple causes may lead to xerostomia, also referred to as burning mouth syndrome. This condition may or may not include hyposalivation³. 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 breathing⁵⁹.

There are many causes that can induce hyposalivation, the most common are the adverse effects of pharmacological agents, considered as a iatrogenic consequence, the most prevalent being SS, external beam radiotherapy, and diabetes mellitus (more than half of the patients with dia-

betes type I and II have hyposalivation), among others⁶³⁻⁶⁹ (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 sialadenitis, stomatitis, dry mouth and dry mucous membranes, halitosis², dental caries (with rapid evolution and prevalence in the cervical area), oral candidiasis²³ (a prevalence of chronic atrophic candidiasis of 37% in SS have been reported²²); periodontal disease^{24,25}, angular cheilitis, tongue depapilation, dysphonia, dysphagia²⁶, erythematous and cracked tongue and atrophic fissured mucosa, burning mouth²⁷, among others²⁰⁻²⁸ (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 groups⁷¹. 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 periodon-

tal condition in patients with SS²⁶.

Development of neoplasia: A large number of autoimmune diseases predispose to the development of neoplasia⁷². In the case of SS the risk has been estimated to be 44 times that of the general population⁷³. It has been reported that stimulation of cytokines, parotidomegaly⁷⁴, environmental factors, viral infections⁷⁵ and vitamin deficiencies predispose to the development of these lesions⁷⁶.

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 SS⁷⁸.

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 SS¹⁹. Although there is no definite treatment for SS⁷⁹, 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 recommended⁶²:

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 gingival disease. Patients should visit the dentist periodically every 4 or 6 months to control plaque and to receive mechanical preventive therapy⁶². 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 recommended⁴.

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 mouthwash⁶⁶.

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 affected⁸⁰.

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 chlorhexidine⁸¹, and the use of nystatin or clotrimazole cream 4 times a day in cases of angular cheilitis is recommended⁴.

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 gum⁸¹ and healthy products containing xylitol, lactoperoxidase, or glucose oxidase, as they reduce the level of cariogenicity⁶².

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 imbalance⁸⁰.

There are plenty of salivary substitutes available: mouthwash solution, gels, sprays and toothpastes, which are based on mucopolysaccharides, mucins⁴ and sodium carboxymethyl-cellulose⁸². Biotene® is a saliva substitute based on polyglycerilmetacrilate, lactoperoxidase and glucose oxidase, with antimicrobial activity and available in toothpaste, chewing gum and mouthwash²³.

Artificial saliva substitutes do not replace the antibac-

terial and immune protective functions of natural saliva and, therefore, do not leave out the need for regular dental care and proper oral hygiene⁸³. However it has been shown that the use of these products does mitigate symptoms of severe xerostomia produced by glandular dysfunction⁸². Xialine® improves problems with speech and senses⁸⁴. However it has been shown that the use of Buccotherm® in spray is not more effective than a placebo in patients with xerostomia⁶⁸.

Sialogogue drugs: Pilocarpine is a cholinergic agonist that stimulates muscarinic receptors of the salivary glands and increases salivary flow⁸⁵. This drug, approved by the FDA, is used to treat the impairment of salivary glands², however its use may have adverse effects such as sweating, rhinitis, nausea, increased urinary frequency, as well as increased gastrointestinal secretion of hydrochloric acid^{86,87}. Pilocarpine is also contraindicated in asthma, acute rhinitis, glaucoma, obstructive lung diseases⁸³, uncontrolled peptic ulcer, high blood pressure and interaction with β -adrenergic blockers⁸⁸. The recommended dose to treat hyposalivation in primary SS is 5mg 3 times a day⁸⁹.

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)⁹⁰.

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%⁹¹. Other drugs to treat hyposalivation are bethanechol, methacholine, carbachol and pyridostigmine, but their use has been decreasing due to their lower pharmacological potency⁸².

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 effects⁷⁰.

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 humans⁹².

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 therapy⁹³:

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 flow⁹⁴. 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 flow⁹⁵. 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 SS⁹⁶.

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 glands². 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^{60,56}:

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 unsuccessful⁶⁰.

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 reported⁵⁶.

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 patient⁶⁰.

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^{93,97}.

