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## **Sjögren's syndrome and its impact in the oral cavity**

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### **Abstract**

Sjögren's syndrome is an autoimmune disease that affects salivary gland tissue. Patients can show different degrees of phenotype that can vary from mild to severe systemic symptoms. So far, the etiopathogenesis of this condition is still not fully unraveled but it is believed that genetic and environmental factors are involved.

The purpose is to understand the role of genetics on the appearance of the Sjögren's syndrome and describe the clinical signs that might alert for the presence of a patient with this condition.

The most impacting oral manifestation is xerostomia. The role of the dental doctor in the diagnosis, treatment and oral rehabilitation of these patients, is crucial to ensure a good quality of life.

**Keywords:** Sjögren syndrome; oral manifestations; Xerostomia; autoimmune disease

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### **1. Introduction**

The Sjögren's syndrome is a chronic autoimmune disorder that affects mainly the epithelium of the lacrimal and salivary glands. Clinically, its presentation can vary between relatively mild symptoms of xerostomia and xerophthalmia, arthralgias, fatigue and fibromyalgia, to more severe systemic symptoms<sup>[1]</sup>.

This syndrome can be classified in two different forms: primary Sjögren's syndrome that develops as an isolated disease; or secondary Sjögren's syndrome associated with another autoimmune disease<sup>[2]</sup>.

The etiopathogenesis of the Sjögren's syndrome is not completely understood, and some studies report a set of immunological changes of infectious and/or genetic origin associated with the development of the autoimmune process<sup>[1]</sup>.

The treatment of the Sjögren's syndrome involves a wide variety of medical specialties, such as rheumatology, dermatology, ophthalmology, immunology, pneumology, gynecology and dentistry<sup>[3]</sup>. The dental doctor plays an important role in the diagnosis of this syndrome, since, in most cases, is responsible for the detection of the first symptoms<sup>[4]</sup>.

The main goals of this review are the characterization and etiology, the importance of genetics, the oral clinical manifestations, the diagnosis, the different treatment options, and the prevention of Sjögren's syndrome.

#### **1.1. Methodology**

To carry out the present work, a bibliographic search of scientific articles published in indexed journals, available in the PUBmed database, was carried out, using the keywords Sjögren syndrome; Oral manifestations; Xerostomia; Autoimmune disease. The Boolean operator "AND" was used to establish a relationship between the search terms, to refine it and obtain more accurate results.

The research was limited to publications in English, Portuguese or Spanish, starting in 2009, with available abstract. Narrative and systematic review articles, guidelines, observational studies, and clinical trials were considered.

### **2. Characterization and etiology**

The Sjögren's syndrome is an inflammatory process that is present in the epithelial cells and in the exocrine glands, namely in the lacrimal and salivary glands, which causes characteristic symptoms<sup>[5]</sup>.

This disease has an unknown etiology, affecting 0.5-1% of the population. Its most dominant manifestations are excessive weakness, xerostomia, xerophthalmia and arthritis. Taking into account the international criteria created in 2002, the diagnosis can be confirmed in the presence of 3 of the 4 groups of symptoms: ophthalmic manifestations (dry eye), oral manifestations (lesions in the salivary glands), histopathological or laboratory manifestations<sup>[6]</sup>.

The Sjögren's syndrome occurs nine times more often in women than in men. This pathology is characterized by two moments: one between 20 and 30 years of age and the other in the middle of the fifth decade of life. It can appear as a primary condition, that is, as a disease without any other symptoms or as a secondary disease that appears simultaneously with other autoimmune diseases, such as rheumatoid arthritis, lupus erythematosus, dermatomyelitis, scleroderma, or primary liver cirrhosis. Patients with Sjögren's syndrome also show a tendency towards fibromyalgia, migraines, hypothyroidism, Raynaud's syndrome, and lymphomas<sup>[6,7]</sup>.

This syndrome has a complex nature since it is a lymphocytic infiltration of the exocrine glands, eliminating them, as is the case of decreased salivary and lacrimal flow<sup>[8]</sup>.

