# ORAL DISORDERS IN SJÖGREN'S SYNDROME

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## ABSTRACT

*Sjögren's syndrome (SS) is a complex, chronic, systemic, autoimmune disease that mainly affects the exocrine glands, especially the salivary and lacrimal glands, leading to the dryness of the mouth and eyes, along with fatigue, joint and muscle pain. The prevalence of SS is estimated to be between 0.05% and 1% in European population. Diagnosis of SS is based on the revised criteria of the American-European consensus group (AECG). Sjögren's syndrome can be subclassified into primary disease (primary Sjögren syndrome, pSS) and a secondary disease (secondary Sjögren syndrome, sSS) when present with rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and systemic sclerosis. The decrease in salivary flow and qualitative alterations in saliva could explain many of the oral manifestations frequently present in patients with SS. Low salivary flow may affect chewing, swallowing, speech and sleeping in pSS patients. Oral manifestations include dental erosion, dental caries, mucosal infection, ulcers and oral candidiasis. Recent studies reveal that pSS patients experience impaired olfactory and gustatory functions and have higher occurrence of oral complications such as dysgeusia, burning sensation in the tongue (BST) and halitosis. The exocrine manifestations and systemic involvement in SS significantly impact the patient's perception of oral health related quality of life (OHRQoL).*

***Keywords***: *Sjögren's syndrome, xerostomia, oral manifestations, chemosensory disorders.*

## INTRODUCTION

Sjögren's syndrome (SS) is a complex systemic autoimmune disease in which body's immune system *attacks* exocrine glands, most commonly the salivary and lacrimal glands. The hallmarks of this autoimmune disease are lymphocytic infiltration of the exocrine glands and thepresence of circulating autoantibodies (anti-Ro/SS-A and anti-La/SS-B). The most common symptoms that occur inpatients with SS are dryness of the mouth and eyes, along with fatigue, muscle and joint pain (1).

This common rheumatic disease has insidious onset and affects primarily older women. Genetic traits and triggering factors such as infections, stress and hormonal factors play a role in the pathogenesis of Sjögren's syndrome (SS). Sjögren's syndrome can be subclassified into primarydisease (primary Sjögren syndrome, pSS), and a secondarydisease (secondary Sjögren syndrome, sSS) when present with other autoimmune rheumatic diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE)and systemic sclerosis. The overall prevalence of pSS is between 0.05-1% in European countries (1, 2).

The impaired function of salivary glands accompanied with insufficient secretion of saliva results in many oral complications such as infections, periodontal disease, caries and gustative and olfactory dysfunctions that affect oralhealth-related quality of life (OHRQoL) in patients with pSS. Patients with pSS commonly experience oral disorderson a daily basis which indicates that dental professionals have to pay more attention and recognize initial symptoms and various oral manifestations of Sjögren's syndrome andto keep close communication with rheumatologists (3).

## PATHOPHYSIOLOGY OF SJÖGREN'S SYNDROME

Although the pathogenesis of pSS in not completely understood the convincing data demonstrate the important role of genetics, innate and adaptive immune cells such as dendritic cells (DCs), T and B cells in this autoimmune disease. Circulating autoantibodies form immune complexes which when precipitated cause damage of affected tissues and organs (4).

### Genetic predisposition to Sjögren's syndrome

There is strong evidence that genes involved in the function of innate and adaptive immune cells are associated with the susceptibility to primary SS including genes involved in the interferon (IFN) signaling pathway, antigenpresentation, lymphocyte signaling and NF-kB pathway. Genetic studies in pSS patients revealed single nucleotide polymorphisms (SNPs) in HLA alleles (HLA-DRA, HLA-DQB1, HLA-DQA1), STAT4, IRF5, IL-12A and TNIP1.

The strongest genetic link apart from HLA antigen region is in the IRF5 gene locus. In response to type IFN-α, IRF5 gene encodes IRF5 protein in monocytes which promotes production of type 1 IFN, interleukin (IL)-6, IL-12, and tumor necrosis factor alpha (TNF-α). The genetic variants ofSTAT4 and IL-12A (p35 subunit of IL-12) genes involved in regulation of IFN-γ secretion are associated with heritable predisposition to pSS. Polymorphisms within thegene for B lymphocyte tyrosine kinase (BLK), the kinase involved in B cell development and differentiation and in gene for TNFAIP3-interacting protein 1 (TNIP1) of the NF-kB pathway have also shown associations with the susceptibility to pSS (5). Recent study using novel approach which combines concept profile analysis (CPA), an online tool that retrieves literature based on the concepts of interest and gene expression data on peripheral blood cells and exocrine glands in female patients with SS identified several candidate genes that regulate the expression ofmatrix metalloproteinase (MMP) 9. The identified genes are CHEK1 (Checkpoint kinase 1), ETS1 (avian erythroblastosis virus E26 oncogene homolog 1), LEF1 (Lymphoid enhancer-binding factor-1), X-linked gene TIMP1 (MMPsinhibitor), and CXCL10. CHEK1 gene encodes serine/ threonine-specific protein kinase and together with the ETS1 regulates development of tumors through the transcriptional regulation of MMPs. LEF1, a member of high mobility group (HMG) protein family is expressed in pre-B and T cells and plays an important role in cancer development. CHEK1, ETS1, LEF1 and CXCL10 increase the expression of MMP9, the enzyme that has been implicated inthe pathogenesis of SS. MMP9 could deteriorate the structural integrity of the salivary glands resulting in decreased salivary flow rate in patients with SS (6).