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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Perspectiva odontológica del síndrome de Sjögren: revisión de literatura.

Resumen: El ser humano secreta alrededor de 500 a 600 mL de saliva diariamente, sin embargo, al encontrarse valores de 0.1 - 0.2 mL/min de saliva en reposo se presenta una condición llamada hiposalivación o hiposialia, la cual puede ser manifestada por una numerosa cantidad de condiciones sistémicas, entre ellas el síndrome de Sjögren, la cual es una enfermedad autoinmune crónica presente en entre el 0.1 y 3% de la población mundial, y es caracterizada por exocrinopatía de las glándulas salivales conllevando a la hipofunción glandular y disminuyendo así el flujo salival normal. Debido a que la saliva forma parte de la inmunidad innata, al presentarse una disminución en su secreción proteica se desencadenan numerosas manifestaciones orales, tales como

caries dental, candidiasis, enfermedad gingival, queilitis angular, linfomas de las glándulas salivales, disfagia, lengua eritematosa y fisurada, entre otras. Actualmente no existe un tratamiento odontológico definido, sin embargo se tienen alternativas de tratamiento mediante fármacos sialogogos y sustitutos salivales, además de terapias no farmacológicas, las cuales intentan mantener la ecología y las condiciones orales estables, además de los tratamientos odontológicos preventivos y restaurativos para lesiones ya establecidas por consecuencia de la enfermedad. El objetivo del presente estudio es realizar una revisión de literatura sobre las características, criterios de clasificación, manifestaciones orales y el manejo odontológico del Síndrome de Sjögren.

Palabras clave: *Síndrome de Sjögren, Hiposalivación, Xerostomía, Hiposialia, Manejo odontológico.*

REFERENCES.

1. Yoshimoto K, Fujimoto T, Itaya A, 2010;55(3):238-44.
2. Aframian D, Helcer M, Livni D, Robinson S, Markitzu A, Nadler C. Pilocarpine treatment in a mixed cohort of xerostomic patients. *Oral Dis.* 2007;13(1):88-92.
3. Hopcraft M, Tan C. Xerostomia: an update for clinicians. *Aust Dent J.* 2010;55(3):238-44.
4. Napeñas JJ, Brennan MT, Fox PC. Diagnosis and treatment of xerostomia (dry mouth). *Odontology.* 2009;97(2):76-83.
5. Guíñales J, Martorell V, Sanchez R, del Castillo JL, Burgueño M. Síndrome de Sjögren: criterios diagnósticos mediante resonancia magnética. *Rev Esp Cir Oral Maxilofac.* 2012;34(4):186-7.
6. Maślińska M, Przygodzka M, Kwiatkowska B, Sikorska K. Sjögren's syndrome: still not fully understood disease. *Rheumatol Int.* 2015;35(2):233-41.
7. Goldblatt F, O'Neill SG. Clinical aspects of autoimmune rheumatic diseases. *Lancet.* 2013;382(9894):797-808.
8. González S, Sung H, Sepúlveda D, González M, Molina C. Oral manifestations and their treatment in Sjögren's syndrome. *Oral Dis.* 2014;20(2):153-61.
9. Mathews SA, Kurien BT, Scofield RH. Oral manifestations of Sjögren's syndrome. *J Dent Res.* 2008;87(4):308-18.
10. Shahane A, Patel R. The epidemiology of Sjögren's syndrome. *Clin Epidemiol.*