Bolstand *et al.* [8] stated that, although clinically the manifestations of the Sjögren's syndrome are complex, in almost all patients certain relevant aspects emerge that allow the diagnosis, as is the case of autoantibodies, specifically anti-SSA/Ro and anti-SSB/La. Thus, many patients report certain symptoms such as dry eyes with the sensation of sand and dry mouth. Clinically, these patients may have ulcerations, infections, and impaired vision. Symptoms related to the eyes are usually present before those of the mouth. Dryness in other regions of the body, such as the nose, skin, and vagina, is also frequently reported [1].

### 3. Genetic susceptibility

The Sjögren's syndrome is a highly complex condition, which seems to have a polygenic etiology, and can be associated with other autoimmune pathologies such as rheumatoid arthritis and systemic lupus erythematosus [1, 9]. Its development has multifactorial causes, involving besides the polygenic nature, the presence of environmental factors [10]. A complex interaction of multiple genes influenced by environmental factors contributes to the etiology of the Sjögren's syndrome. Nezos and Mavragani [11] observed a greater predisposition (seven times greater) for the development of autoimmune irregularities, in individuals with family relationship with patients with this pathology.

The genetic contribution to the pathogenesis of this disease was demonstrated for the first time in the late 1970s and 1980s. The susceptibility to the disease was associated with the MHC (main histocompatibility complex) class II HLA (human leukocyte antigen) alleles [12].

HLA is a group of proteins that helps the immune system to distinguish the body's own proteins from proteins produced by invaders, such as viruses and bacteria. The HLA is the human version of the MHC. In humans, the MHC complex is made up of more than 200 genes, all close and located on chromosome 6. The genes of this complex are categorized into three basic groups: classes I, II, and III. Class II MHC in humans consists of 6 genes: HLA-DPA1, HLA-DPB1, HLA-DQA1, HLA-DQB1, HLA-DRA and HLA-DRB1. These genes encode proteins almost exclusively present on the surface of certain cells of the immune system.

So, concerning genetic causes, there is a clear distinction between the primary and secondary Sjögren's syndrome alleles. In primary Sjögren's syndrome the HLA-DR2 and HLA-DR3 subtypes appear more frequently, and in turn the HLA-DR4 subtypes are present in a less degree. However, these subtypes, when compared with individuals with secondary Sjögren's syndrome, do not present differences that can be considered significant [10].

Several genes have been the target of study and seem to be related to the individual's greater predisposition to the development of the Sjögren's syndrome, such as the gene encoding the interferon regulatory factor 5 (IRF5) [11, 13]. Likewise, genes implicated in B-cells or B-cell activating factor (BAFF) also known as B lymphocytes stimulator (BLyS), lymphotoxin  $\alpha$  and  $\beta$  and tumor necrosis factor (TNF), are also considered [14].

IRF5 acts as a transcription factor, which means that it binds to specific regions of DNA and helps to control the activity of certain genes. Interferons control the activity of genes that help to block the replication of viruses and stimulate the activity of certain cells of the immune system, the natural killer cells.

Certain viruses, such as the human T-cell lymphotropic virus type-1 (HTLV-1), cytomegalovirus (CMV) and hepatitis C virus (HCV), are possible factors for the development of the Sjögren's syndrome. HTLV-1 and in the same way CMV, or other retroviral components, are similar to self-antigens, which are etiologically part of the Sjögren's syndrome [14].

## 4. Manifestations in the oral cavity

Individuals with the Sjögren's syndrome may demonstrate oral manifestations of the disease that result mainly from salivary hypofunction, including dental caries and less frequently secondary burning mouth syndrome, as well as fungal infection. Patients may also have difficulty in speaking and often report dysphasia [15].

Due to the Sjögren's syndrome the gums and oral mucosae are not protected, as a consequence of poor lubrication of the tissues, which in turn leads to the inflammation of the oral mucosa, appearance of erythematous mucosa, oral desquamation and traumatic ulcers [7]. In more serious situations, individuals may also lack tongue papilla [4].