### Innate immunity in Sjögren's syndrome

Emerging evidence suggest an important role for the innate immune system in the pathogenesis of pSS. The pattern recognition receptors (PRRs) including TLRs and nucleotide oligomerization domain (*NOD*)-like *receptors* (NLRs) in innate immune cells detect pathogenassociated molecular patterns (PAMPs) and endogenous molecules from damaged cells (DAMPs). Initial events in pSS might be viral infection and hypoestrogenism that lead to activation of salivary and lacrimal gland epithelium. The activation of salivary gland epithelial cells (SGECs) and antigen presenting cells (DCs and macrophages) via PRRs result in the upregulation of MHC class I and II and co-stimulatory molecules and secretion of proinflammatory cytokines. Under the influence of IFN-γ and TNF-α secreted from innate immune cells tight junction proteins in SGECs lose their integrity causing decreased saliva production.

The activated plasmocytoid DCs (pDCs) via TLRs in salivary glands produce high levels of IFN-α particularlyin individuals with the IRF5 and STAT4 risk alleles. DCs function as antigen presenting cells in salivary tissue and promote expansion of autoreactive T cells and somatic hypermutation of B cells. On the other hand, DCs may exert tolerogenic activities by promoting expansion of SS-A autoantigen specific regulatory T cells (Trges) inpSS. Macrophages are recruited to salivary glands prior to lymphocytes and express proinflammatory IL-18 and IL-12 thereby amplifying ongoing

inflammation. The role of natural killer (NK) cells in pSS remains elusive. NK cells express NCR3/NKp30, an activating receptor that after ligation to NKp30 ligands on SGECs promotes IFN-γ secretion and polarization of Th1 cells.

TLR2 and TLR4 expression is increased in SGECs in patients with pSS and ligation of these PRRs results in production of high levels of the proinflammatory IL-17A. TLR3 binds double-stranded RNA of viral origin and leadsto secretion of proinflammatory cytokines and BAFF fromSGECs. In pSS, antibodies against SS-A in complex with hYRNA can bind and stimulate TLRs causing an inflammatory response. Microbial or tissue components may also be recognized by cytoplasmic receptors NLRs. Oneof the NLRs, NLRP3 oligomerise to form inflammasome multiprotein complex that activates caspase proteins and subsequent secretion of IL-1 and IL-18. In pSS, the NLRP3inflammasome is activated by concomitant stimulation of TLRs and purinergic P2X4/P2X7 receptors. Upregulation of P2X7, NLRP3 and caspase-1 genes correlate with focal lymphocytic sialadenitis, and increased expression of bothIL-1 and IL-18 indicate inflammasome hyperactivity in patients with pSS (7-9).