- 2014;6(1):247-255.
11. Manoussakis MN, Georgopoulou C, Zintzaras E, Spyropoulou M, Stavropoulou A, Skopouli FN, Moutsopoulos HM. Sjögren's syndrome associated with systemic lupus erythematosus: Clinical and laboratory profiles and comparison with primary Sjögren's syndrome. *Arthritis Rheum.* 2004;50(3):882-91.
12. Isenberg DA. Systemic lupus erythematosus and Sjögren's syndrome: Historical perspective and ongoing concerns. *Arthritis Rheum.* 2004;50(3):681-3.
13. Vitali C, Bombardieri S, Jonsson R, Moutsopoulos HM, Alexander EL, Carsons SE, Daniels TE, Fox PC, Fox RI, Kassan SS, Pillemer SR, Talal N, Weisman MH. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheum Dis.* 2002;61(6):554-8.
14. De Azevedo BB, Bussoloti I. Evaluation of sialometry and minor salivary gland biopsy in classification of Sjogren's Syndrome patients. *Braz J Otorhinolaryngol.* 2005;71(3):346-54.
15. Delaleu N, Immervoll H, Cornelius J, Jonsson R. Biomarker profiles in serum and saliva of experimental Sjogren's syndrome: associations with specific autoimmune manifestations. *Arthritis Res Ther.* 2008;10(1):1-14.
16. Baldini C, Giusti L, Bazzichi L, Lucacchini A, Bombardieri S. Proteomic analysis of the saliva: A clue for understanding primary from secondary Sjögren's syndrome? *Autoimmun Rev.* 2008;7(3):185-91.
17. Avouac J, Sordet C, Depinay C, Ardizzone M, Vacher MC, Sibia J, Kahan A, Allanore Y. Systemic sclerosis-associated Sjögren's syndrome and relationship to the limited cutaneous subtype: Results of a prospective study of sicca syndrome in 133 consecutive patients. *Arthritis Rheum.* 2006;54(7):2243-9.
18. Bikker A, van Woerkom JM, Kruijze AA, Wenting M, de Jager W, Bijlsma JW, Lafeber FP, van Roon JA. Increased expression of interleukin-7 in labial salivary glands of patients with primary Sjögren's syndrome correlates with increased inflammation. *Arthritis Rheum.* 2010;62(4):969-77.
19. Delaleu N, Jonsson R, Koller MM. Sjögren's syndrome. *Eur J Oral Sci.* 2005;113(2):101-13.
20. Plemons JM, Al-Hashimi I, Marek CL. Managing xerostomia and salivary gland hypofunction. *J Am Dent Assoc.* 2014;145(8):867-73.
21. Samarawickrama D. Saliva substitutes: how effective and safe are they?. *Oral Dis.* 2002;8(4):177-9.
22. Anil S, Vellappally S, Hashem M, Preethanath RS, Patil S, Samaranayake LP. Xerostomia in geriatric patients: a burgeoning global concern. *J Investig Clin Dent.* 2014;5(2014):1-8.
23. Deepak D, Gopakumar R. Xerostomia, its Association with Oral Manifestation and Ocular Involvement: A Clinical and Biochemical Study. *J Indian Acad Oral Med Radiol.* 2011;23(4):513-7.
24. Kho H, Park M, Chang J, Kim Y. Yam tuber mucilage as a candidate substance for saliva substitute: in vitro study of its viscosity and influences on lysozyme and peroxidase activities. *Gerodontology.* 2014;31(1):34-41.
25. Kuru B, McCullough MJ, Yilmaz S, Porter SR. Clinical and microbiological studies of periodontal disease in Sjögren's syndrome patients. *J Clin Periodontol.* 2002;29(2):92-91.
26. Antoniazzi RP, Miranda LA, Zanatta FB, Islabão AG, Gustafsson A, Chiapinotto GA, Oppermann RV. Periodontal Conditions of Individuals With Sjögren's Syndrome. *J Periodontol.* 2009;80(3):429-35.
27. Eveson JW. Xerostomia. *Periodontol.* 2000. 2008;48(1):85-91.
28. Margaix M, Bagán JV, Poveda R, Jiménez Y, Sarrión G. Sjögren's syndrome of the oral cavity. Review and update. *Med Oral Patol Oral Cir Bucal.* 2009;14(7):325-30.
29. Vishwanath S, Everett S, Shen L, Malyavantham K, Suresh L, Ambrus JL. Xerophthalmia of Sjögren's Syndrome Diagnosed with Anti-Salivary Gland Protein 1 Antibodies. *Case Rep Ophthalmol.* 2014;5(2):186-9.
30. Sood S, Anthony R, Pease C. Sjögren's syndrome. *Clin Otolaryngol.* 2000;25(5):350-7.
31. Larrarte JPM, Pineda YR. Síndrome de Sjögren. *Rev Cubana Med.* 2010;49(2):61-76.
32. Van Stein D, Tan J, Bloemena E, van Vugt R, Voskuyl A, Santana N, van der Waal I. The role of a labial salivary gland biopsy in the diagnostic procedure for Sjogren s syndrome; a study of 94 cases. *Med Oral Patol Oral Cir Bucal.* 2014;19(4):372-6.
33. Gyöngyösi M, Pokorný G, Jambrik Z, Kovacs L, Kovacs A, Makula E, Csanády M. Cardiac manifestations in primary Sjögren's syndrome. *Ann Rheum Dis.* 1996;55(7):450-4.
34. Kittridge A, Routhouska SB, Korman NJ. Dermatologic manifestations of Sjögren syndrome. *J Cutan Med Surg.* 2011;15(1):8-14.
35. Elaine L. Alexander, Thomas T. Provost. Cutaneous manifestations of Primary Sjögren's Syndrome: A Reflection of vasculitis and Association with Anti-RO(SSA) Antibodies. *J Invest Dermatol.* 1983;80(5):386-91.
36. Karnell JL, Mahmoud TI, Herbst R, Ettinger R. Discerning the kinetics of autoimmune manifestations in a model of Sjögren's syndrome. *Mol Immunol.* 2014;62(2):277-82.
37. Hu S, Gao K, Pollard R, Arellano M,