### 4.1. Xerostomia

One of the most uncomfortable symptoms of this syndrome is xerostomia, which is characterized by deprivation of saliva and its natural lubricating, protective and antibacterial properties in the oral cavity [6]. As a result of hyposalivation, the patient shows dry mouth, which in turn leads to difficulties in speaking, swallowing and chewing. Degeneration of the composition of the saliva is also frequent [4].

These patients have a significant decrease in the quantity and/or quality of the produced saliva. Most individuals refer to the sensation of dry mouth, whose prevalence is practically 100% of the cases [16]. Sjögren's syndrome affects the major and minor salivary glands, and 50% of all cases show an increase in volume of the parotid glands, symmetrical on both sides [17].

These changes can have significant repercussions on the lives of individuals, as they can lead to changes in the tone of voice or dry tongue, as well as decreased taste acuity or even the development of some oral diseases such as halitosis, gingivitis, periodontitis and dental caries [16]. Patients may also notice sticky lips, difficulty eating, speaking, chewing, swallowing, and retaining removable dental prostheses [18]. All these factors have a significant impact on the quality of life and well-being of individuals with Sjögren's syndrome, since it can be highly disabling and can lead to social isolation [19].

### 4.2. Dental caries

Saliva contains phosphates, bicarbonates, and proteins. In patients with salivary hypofunction, there is a consequent reduction in the quality of the saliva, with dysregulation of salivary pH. Studies show that patients with this syndrome accumulate bigger amounts of cariogenic microorganisms in the dentition than individuals with normal salivation [15]. Consequently, according to Bayetto *et al.* [7], these patients will be more predisposed to the appearance of dental caries. Some authors report that this dental caries tends to appear in unusual areas, namely in places with less protection resulting from bacterial plaque, such as the gingival line and incisal edges [4, 8]. These patients have a high incidence of plaque, infections in the

gums and bleeding [4].

This increased risk of developing dental caries results from the irregular pH of saliva, since it does not have its buffering effect [4]. Thus, there is a loss of the antibacterial properties of saliva, giving the feeling of dry mouth, which in turn enhances the development of dental caries. Consequently, these patients need medical and dental services more frequently, and have a higher propensity for tooth loss, as well as the incidence of a greater number of restored teeth, compared to individuals who do not have any type of pathology [4].

#### 4.3. Halitosis and periodontal disease

Halitosis may have periodontal pathologies in its genesis, or result from cariogenic lesions, that is, infections in the oral cavity. In this sense, halitosis arises because of low salivary flow and infection, which in turn leads to bacterial putrefaction [4]. Periodontal disease is an infectious disease that results from inflammation, which can lead to the destruction of periodontal tissues and consequent bone loss [20].

Scientific evidence still does not allow to state that Sjögren's syndrome is a predictor for the appearance of periodontal disease. Although some authors refer to the predisposition of patients with Sjögren's syndrome to the development of periodontal disease, this relationship is not yet strongly corroborated in view of, for example, the problem of increased appearance of dental caries [21].

However, studies show that individuals with Sjögren's syndrome do not have a special need for follow-up regarding periodontal care, as they have a similar picture to healthy individuals. Although Sjögren's syndrome is systemic in nature, it does not in itself represent a greater risk of developing periodontal disease, although there is evidence of a 2.2-fold higher rate for the occurrence of periodontal disease in individuals with Sjögren's syndrome compared to healthy individuals [20].

#### 4.4. Oral candidiasis

The reduction in salivary flow contributes to the appearance of fungal infections such as *Candida albicans*. About 80% of individuals with Sjögren's syndrome have oral candidiasis, which can present as acute erythematous candidiasis or even as angular cheilitis. Angular cheilitis develops in dry, fissured, and erythematous lesions in the labial commissures [4].

In individuals whose symptoms present with signs of dry mouth, the appearance of candidiasis is not caused by the development of thrush, but by wide erythema in the oral mucosa, leading to the loss of filiform papillae on the back of the tongue [2].