**Adaptive immunity in Sjögren's syndrome**

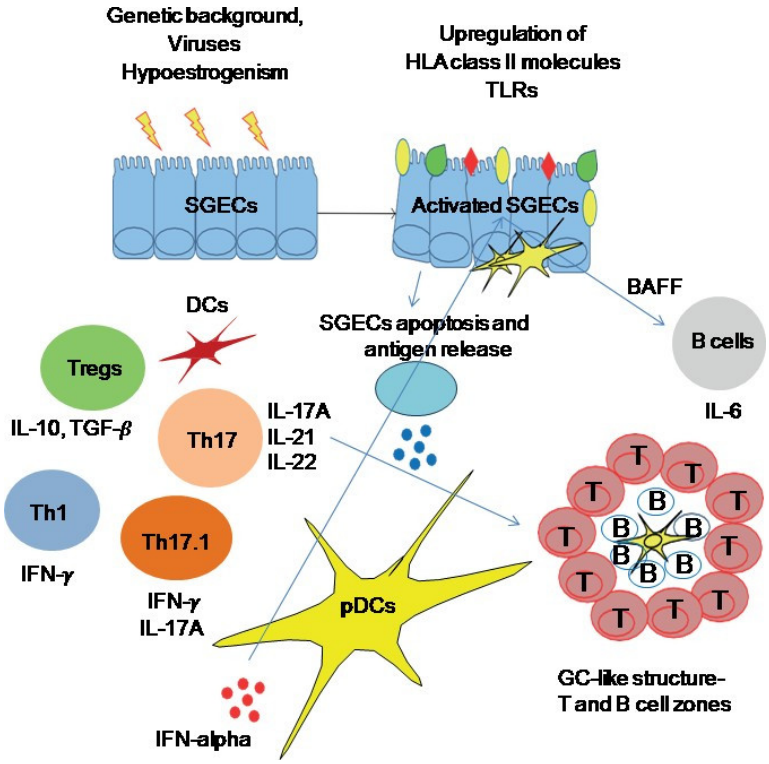
$CD4^+$ T cells, but also $CD8^+$ T cells, B cells and DCs are present in salivary gland infiltrates in patients with pSS. These immune cells form tertiary ectopic lymphoid structures with T- and B-cell zones in advanced lesions. The pathogenic role of various $CD4^+$T helper (Th) subsets,Th1, Th2, Th17, Treg cells and follicular helper T (Tfh) cells in pSS are incompletely understood. Naive $CD4^+$T lymphocyte differentiate towards Th17 cells in the concurrent presence of IL-6, TGF-$\beta$, IL-21, IL-1$\beta$, and IL-23. Th17 cells have upregulated retinoic acid orphan receptor(ROR)$\gamma$t transcription factor and express IL-17, but also IL-21 and IL-22. High and consistent expression of IL-17 in the periductal infiltrates of all minor salivary glands hasbeen documented in patients with pSS. Th17 are the mainsource of IL-17 in affected exocrine glands, but γδ T cells, NK cells, innate lymphoid cells (ILCs) and CD8+ T cells also produce IL-17. Th17 cells in salivary glands may be locally differentiated from naive T cells or recruited from theblood. Th17 cells are elevated in patients with moderate-to-high systemic disease activity, the findings that suggest its association with disease severity and/or with certain stages of the disease. Th17 cells in affected exocrine glandsmight promote B cell activation and formation of germinalcenters. Abundant expression of IL-17 in salivary glandsin patients with pSS may drive the transformation of Th17cells towards both IFN-γ single producing Th1 cells and Th17.1 cells which produce both IL-17 and IFN-γ and coexpress CXCR3 and CCR6 receptors. Th17.1 cells may contribute to disease progression in pSS considering the well-established role of IFN-$\gamma$ in the pathogenesis of pSS. In addition, most of the cytokines that support the Th17 phenotype such as IL-6, IL-21, IL-22, and IL-23 and their receptors, are consistently expressed in salivary glands of patients with pSS (10, 11).

Recent evidence suggests the pathogenic role of IL-17 in the initiation and progression of pSS. IL-17 stimulates the production of proinflammatory cytokines and MMPs that may cause destruction of salivary glands. The recent meta-analysis revealed that IL-17 is increased in the serum,tears, saliva, and salivary glands of pSS patients, particularly in RF positive patients and in patients without immuno-suppressive therapy. The levels of IL-17 correlated with thedisease severity of pSS. Moreover, pSS disease severity hasbeen linked to increased co-expression of IL-17 and IL-18 in pSS. In addition, IL-17 could be a key prognostic factor for lymphoma development in patients with pSS (12, 13).

Treg cells express high levels of CD25 and forkhead box protein P3 (FoxP3) transcriptional factor and suppress autoreactive lymphocytes via either cell-cell contact or the release of IL-10 and transforming growth factor $\beta$ (TGF-$\beta$). TGF-$\beta$ is required for differentiation of bothTregs and pathogenic Th17 cells, but the concurrent presence or absence of IL-6 leads to the generation of either Th17 or Tregs, respectively. The role of Treg cells in pSS pathogenesis is not clear. Several studies reported an overall reduction of $CD25^{high}$Treg cells in peripheral blood of pSS patients, whereas other studies reported an increaseof circulating Tregs. Similarly, no definitive conclusioncan be made regarding the role of Tregs in salivary gland tissue. FoxP3 positive Tregs were detected in minor salivary glands in pSS and their expression correlated withthe severity of tissue inflammation. Whether Treg cells exert their suppressive activity *in vivo* is not certain. Also, Treg cells can be turned into a Th17 cells in the presence of appropriate stimuli. Transcriptional factors, RORγt andFoxP3, interact and block each other's function and in the course of pSS TLRs-stimulated production of IL-6 along with IL-23 by DCs, will lead to generation of pathogenic Th17 cells (14).