- Zhou H, Zhang L, Elashoff D, Kallenberg CG, Vissink A, Wong DT. Preclinical validation of salivary biomarkers for primary Sjögren's syndrome. *Arthritis Care Res*. 2010;62(11):1633–8.
38. Al-Hashimi DI. Xerostomia Secondary to Sjögren's Syndrome in the Elderly. *Drugs Aging*. 2012;22(11):887–99.
39. Shiboski SC, Shiboski CH, Criswell LA, Baer AN, Challacombe S, Lanfranchi H, Schiødt M, Umehara H, Vivino F, Zhao Y, Dong Y, Greenspan D, Heidenreich AM, Helin P, Kirkham B, Kitagawa K, Larkin G, Li M, Lietman T, Lindegaard J, McNamara N, Sack K, Shirlaw P, Sugai S, Vollenweider C, Whitcher J, Wu A, Zhang S, Zhang W, Greenspan J, Daniels T. American College of Rheumatology classification criteria for Sjögren's syndrome: A data-driven, expert consensus approach in the Sjögren's International Collaborative Clinical Alliance Cohort. *Arthritis Care Res*. 2012;64(4):475–87.
40. Colella G, Cannavale R, Vicidomini A, Itró A. Salivary gland biopsy: a comprehensive review of techniques and related complications. *Rheumatology*. 2010;49(11):2117–21.
41. Caporali R, Bonacci E, Epis O, Bobbio F, Morbini P, Montecucco C. Safety and usefulness of minor salivary gland biopsy: Retrospective analysis of 502 procedures performed at a single center. *Arthritis Rheum*. 2008;59(5):714–20.
42. Lida Santiago M, Seisdedos MR, García Salinas RN, Secco A, Marino Claverie L, Techera L, Takashima L, Aicardi P, Sandi MA, Knobel E. Frecuencia de complicaciones y rédito de la biopsia de glándula salival menor. *Reumatol Clin*. 2012;8(5):255–8.
43. Lawrence HP. Salivary markers of systemic disease: noninvasive diagnosis of disease and monitoring of general health. *J Can Dent Assoc*. 2002;68(3):170–5.
44. Issaq HJ, Veenstra TD. The role of electrophoresis in disease biomarker discovery. *Electrophoresis*. 2007;28(12):1980–8.
45. Loos BG, Tjoa S. Host-derived diagnostic markers for periodontitis: do they exist in gingival crevice fluid?. *Periodontol* 2000. 2005;39(1):53–72.
46. Giannobile WV, Beikler T, Kinney JS, Ramseier CA, Morelli T, Wong DT. Saliva as a diagnostic tool for periodontal disease: current state and future directions. *Periodontol* 2000. 2009;50(1):52–64.
47. Sreebny LM, Zhu WX. The use of whole saliva in the differential diagnosis of Sjögren's syndrome. *Adv Dent Res*. 1996;10(1):17–24.
48. Taylor JJ. Protein Biomarkers of Periodontitis in Saliva. *ISRN Inflamm*. 2014; 2014(2014):1–18.
49. Younes R, Yousfi M, Ghorra C, Khalife S, Igondjo S, Willig C, Senni K, Charpiot P, Naaman N, Godeau G. The defensive role of lysozyme in human gingiva in inflammatory periodontal disease. *J Periodontal Res*. 2009;44(5):578–87.