The risk of developing oral candidiasis is greater in patients using removable prostheses [20].

#### 4.5. Papillary atrophy and others

Papillary atrophy occurs in the lip and tongue, resulting in reduced salivary flow. In this way, the defense mechanisms of the oral cavity are compromised, which leads to the appearance of a burning sensation and atrophy [22].

One of the consequences of atrophy is the lingual depapillation, which can lead to changes in taste and the sensation of pain when in contact with certain foods [23].

There are countless injuries that can arise in individuals with Sjögren's syndrome after consuming rough foods. These

traumatic injuries happen since saliva does not play its role correctly. Normally, saliva has a lubricating role on the oral mucosa, however, in these cases this does not happen due to the substantial decrease in its production [4, 18, 24].

Likewise, these patients have dry and chapped lips, and the tongue is dry, with fissures and a sticky touch because of the previously mentioned depapillation [4].

### 5. Diagnosis

Regarding the diagnosis, the American-European Consensus Group (AECG) gathered rules of agreement among experts [25]. This classification comes from a more subjective correlation of symptoms, namely at the level of dry eyes and mouth together with more objective symptoms, such as hyposialia and dry keratoconjunctivitis [26,27].

According to the classification of the AECG for this syndrome to be diagnosed, it is necessary for the patient to present 4 to 6 criteria, as is the case of positive or negative salivary gland biopsy, as well as the presence of certain antibodies that may be SSA/Ro or SSB/La [28].

However, since 2012, the Sjögren's International Collaborative Clinical Alliance Research Groups, and the American College of Rheumatology, presented other standards that differ from those presented by the AECG. In this new group of criteria, the symptoms of glandular manifestations are not considered, and there are no differences between the primary and secondary Sjögren's syndrome [29]. Individuals who were submitted to radiotherapy of the neck and head, as well as individuals with hepatitis C, sarcoidosis, amyloidosis, graft-host reaction, acquired immunodeficiency and individuals with Ig4-related pathologies are also excluded [26, 29].

However, the criteria for positive salivary gland biopsy are part of both groups, as well as the presence of SSA or SSB [28].

The aim of these two groups is the establishment of unanimous criteria, aiming a more accurate diagnosis. Considering the complexity of this pathology and the diversity of symptoms, the diagnosis must involve several specialties. Therefore, the diagnosis involves a wide variety of dental and medical specialties, such as dentistry, rheumatology, dermatology, ophthalmology, immunology, pneumology and gynecology, due to the wide spectrum of glandular and extraglandular manifestations [3, 27].

According to the most recent criteria, patients with Sjögren's syndrome must show 2 of the following 3 items: 1) have anti-SSA/Ro and/or Anti-SSB/La or rheumatoid factor and antinuclear antibody  $\geq 1:320$ ; 2) dry keratoconjunctivitis with a staining score  $\geq 3$ ; 3) biopsy of minor salivary glands showing focal lymphocytic sialadenitis with a focus with calcification  $> 1$  per  $4 \text{ mm}^2$  of glandular tissue [30, 31].

### 6. Treatment and prevention

Currently, there are no specific treatments to cure Sjögren's syndrome patients. Thus, the type of therapies used focuses essentially on symptoms relieve, providing better well-being to the patient. To achieve this, drugs are used to prevent more severe periodontal pathologies, such as dental caries or periodontal disease [15].

Regarding local treatments, as is the case with oral or tear substitutes, these, although limited, allow to deal with a vast

number of symptoms<sup>[18]</sup>. In cases of xerophthalmia, the treatment involves the use of lacrimal substitutes and lubricating ointments during the day and at night. Evidence has shown that the use of pilocarpine or cyclosporine is somewhat successful, and in severe cases of xerophthalmia, anti-inflammatory agents can also be used<sup>[16, 32]</sup>.