IL-12 is composed of p35 and p40 subunits, and bioactive IL-12p70 in myeloid cells induces IFN-γ production and polarization of Th1 cells. Recently, a novel anti-inflammatory cytokine composed of the IL-12p35 and EBI3 subunits has been identified as IL-35. Recently, significant association between a SNP within the IL-12A locus (rs485497) and susceptibility to pSS has been shown. IL-12p70 level is elevated in sera of pSS patients and correlates with active disease and IL-12 positive cells infiltrate salivary glands of pSS patients. IL-35 exerts immunosuppressive effects on Th17 cells and induces the generation of novel regulatory cell population, iTr35 cells. pSS patients with high disease activity have low level of circulating IL-35, indicating that IL-35 could efficiently control the disease activity and possibly prevent the occurrence oflymphoma (15).

**Figure 1.** Current model of pSS immuno-pathogenesis




Initial event in the pathogenesis of primary Sjögren's syndrome is the activation of salivary gland epithelial cells (SGECs) and upregulation of HLA class I and II antigens, TLRs and autoantigen presentation. The subsequent activation of plasmacytoid dendritic cells (pDCs) induces the production of high levels IFN-α in individuals with the risk alleles of the susceptibility genes IRF5 and STAT4, which induces production of B-cell activating factor (BAFF) from SGECsthat stimulate B cells.

Activated SGECs and DCs secrete proinflammatory cytokines and chemokines leading to activation of Th17 cells in salivary gland infiltrates. Th17 cells differentiate towards Th17.1 cells or Th1 cells. IL-17A, IL-22, IL-21 and IFN-γ amplify ongoing inflammation, promote expression of MMPs and induce germinal center (GC) formation in salivary glands along with autoantibodies production. B cells in salivary glands produce IL-6, and further stimulate formation of Th17 cells. Tregs cells via IL-10 and TGF-β suppress proinflammatory Th1 cells, Th17 cells and the Th17.1.

The cause of pSS is not known, but it is presumed that microbial pathogens (viral antigens) may lead to activationof pDCs and production of IFN-α. B cells are adaptive immune cells that produce antibodies and B cell activating factor (BAFF) which is induced by type I and type II interferons and promotes activation, proliferation and maturation of B cells. Elevated BAFF levels in circulation and salivary gland tissues and increased expression of genes related to interferon type I or type II are linked to more severe pSS. Salivary glands in pSS contain ectopic germinal centers which further highlight the role of activated B cells in pSS. There is plethora of autoantibodies in sera of patients with pSS, among which some of them are diagnostic or associated with early disease onset, enlargement of parotid gland or extraglandular manifestations (16). Fig.1 summarizes the current concept of the pathogenesis of pSS. Research of the immune-mediated mechanisms in the pathogenesis of pSS will yield the new insights into potential new targets for biologic therapies in this disease.

## AUTOANTIBODIES IN SJÖGREN'S SYNDROME

Patients with pSS have many circulating autoantibodiesdirected against self-antigens and current research aims indefining new biomarkers for early diagnosis of pSS. The most common autoantibodies in patients with pSS areshown in Table 1. Autoantibodies may be present in patients` sera years prior to the diagnosis of the pSS. Anti-Ro/SS-A and anti-La/SS-B autoantibodies are detected in two-thirds of patients with pSS and have been associated with more severe dysfunction of exocrine glands and morepronounced lymphocytic infiltrates in the minor salivary glands. Rheumatoid factor is often found in patients with pSS and is usually associated with positive anti-Ro/SS-A and anti-La/SS-B autoantibodies (17).

**Table 1**. Common autoantibodies in patients with pSS

| Autoantibodies in pSS | Prevalence | Clinical Association |
|---|---|---|
| Anti-Ro/SSA | 50-70% | Younger age, severe disease, extraglandular manifestations, neonatal lupus |
| Anti-La/SSB | 25-40% | Extraglandular manifestations, neonatal lupus |
| RF | 36-74% | Systemic disease, severe disease |
| Anti-CCP | 3-10% | Arthritis |
| AMA | 3-10% | Elevated liver enzymes |
| ACA | 3-27% | Raynaud's phenomenon |