50. Padma TP, Deepa MS, Nanda K. Salivary proteomic biomarkers in the diagnosis of periodontal diseases. *Health Sci*. 2014;1(3):1–15.
51. Riva A, Puxeddu P, Del Fiacco M, Testa F. Ultrastructural localization of endogenous peroxidase in human parotid and submandibular glands. *J Anat*. 1978;127(1):181–191.
52. Sang Goo Lee, Hyung Il Kim, Hong Seop Kho. Influences of peroxidase on lysozyme activity. *Oral Med*. 2008;33(1):1–8.
53. Murakami Y, Nagata H, Amano A, Takagaki M, Shizukuishi S, Tsunemitsu A, Aimoto S. Inhibitory effects of human salivary histatins and lysozyme on coaggregation between *Porphyromonas gingivalis* and *Streptococcus mitis*. *Infect Immun*. 1991;59(9):3284–6.
54. Löfgren CD, Wickström C, Sonesson M, Lagunas PT, Christersson C. A systematic review of methods to diagnose oral dryness and salivary gland function. *BMC Oral Health*. 2012;12(1):12–29.
55. Denny P, Hagen FK, Hardt M, Liao L, Yan W, Arellanno M, Bassillian S, Bedi GS, Boonthueung P, Cociorva D, Delahunty CM, Denny T, Dunsmore J, Faull KF, Gilligan J, González M, Halgand F, Hall SC, Han X, Henson B, Hewel J, Hu S, Jeffrey S, Jiang J, Loo JA, Ogorzalek RR, Malamud D, Melvin JE, Miroshnychenko O, Navazesh M, Niles R, Park SK, Prakhobol A, Ramachandran P, Richert M, Robinson S, Sondej M, Souda P, Sullivan MA, Takashima J, Than S, Wang J, Whitelegge JP, Witkowska HE, Wolinsky L, Xie Y, Xu T, Yu W, Ytterberg J, Wong DT, Yates JR, Fisher SJ. The Proteomes of Human Parotid and Submandibular/Sublingual Gland Salivas Collected as the Ductal Secretions. *J Proteome Res*. 2008;7(5):1994–2006.
56. Proctor GB, Carpenter GH. Regulation of salivary gland function by autonomic nerves. *Auton Neurosci*. 2007;133(1):3–18.
57. Banderas JA, González M, Sánchez M, Millán E, López A, Vilchis A. Flujo y concentración de proteínas en saliva total humana. *Salud Publica Mex*. 1997;39(5):433–43.
58. Falcão DP, Mota LMH da, Pires AL, Bezerra ACB. Sialometry: aspects of clinical interest. *Rev Bras Reumatol*. 2013;53(6):525–31.
59. Tenovuo J. Antimicrobial agents in saliva—protection for the whole body. *J Dent Res*. 2002;81(12):807–9.
60. Chapa G, Garza B, Garza M, Martínez G. Hiposalivación y xerostomía: diagnóstico, modalidades de tratamiento en la actualidad: Aplicación de neuroelectroestimulación. *Rev Mex Periodontol*. 2012;3(1):38–46.
61. Silvestre F, Miralles L, Martínez V. Tratamiento de la boca seca: puesta al día. *Med Oral*. 2004;9(1):273–9.
62. Jensen SB, Pedersen AML, Vissink A,