### 6.1. Oral cavity treatment and rehabilitation

In oral treatment, both sugar-free chewing gums and salivary substitutes have helped in cases of mild to moderate xerostomia<sup>[7]</sup>. In cases where xerostomia is not very pronounced, pilocarpine and cevimeline are usually the choice used in the treatment<sup>[7, 16, 18]</sup>. These drugs act as stimulators of the M1 and M3 receptors, present in the salivary glands, thus enhancing salivary secretion<sup>[18, 33]</sup>. These receptors are characterized by being present in the salivary glands, where M1 corresponds to gastric tissue and M3 corresponds to smooth muscle/glands. When these receptors are stimulated, there is an increase in gastric juice (M1) and mucus secretion (M3), as well as an increased chance of sweating (M3)<sup>[34]</sup>.

According to Margaix-Muñoz *et al.*<sup>[32]</sup>, pilocarpine, acting as a cholinergic agent, is the most used with a dosage of about 5 mg/day, working as a systemic salivary stimulator<sup>[4]</sup>. However, there are also other therapies, such as certain hydrogels, which release the pilocarpine agent more slowly in the oral cavity<sup>[4]</sup>.

Thus, at the treatment level, both the drug side and the buccal aspect, help to prevent and improve the symptoms and effects of xerostomia<sup>[32]</sup>.

As previously mentioned, these patients show a higher incidence of dental caries and consequently greater tooth loss due to tooth decay. Prevention is a key point, but when it is too late, removable dentures are an alternative. However, patients with xerostomia have reduced retention and therefore low acceptance. The use of prostheses can lead to dental abrasions, stains, ulceration, irritation, and pain in the mucous membranes. Dental implants appear to be an ideal treatment alternative, although studies are still not conclusive. In some cases, patients with Sjögren's syndrome need corticosteroids to control symptoms, which are a contraindication for the use of dental implants<sup>[20]</sup>.

The treatment of oral candidiasis involves the use of topical antifungals such as nystatin, clotrimazole or miconazole. Sometimes chlorhexidine is also recommended. Treatment must be carried out for at least 2-3 weeks<sup>[20]</sup>.

Regarding extra glandular symptoms, although there is no specific treatment, certain corticosteroids and immunomodulating agents are used<sup>[16]</sup>.

However, there are other aspects of treatment and rehabilitation of the oral cavity, such as the constant water intake<sup>[7]</sup>.

Genetic studies in complex diseases allow the identification of genetic variants that contribute to their susceptibility, providing important information about the pathogenesis and hopes for future gene therapy. Experimental animal models, genetically and environmentally controlled, are used to study hereditary factors<sup>[9]</sup>.

### 6.2. Prevention of symptoms in the oral cavity

There are certain behaviors that should be avoided in patients with Sjögren's syndrome, such as tobacco and alcohol consumption, and others that must be meticulously followed,

such as correct and regular oral hygiene<sup>[4]</sup>.

It is important to alert these patients to decrease their consumption of foods and drinks high in sugar and carbonated drinks. The prostheses must be regularly disinfected, and their use during the night should be avoided<sup>[20]</sup>.

In patients with Sjögren's syndrome, the prevention of dental caries is imperative, by chemically controlling the oral microbiota using chlorhexidine, xylitol, and fluoride<sup>[20]</sup>. Fluoride present in oral solutions or in toothpaste can be used but can also be applied on gel and varnish locally by a professional. For the control of oral and pathogenic microbiota, the use of daily mouthwashes of 0.12% chlorhexidine is advised<sup>[8, 32]</sup>.

These patients with hyposalivation should also be encouraged to take measures to increase the level of saliva as it is crucial to maintain the dentition free of caries<sup>[15]</sup>.

The use of probiotics, such as *Lactobacillus* and *Bifidobacterium* spp, is a new effective strategy in the prevention of symptoms in Sjögren's syndrome patients. These living microorganisms have therapeutic applications in dental caries, periodontal disease, and candidiasis<sup>[20]</sup>.

## 7. Discussion

The Sjögren's syndrome is an autoimmune disease that affects the lacrimal and salivary glands. Although the genetic or environmental causes responsible for the development of this condition are being surveyed, the determination of its etiology is still far from unraveled<sup>[32]</sup>.