Anti-Ro/SSA and anti-La/SSB antibodies were originally described as two antibodies reacting with salivary andlacrimal glands' antigens in patients with SS. Ro/SS-A antigen is a RNP complex constituted by two different Ro proteins of 52kDa, and 60 kDa that binds to small cytoplasmic RNAs known as hY-RNAs. The biological functions of Ro/SS-A complex are not known, but there is some evidence that the Ro 60-kD protein is involved in a discard pathway for defective 5S rRNA precursors. La/SS-B antigen isa 48 kDa phosphorylated protein, located in nucleus and cytoplasm which binds to many RNA molecules during thecell cycle. Functionally, La/SS-B protein is a transcription termination factor for RNA polymerase III transcripts. Unlike SS-A and SS-B antigens which are found in every cell, novel autoantibodies as biomarkers of SS are directedto proteins selectively present in the salivary and lacrimal glands. These are auto-antibodies to salivary protein-1 (SP-1), parotid secretory protein (PSP), and carbonic anhydrase VI (CA-6). SP-1, PSP, CA-6 proteins have various physiologic activities, including roles in the attenuation of microbial agents. PSP is a protein that is involved in the binding and clearance of infectious agents, while CA-6 is an enzyme in the acinar cells of submandibular and parotidglands involved in buffering of saliva (18).

Patients with pSS have autoantibodies directed against muscarinic acetylcholine type 3 receptors (M3R)in their sera and these IgG antibodies functionally inhibit salivary secretion. Namely, acetylcholine (ACh) released from parasympathetic nerves regulate water and electrolyte transport in salivary glands via M3R, a prototypical G-protein-coupled receptor (GPCR), endogenously expressed in salivary glands. M3R IgG autoantibodies may directly bind and occupy M3R receptors and their continued presence lead to M3R internalization and progressive loss of M3R function. Borda et al. (19) recently demonstrated that autoantibody to M3R and pilocarpine induced the increment of superoxide dismutase (SOD) and catalase (CAT) and the production of nitric oxide (NO) and prostaglandin E2 (PGE2) in patients with pSS. The increased activity of SOD and CAT in pSS patients maybe regarded as a defensive reaction to the increased reactive oxygen species (ROS), which may cause damage of salivary glands. Kim et al. (20) reported that downregulation of MHC I from the cell membrane is associated with the presence of anti-M3R autoantibodies which is a novel pathogenic mechanism in pSS.

The most specific autoantibodies for both the classification and the diagnosis of pSS are directed towards intracellular antigens Ro52/SS-A, Ro60/SS-A and La/SS-B. Rheumatoid factor (RF) is commonly found in the sera of patients with autoimmune rheumatic diseases including pSS. RF is associated with the presence of anti-Ro/SS-A and anti-La/SS-B antibodies as well as systemic disease and is associated with disease severity and more severe exocrine gland manifestations (keratoconjunctivitis sicca).

RF and cryoglobulins are detectable in 35-70% and 5-10%of patients, respectively and correlate with clinical featuresof pSS such as lymphomagenesis (17). Anticentromere antibodies are present in 5-15% of pSS patients and these patients have more frequent Raynaud's phenomenon, 'scleroderma-like clinical features' and primary biliary cirrhosis and more pronounced dysfunction of exocrine glands with higher risk of developing salivary gland lymphoma. Anti-mitochondrial antibodies and anti-smoothmuscle antibodies have been described in pSS patients in association with primary biliary cirrhosis and autoimmuneliver involvement. Anti cyclic-citrullinated peptides (anti-CCP) antibodies, found in low prevalence in pSS patients, are related with nonerosive arthritis and RF positivity (21).

## CLINICAL MANIFESTATIONS IN SJÖGREN'S SYNDROME

Patients with pSS may present with sicca syndrome, general symptoms and systemic manifestations. Classical symptoms of pSS are combination of dryness of the eyes (xeropthalmia) and oral cavity (xerostomia). Xerostomia may predispose to oral complications such as oral candidiasis, dental caries and periodontal disease. Ocular infections, photosensitivity and destruction of the cornea are possible complications of xerophtalmia. Sicca syndrome may also present as hoarseness, non-productive cough, skin dryness and, in woman, dyspareunia. Among general symptoms, fatigue is most commonly present in the majority of patients with pSS. In addition, pSS patients experience chronic pain due to accompanying fibromyalgia and/ or polyarthralgia along with depression and anxiety whichare often seen in pSS patients. SS is a systemic disease strongly associated with organ specific and systemic autoimmunity. Numerous systemic manifestations are presentin patients with SS (22, 23) as shown in Fig. 2.