- Andersen E, Brown CG, Davies AN, Duttilh J, Fulton JS, Jankovic L, Lopes NN, Mello AL, Muniz LV, Murdoch CA, Nair RG, Napeñas JJ, Nogueira A, Saunders D, Stirling B, von Bültzingslöwen I, Weikel DS, Elting LS, Spijkervet FK, Brennan MT. A systematic review of salivary gland hypofunction and xerostomia induced by cancer therapies: management strategies and economic impact. *Support Care Cancer*. 2010;18(8):1061–79.
63. van Den Berg I, Pijpe J, Vissink A. Salivary gland parameters and clinical data related to the underlying disorder in patients with persisting xerostomia. *Eur J Oral Sci*. 2007;115(2):97–102.
64. Piboonniyom S, Suwantuntula T, Thaweeboon S, Mitirattanakul S, Chomkhakhai U, Khovidhunkit W. Xerostomia, Hyposalivation, and Oral Microbiota in Type 2 Diabetic Patients: A Preliminary Study. *J Med Assoc Thai*. 2009;92(9):1220–8.
65. Navazesh M, Mulligan R, Komaroff E, Redford M, Greenspan D, Pkelan J. The Prevalence of Xerostomia and Salivary Gland Hypofunction in a Cohort of HIV-positive and At-risk Women. *J Dent Res*. 2000;79(7):1502–7.
66. Jiménez DJ. Aspectos clínicos y tratamiento de la xerostomía. *Acta Otorrinolaringol Cir Cabeza Cuello*. 2005;33(1):14–20.
67. Gallardo J. Xerostomía. *Rev Med Inst Mex Seguro Soc*. 2008;46(1):109–16.
68. Alpöz E, Çankaya H, Güneri P, Epstein JB, Boyacioglu H, Kabasakal Y, Ocakci PT. Impact of Buccotherm® on xerostomia: a single blind study. *Spec Care Dentist*. 2015;35(1):1–7.
69. Looström H, Åkerman S, Ericson D, Tobin G, Götrick B. Tramadol-induced oral dryness and pilocarpine treatment: Effects on total protein and IgA. *Arch Oral Biol*. 2011;56(4):395–400.
70. Rodríguez J, Sánchez R, Garza M, Nakagoshi M, Solís J, Arévalo K, Garza E. Physicochemical and antimicrobial evaluation of chitosan and hydroxypropyl methylcellulose films for prolonged release of pilocarpine. *J Oral Res*. 2015;4(1):25–31.
71. Pers J, d'Arbonneau F, Devauchelle V, Saraux A, Pennec Y, Youinou P. Is periodontal disease mediated by salivary baffle in Sjögren's syndrome?. *Arthritis Rheum*. 2005;52(8):2411–4.
72. Jordan RC, Speight PM. Lymphoma in Sjögren's syndrome. From histopathology to molecular pathology. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 1996;81(3):308–20.
73. Keszler A, Adler LI, Gandolfo MS, Bisio PM, Smith AC, Vollenweider CF, Heidenreich AM, de Stefano G, Kambo MV, Cox DP, Narbaitz M, Lanfranchi HE. MALT lymphoma in labial salivary gland biopsy from Sjögren syndrome: importance of follow-up in early detection. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2013;115(3):28–33.
74. Kovács L, Szodoray P, Kiss E. Secondary tumours in Sjögren's syndrome. *Autoimmun Rev*. 2010;9(4):203–6.
75. Mariette X. Lymphomas complicating Sjögren's syndrome and hepatitis C virus infection may share a common pathogenesis: chronic stimulation of rheumatoid factor B cells. *Ann Rheum Dis*. 2001;60(11):1007–10.
76. Dong L, Chen Y, Masaki Y, Okazaki T, Umehara H. Possible Mechanisms of Lymphoma Development in Sjögren's Syndrome. *Curr Immunol Rev*. 2013;9(1):13–22.
77. Van NM. B cell MALT lymphoma diagnosed by labial minor salivary gland biopsy in patients screened for Sjögren's syndrome. *Ann Rheum Dis*. 2004;64(3):471–3.
78. Jordan R, Diss TC, Lench NJ, Isaacson PG, Speight PM. Immunoglobulin gene rearrangements in lymphoplastic infiltrates of labial salivary glands in Sjögren's syndrome. A possible predictor of lymphoma development. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 1995;79(6):723–9.
79. De Mendonça M, Finger A, Vale G, Naval MÂ, Soares AA, Compagnoni M. Management of Sjögren's Syndrome Patient: A Case Report of Prosthetic Rehabilitation with 6-Year Follow-Up. *Case Rep Dent*. 2014;2014(2014):1–5.
80. Rivera H, Valero L, Escalona L, Roja F, Ríos MP. Manejo Multidisciplinario del paciente diagnosticado con el Síndrome de Sjögren. *Acta Odontol Venez*. 2009;47(3):122–30.
81. Al-Hashimi I. The management of Sjögren's syndrome in dental practice. *J Am Dent Assoc*. 2001;132(10):1409–17.
82. Oh D, Lee J, Kim Y, Kho H. Effects of carboxymethylcellulose (CMC)-based artificial saliva in patients with xerostomia. *Int J Oral Maxillofac Surg*. 2008;37(11):1027–31.
83. Dirix P, Nuyts S, Van den Bogaert W. Radiation-induced xerostomia in patients with head and neck cancer: A literature review. *Cancer*. 2006;107(11):2525–34.
84. Jellema AP, Langendijk H, Bergenhenegouwen L, van der Reijden W, Leemans R, Smelee L, Slotman BJ. The efficacy of Xialine® in patients with xerostomia resulting from radiotherapy for head and neck cancer: a pilot-study. *Radiother Oncol*. 2001;59(2):157–60.
85. Babaee N, Zahedpasha S, Zamaninejad S, Gholizadehpasha A, Moghadamnia Y, Moghadamnia A. Effects of milk curd on saliva secretion in healthy volunteer compared to baseline, 2% pilocarpine and equivalent pH adjusted acetic acid solutions. *Indian J Dent Res*. 2011;22(4):547–551.
86. Bernardi R, Perin C, Becker FL, Ramos GZ, Gheno GZ, Lopes LR, Pires M, Barros HM. Effect of pilocarpine