Although the cellular and humoral autoimmune reactions are not completely clarified, there is evidence that points to B and T lymphocytes as involved in the genesis of this pathology<sup>[35, 36]</sup>. It is evident in the literature that several factors are involved in the etiology of this disease, namely of an endocrine and genetic nature and viral infections<sup>[3]</sup>.

Thus, the main manifestations at the oral level in patients with Sjögren's syndrome occur with the presentation of difficulty in speech, swallowing and chewing, with a dry mouth. Patients also report changes in taste, as well as a burning sensation and pain in the salivary glands associated with food intake<sup>[15]</sup>.

Many individuals with Sjögren's syndrome still have dry and cracked lips and tongue, together with caries and early occlusal wastage of dental structures. Furthermore, 70 to 80% of these patients have chronic erythematous candidiasis, which may have repercussions on the palate and tongue and lead to the appearance of fissures in the lips. There may also be a bilateral swelling that can last from days to months or may go through periods with complete remission<sup>[6, 15, 32]</sup>.

In terms of vision, the main symptoms are xerophthalmia, with a sensation of itching, pain, or sand in the eyes, with visual sensitivity, photosensitivity, erythema and eye fatigue<sup>[32, 37]</sup>. All these factors converge on the possibility of the occurrence of destruction of the bulbar and corneal epithelium, with dilation of the vessels of the bulbar conjunctiva, or changes in the corneal image<sup>[37]</sup>.

Since Sjögren's syndrome is a systemic pathology, there are some dysfunctions that should be highlighted, such as the case of autoimmune thyroid disease found in 45% of patients<sup>[18, 38]</sup>. In these cases, 50% of these individuals show symptoms of extreme fatigue. Although there is no concrete cause, hypothyroidism is referred to as frequent and can contribute to this situation<sup>[18, 38]</sup>.

Another fact to highlight is the higher predisposition of individuals with Sjögren's syndrome for the development of leukemias or lymphomas, being identified in about 5% of these patients. Likewise, they may also have renal involvement and neurological changes that may include either the cranial, peripheral nerves or even the central nervous system<sup>[18]</sup>.

## 8. Conclusion

The present study allowed to analyze some of the main characteristics of Sjögren's syndrome in the light of scientific contributions that have been developing over the years. The Sjögren's syndrome is a complex, chronic, autoimmune pathology with the capacity to manifest itself under different prisms, that is, clinically there are a variety of characteristics that can be indicative signs of this pathology, which thus makes the diagnostic process quite complex.

The diagnosis focuses on the clinical history and uses as a resource some evaluation exams that are in accordance with the criteria instituted internationally for situations of Sjögren's syndrome. As already mentioned, since the clinical signs can be of different types, the diagnosis is hampered. Thus, the dental doctor should not limit his intervention to the symptoms that encompass his universe of activity. This is a procedure that covers different specialties that together facilitate early diagnosis, so that the treatment is carried out effectively and on time.

The Sjögren's syndrome has no cure, so symptom relief is crucial to ensure the patient's well-being. Prophylaxis is also a measure to be taken to avoid that infectious conditions or other periodontal diseases develop.

Thus, early diagnosis directly influences the quality of life of the individual with Sjögren's syndrome, since this in severe cases can be fatal because patients with Sjögren's syndrome can also develop other milder or severe autoimmune diseases.

**Ethical Statement:** This article does not contain any studies with human participants or animals performed by any of the authors.