## DIAGNOSIS OF SJÖGREN'S SYNDROME

The diagnosis of pSS is based on the American-European consensus group (AECG) classification criteria for Sjögren syndrome (24). These criteria include: subjective presence of ocular dryness; subjective presence of oral dryness; objective measures of ocular dryness by Schirmer's test or corneal staining; focus score > 2 in a salivary gland biopsy; salivary scintigraphy showing reduced salivary flow (1.5 mL in 15 minutes) and/or diffuse sialectasias andpositive autoantibodies against SS-A and/or SS-B. PrimarySS is diagnosed when 4 out of 6 items are present; either salivary gland pathology or the presence of autoantibodiesagainst SS-A/SS-B is mandatory. The diagnosis of secondary SS is made when patients present with underlying autoimmune diseases such as RA, systemic SLE or scleroderma which were diagnosed prior to developing their sicca symptoms.

**Figure 2.** Clinical manifestations in pSS

**Neurological complications**
peripheral neuropathy
cranial neuropathy

**Dry eyes**

**Dry mouth**

**Glandular problems**
parotid, submandibular and
lacrimal gland enlargement

**Pulmonary involvement**
bronchitis
lymphocytic interstitial pneumonitis
pleurisy

**Liver complications**
hepatitis
cirrhosis

**Vascular Problems**
vasculitis
Raynaud's phenomenon

**Kidney problems**
interstitial nephritis
renal tubular acidosis
hypokalemia

**Arthralgia/Arthritis**

**Fatigue**

Ultrasonography of the major salivary glands (parotid and submandibular glands) is not included in classificationcriteria, but may be helpful in diagnosis or follow-up of patients with pSS (25-28).

EULAR validated two indexes for the assessment of disease activity in primary Sjögren's syndrome. The EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) is the mean of three visual-analogue scales that measure mouth and eye dryness, fatigue, and pain in a simple patient-administered questionnaire (29). The EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) 20 assesses systemic complications of the disease in 12 domains and is used mainly in clinical trials (30). ESSPRI and ESSDAI do not have diagnostic value in pSS. 2016 ACR/EULAR criteria incorporated ESSDAI to be assessed in patients with suspected SS who complain of either ocular or oral drynessor systemic involvement. There is a need for subjective or objective determination of the level of the disease activity in clinical practice. However, ESSPRI and ESSDAI are mainly used in clinical trials. In the last years, a numberof clinical trials using biological therapy for the treatment of SS have been performed and some are still ongoing. In order to define key inclusion criteria and response criteriain clinical trials with biologic drugs, it is important to haveobjective measures of both, disease activity and disease damage which could also improve clinical research in primary SS. European League Against Rheumatism (EULAR)SS study group recommends use of ESSDAI and ESSPRIin assessment disease activity in the clinical studies. A criterion for applying systemic therapy in SS is ESSAI $\geq$ 5, whereas therapeutic response is achieved when ESSDAI isdecreased for $\geq$ 3.

## THERAPY OF SJÖGREN'S SYNDROME

There is no cure for SS and the main treatment goals are relieving of symptoms, prevention of complications and selection of patients for immunosuppressive therapy. Therapy of SS requires multidisciplinary approach with the *team* including a *rheumatologist*, a *dentist* and an ophthalmologist since the occurrence of oral and ocular manifestations and complications are frequent. If systemiccomplications exist the contribution of other specialists is needed.

Therapy of SS is mainly symptomatic. At present, the data from a small number of randomized clinical studies are not conclusive regarding the use of systematic therapyin patients with SS. Management of oral manifestations includes intense oral hygiene, prevention and treatmentof oral infections, use of saliva substitutes, and local and systematic stimulation of salivary secretion. Cholinergic agents, such as pilocarpine is the cornerstone of current therapy in SS. The treatment of patients with SS includes substitution therapy with artificial tears and saliva. Patientsare advised to take fluids more frequently and sugar-free chewing gums as local active sialogouges. Smoking, use of alcohol beverages and sparkling water should be avoided. When hyposalivation exist the oral cavity is less protected and oral mucosa becomes vulnerable to various physical and microbial insults. Therefore, keeping the oral hygiene is of utmost importance in prevention of oral complications and regular visits to dentist are recommended.

Given the fact that exocrine gland dysfunction in SS is related to chronic inflammation it is surprising that treatment of patients with low dose corticosteroids or immunosuppressive agents such as methotrexate, cyclosporine and azathioprine have not been efficient in achieving increased function

of lacrimal or salivary glands (31). Hydroxychloroquine is0 efficient treatment drug for numerous extraglandular manifestations of the disease and also for increasing the lacrimal and salivary flow rate (31). Anti-TNF therapy (infliximab and etanercept) have not demonstrated any efficacy in patients with extraglandular disease (32). The anti-B-cell therapy with anti-CD20 autoantibody (rituximab) and anti-CD22 monoclonal antibody (epratuzumab) is a promising option for glandular and extraglandular manifestations of the disease, as well asfor the management of SS-associated lymphoma (33, 34). Several immune pathways exist that biological drugs couldinterfere as a target therapy such as BAFF-APRIL pathway,modulation of T cell co-stimulation, IL-17 and chemokinesblockers, and IL-6 blockers as a clinical trial aimed at assessing Tocilizumab in pSS is actually ongoing (35).