- mouthwash on salivary flow. *Braz J Med Biol Res.* 2002;35(1):105-10.
87. Nakamura N, Sasano N, Yamashita H, Igaki H, Shiraishi K, Terahara A, Asakage T, Nakao K, Ebihara Y, Ohtomo K, Nakagawa K. Oral pilocarpine (5mg t.i.d.) used for xerostomia causes adverse effects in Japanese. *Auris Nasus Larynx.* 2009;36(3):310-3.
88. Hua LV, Kawasaki P, Pokala VN, Hayes J. An Interprofessional Study of the Effects of Topical Pilocarpine on Oral and Visual Function. *Health Interprofessional Pract.* 2012;1(3):1-10.
89. Wall GC, Magarity ML, Jundt JW. Pharmacotherapy of xerostomia in primary Sjögren's syndrome. *Pharmacotherapy.* 2002;22(5):621-9.
90. Brimhall J, Jhaveri MA, Yepes JF. Efficacy of cevimeline vs. pilocarpine in the secretion of saliva: a pilot study. *Spec Care Dentist.* 2013;33(3):123-7.
91. Noaiseh G, Baker JF, Vivino FB. Comparison of the discontinuation rates and side-effect profiles of pilocarpine and cevimeline for xerostomia in primary Sjögren's syndrome. *Clin Exp Rheumatol.* 2014;32(4):575-7.
92. Rodríguez J, Sánchez R, Garza M, Nakagoshi M, Solís J, Arévalo K, Garza E. Salivary stimulation by prolonged release of pilocarpine using films in diabetic rats. *J Oral Res.* 2015;4(2):103-8.
93. Furness S, Bryan G, McMillan R, Birchenough S, Worthington HV. Interventions for the management of dry mouth: non-pharmacological interventions. *Cochrane Database Syst Rev* 2013. 2013;1(9):1-49.
94. Cho JH, Chung WK, Kang W, Choi SM, Cho CK, Son CG. Manual acupuncture improved quality of life in cancer patients with radiation-induced xerostomia. *J Altern Complement Med.* 2008;14(5):523-6.
95. O'Sullivan EM, Higginson IJ. Clinical effectiveness and safety of acupuncture in the treatment of irradiation-induced xerostomia in patients with head and neck cancer: a systematic review. *Acupunct Med.* 2010;28(4):191-9.
96. Pfister DG, Cassileth BR, Deng GE, Yeung KS, Lee JS, Garrity D, Cronin A, Lee N, Kraus D, Shaha R, Shah J, Vickers AJ. Acupuncture for pain and dysfunction after neck dissection: results of a randomized controlled trial. *J Clin Oncol.* 2010;28(15):2565-70.
97. Lončar B, Stipetić MM, Baričević M, Risočić D. The effect of low-level laser therapy on salivary glands in patients with xerostomia. *Photomed Laser Surg.* 2011;29(3):171-5.