**Conflict of Interest:** Authors declare that there are no conflicts of interest concerning the manuscript.

## 9. References

- Ambrósio BML, Rovai SE, Fukushima H, Silva BAH, Vivas P, Lourenço VS, *et al.* Aspectos relevantes da síndrome de Sjögren para o Cirurgião-Dentista. *Rev Assoc Paul Cir Dent.* 2016; 70(3):285-289.
- Serrano J, López-Pintor RM, González-Serrano J, Fernández-Castro M, Casañas E, Hernández G, *et al.* Oral lesions in Sjögren's syndrome: A systematic review. *Med Oral Patol Oral Cir Bucal.* 2018; 23(4):391-400.
- Pinheiro BJ, Tirapelli C, Silva LHC, Komesu CM, Petean CF, Junior LP, *et al.* Oral nodular lesions in patients with Sjögren's syndrome: unusual oral implications of a systemic disorder. *Braz Dental J.* 2017; 28(3):405-412.
- López-Pintor RM, Castro MF, Hernández G. Afectación oral en el paciente con síndrome de Sjögren primario. Manejo multidisciplinar entre odontólogos y reumatólogos. *Reumatol Clín.* 2015; 11(6):387-394.
- Fox R, Creamer P. Clinical manifestations of Sjögren's syndrome: exocrine gland disease. Wolters Kluwer Health, 2012; 7:210-235.
- Blochowiak K, Olewicz-Gawlik A, Polańska A, Nowak-Gabryel M, Kocięcki J, Witmanowski H, *et al.* Oral mucosal manifestations in primary and secondary Sjögren syndrome and dry mouth syndrome. *Adv Dermatol Allergol.* 2016; 33(1):23-27.
- Bayetto K, Logan R. Sjögren's syndrome: a review of aetiology, pathogenesis, diagnosis and management. *Aust Dental J.* 2010; 55:39-47.
- Bolstad AI, Skarstein K. Epidemiology of Sjögren's Syndrome - from an oral perspective. *Curr Oral Health Rep.* 2016; 3(4):328-336.
- Andersson A. Genetic control of disease in an experimental model for Sjögren's syndrome. *Arthritis Res Ther.* 2009; 11(1):1-2.
- Kokosi M, Riemer EC, Highland KB. Pulmonary Involvement in Sjögren syndrome. *Clin Chest Med.* 2010; 31(3):489-500.
- Nezos A, Mavragani CP. Contribution of genetic factors to Sjögren's syndrome and Sjögren's syndrome related lymphomagenesis. *J Immunol Res.* 2015, 2015:754825.
- Segal BM, Nazmul-Hossain ANM, Patel K, Hughes P, Moser KL, Rhodus NL, *et al.* Genetics and genomics of Sjögren's syndrome: research provides clues to pathogenesis and novel therapies. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2011; 111(6):673-680.
- Jonsson R, Vogelsang P, Volchenkov R, Espinosa A, Wahren-Herlenius M, Appel S, *et al.* The complexity of Sjögren's syndrome: Novel aspects on pathogenesis. *Immunol Lett.* 2011; 141(1):1-9.
- Mašličinska M. Sjögren's syndrome: still not fully understood disease. *Rheumatol Int.* 2015; 35(2):233-241.
- Aljanobi H, Sabharwal A, Krishnakumar B, Kramer MJ. Is it Sjögren's syndrome or Burning Mouth syndrome? Distinct pathoses with similar oral symptoms. *Oral Surg Oral Med Oral Pathol Oral Radiol.* 2017; 123(4):482-495.
- Ramos-Casals M, Stone JH, Sisó A, Bosch X. Treatment of primary Sjögren syndrome - a systematic review. *J Am Med Assoc.* 2010; 304(4):452-460.
- Saccucci M, Di Carlo G, Bossù M, Giovarruscio F, Salucci A, Polimeni A, *et al.* Autoimmune diseases and their manifestations on oral cavity: diagnosis and clinical management. *J Immunol Res.* 2018, 2018:1-6.
- Carr JA, Ng FW, Figueiredo F, Macleod IR, Greenwood M, Staines K, *et al.* Sjögren's syndrome – an update for dental practitioners. *Br Dental J.* 2012; 213:353-357.
- Turner M, Jahangiri L, Ship JA. Hyposalivation, xerostomia and the complete denture: a systematic review. *J Am Dental Assoc.* 2009; 139(2):146-150.
- González S, Sung H, Sepúlveda D, González MJ, Molina C. Oral manifestations and their treatment in Sjögren's syndrome. *Oral Dis.* 2014; 20(2):153-161.
- Kamiński B. Laryngological manifestations of Sjögren's syndrome. *Reumatologia.* 2019; 57(1):37-44.
- Lafurie G, Fedele S, López RMG, Wolff A, Strietzel F, Porter SR, *et al.* Biotechnological advances in neuro-electro-stimulation for the treatment of hyposalivation and xerostomia. *Med Oral Patol Oral Cir Bucal.* 2009; 14(2):E76-80.