## ORAL DISORDERS IN SJÖGREN'S SYNDROME

Sjögren's syndrome is characterized by dysfunction and destruction of the major salivary glands. Patients with pSS may present with parotid enlargement, but also with isolated submandibular gland enlargement. The hallmarks ofpSS are decreased secretion of saliva and xerostomia whichnegatively affect oral health in patients. Optimal saliva secretion is essential for swallowing, eating, oral cleansing, speech, digestion and taste (3).

### Saliva

Saliva contains mainly water and a mixture of proteins, glycoproteins, enzymes, and many antimicrobial molecules such as defensins, proteases, lysozyme essential to maintaining oral health (36). Saliva secretion is regulated by mechanical and chemical factors, and food and chewingstimulate salivary flow. Mechanical and chemical afferent signals are transmitted from sensory receptors in the periodontal ligament and taste buds via the trigeminal, facial, and glossopharyngeal nerves to the salivary nuclei in the medulla oblongata of the brain. Efferent impulses to the salivary glands are transmitted via sympathetic and parasympathetic autonomic nerves (37).

Xerostomia, dryness of the mouth, is associated with diminished saliva secretion when unstimulated salivaryflow is below 50% of the normal. However, recent data suggest that xerostomia in SS patients is a result of the alterations of salivary mucins rather than low salivary flow. Additionally, changes of proteins that maintain cell-cell and cell-extracellular matrix interactions have been reportedin SS patients and these changes may affect the quality of saliva and may even promote chronic inflammation (38).

Dryness of the mouth is not specific symptom for SS and may be found in other diseases (sarcoidosis, diabetes) or could be related to medication use (antidepressants, antihistaminics, diuretics) or by head and neck radiation. Xerostomia Inventory (SXI) is a questionnaire which results represent, subjectively, the severity of xerostomia. 2012 ACR/EULAR criteria excluded the subjective criteria of oral dryness in order to increase the specificity of the criteria. However, 2016 ACR/EULAR criteria included the subjective evaluation of ocular or oral dryness underscoring the importance of anamnestic data and subjective assessment of disease progression. In order to pre-select patients with suspicious SS the 2016 ACR/EULAR criteria are intended to be applied to any patient with at least 1 symptomof ocular or oral dryness (based on American-European Consensus Group [AECG] questions) or suspicion of SS due to systemic features derived from the ESSDAI score.

One of the diagnostic criteria is unstimulated salivary flow (UWS), whereas stimulated salivary flow (SWS) is used for the evaluation of the residual functional tissue of salivary glands. This is important regarding the therapy with *secretagogues*, as these agents are used only if thereis functional tissue remained. Stimulated salivary secretion is used for the evaluation of parotid gland function as these glands produce saliva on stimulation, while submandibular glands continuously produce saliva. Xerostomia is diagnosed if unstimulated salivary flow is ≤1,5ml/15 min. Sialometry has sensitivity of 56% and specificity of 81% forthe diagnosis of SS (39).

Hyposalivation in patients with pSS can cause stomatitis, ulcers and atrophic changes in the oral mucosa. Low salivary flow rate, but also changed quality of salivais causes of intraoral manifestation in patients with pSS. Salivary epidermal growth factor (EGF) is considered an important cytoprotective factor that maintains mucosal integrity. Recently, it was shown that salivary EGF output in SS patients was significantly lower than that in non-SS patients, EGF output decreased with prolonged diseaseduration, and more rapidly than salivary flow rate and wasrelated with poor quality of life in SS patients. These findings suggest that topical EGF supplementation may be a novel therapeutic strategy in patients with pSS (40).

Emerging evidence suggest that patients with pSS have different oral microbiome compared to healthy subjects but whether these changes are disease specific or a consequence of reduced salivary secretion is not elucidated. The recent study demonstrated that patients with pSS hadheterogenous oral bacterial composition and the relative abundance of Haemophilus, *Neisseria* and *Lactobacillus* was related to lower stimulated salivary flow and not with pSS, indicating that hyposalivation is the reason for these changes, while lower *Streptococcus* abundance in patients with pSS appears to be a disease-specific (41).