23. Delaleu N, Nguyen CQ, Peck AB, Jonsson R. Sjögren's syndrome: studying the disease in mice. *Arthritis Res Ther*. 2011; 13(3):217.
24. Thoppay JR, De Rossi SS, Ciarrocca KN. Burning mouth syndrome. *Dental Clinics of North America*, 2013; 57:497-512.
25. Moerman RV, Bootsma H, Kroese FGM, Vissink A. Sjögren's syndrome in older patients. *Drugs & Aging*. 2013; 30(3):137-153.
26. Barone F, Nayar S, Campos J, *et al.* IL-22 regulates lymphoid chemokine production and assembly of tertiary lymphoid organs. *Proc Natl Acad Sci USA*. 2015; 112:11024-11029.
27. Patel R, Shahane A. The epidemiology of Sjögren's syndrome. *Clin Epidemiol*. 2014; 6:247-255.
28. Rasmussen A, Ice JA, Li H, Grundahl K, Kelly JA, Radfar L, *et al.* Comparison of the American-European Consensus Group Sjögren's syndrome classification criteria to newly proposed American College of Rheumatology criteria in a large, carefully characterized sicca cohort. *Ann Rheumatic Dis*. 2014; 73(1):31-38.
29. Stefanski A, Tomiak C, Pleyer U, Dietrich T, Burmester RG, Dörner T, *et al.* The diagnosis and treatment of Sjögren's syndrome. *Dtsch Arztebl Int*. 2017; 114:354-356.
30. Shiboski SC, Shiboski CH, Criswell LA, Baer AN, Challacombe S, Lanfranchi H, *et al.* 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):475-487.
31. Goules AV, Tzioufas AG, Moutsopoulos HM. Classification criteria of Sjögren's syndrome. *J Autoimmun*, 2014; 48-49:42-45.
32. Margaix-Muñoz M, Bagán JV, Poveda R, Jiménez Y, Sarrión G. Sjögren syndrome of the oral cavity: review and update. *Med Oral Patol Oral Cir Bucal*. 2009; 14:325-330.
33. Azuma N, Katada Y, Sano H. Deterioration in saliva quality in patients with Sjögren's syndrome: impact of decrease in salivary epidermal growth factor on the severity of intraoral manifestations. *Inflammation and Regeneration*. 2018; 38(6):1-9.
34. Ramos-Casals M. Primary Sjögren's syndrome: new clinical and therapeutic concepts. *Ann Rheumatic Dis*. 2009; 64(3):347-354.
35. Nikolov NP, Illei GG. Pathogenesis of Sjögren's syndrome. *Curr Opin Rheumatol*. 2009; 21(5):465-470.
36. Shen L, Chun Gao C, Sureshc L, Xianb Z, Songb N, Chavesa L, *et al.* Central role for marginal zone B cells in an animal model of Sjögren's syndrome. *Clin Immunol*. 2016; 168:30-36.
37. Chen X, Aqrabi AL, Utheim PT, Tashbayev B, Utheim A, Reppe S, *et al.* Elevated cytokine levels in tears and saliva of patients with primary Sjögren's syndrome correlate with clinical ocular and oral manifestations. *Sci Rep*. 2019; 9(7319):1-10.
38. Karp JK, Anders RA. Autoimmune hepatitis in patients with primary Sjögren's syndrome: a series of two-hundred and two patients. *Int J Clin Exp Pathol*. 2010; 3:582-586.