Investigation of novel biomarkers is performed for their potential use in diagnosis and the prognosis of pSS. Salivary proteomics is a promising tool since proteins in saliva may closely reflect the underlying disease processes in the salivary glands in pSS. Namely, the decrease in manysecretory proteins has been found including α-amylases precursor, carbonic anhydrase VI, PIP, SPLUNC-2, G3P-DH, and

cystatins. The available data indicate that secretory proteins of acinar origin were reduced in pSS patients,while inflammatory phase proteins are increased in comparison with healthy subjects. The increased expressionof β2-microglobulin, Immunoglobulin κ light chain and Immunoglobulin γ light chain in pSS saliva is thought to reflect both B-cells activation and an increased immunoglobulin synthesis within salivary glands. Furthermore, an increase of proteins related to the systemic and local inflammation (α-enolase, lipocalin and S100-A7 and A9 proteins) was found. Proteomics represents a novel approach for use in diagnosis of pSS. The proteomics studies so far have described putative protein biomarkers that will eventually contribute to diagnosis of pSS and stratification of different disease subsets (42, 43).

**Figure 3.** Oral manifestations in pSS

| |
|---|
| Dental erosion |
| Dental caries |
| Mucosal friability |
| Dry cracked or peeling lips |
| Angular cheilitis |
| Dry plaque laden coarse tongue |
| Erythematous tongue |
| Mucositis |
| Ulcers |
| Oral candidiasis |
| Halitosis |
| Oral/dental infection |

## Oral manifestations

Oral manifestations are commonly present in patients with pSS as shown in Fig. 3. The low salivary secretion leads to less lubrication and diminished antimicrobial propertiesof saliva which results in the increased incidence of various oral disorders. Patients with pSS present with moreoften conditions such as dental erosion, dental caries, drycracked or peeling lips, angular cheilitis, dry plaque ladencoarse tongue, erythematous tongue, mucosal infection,ulcers, oral candidiasis, halitosis and oral/dental infection. The most common oral complication of Sjögren's syndrome is dental caries, specifically, root and incisal caries,which are less frequent in general population. The dentalcaries process involves dental biofilm and bacterial species that colonize tooth surfaces. Sjögren's syndrome patients have been reported to have higher numbers of cariogenic and acidophilic micro-organisms which indicatesalteration in oral microbiota. Sjögren's syndrome patientsdue to low salivary flow cannot sufficiently perform selfcleansing of oral cavity that includes buffering, lubricating and antimicrobial effects. Oral candidiasis is another common and often chronic complication of Sjögren's syndrome. Patients with SS and oral candidiasis usually present with signs such as angular cheilitis, atrophy orloss of filiform papillae on the dorsal tongue or erythema of the tongue and other mucosal surfaces (44). There are several reports describing common oral complications in patients with pSS (45-47).

Musculoskeletal symptoms occur in patients with pSS. The most frequent joints involved are hands, wrists, ankles, and feet, but also temporomandibular joint (TMJ) may be involved. In addition to oral manifestations and rheumatologic implications, Sjögren's syndrome seems to play a role in TMD especially as regards to muscular contracture (high prevalence of myalgia to muscle palpation and positive endfeel) and joint disease (greater pop-noise and deflection during mandibular opening), causing an increase in orofacial painand an altered chewing function (48).

SS is a common and underdiagnosed autoimmune, chronic inflammatory disease of the exocrine glands witha significant impact on oral health. Dentists are frequentlythe first to encounter the patients with early signs of SS. Therefore, dentists should be familiar with the manifestations of the disease and their contribution to the diagnosis,management and treatment of the oral complications of SSare essential.

Chemosensory disorders and other oral complaints in patients with Sjögren's syndrome

Taste and smell impairments have been reported in patients with pSS (49-51). There are scarce data about chemosensory disorders and other oral complaints, such as dysgeusia, burning sensations in the tongue (BST) and halitosis in patients with pSS. Chemosensory disordersinclude gustatory and olfactory dysfunctions, in which the senses of taste or smell can be reduced, distorted, or totally absent. Olfactory disorders are classified as follows: anosmia (complete loss of smell), hyposmia (reduced ability to smell), and dysosmia (distorted smell perception) (52). Gustatory disorders are similarly classified, namely ageusia (complete loss of taste), hypogeusia (partial loss of taste), and dysgeusia (distorted taste perception in the presence of normal stimuli) (53). Many patients with chemosensory disorders experience burning sensations or numbness in the mouth, especially inor on the tongue, the sensations that may originate in the gustatory nerve fibres (54). Burning mouth syndrome (BMS) is defined as the intensive burning sensation inthe tongue (BST), or burning in other mucosal membranes, lasting for at least 4-6 months (55). Patients with both SS and burning mouth syndrome (BMS) often have similar oral complaints; however, these diseases have significantly different etiopathogeneses, diagnostic criteria, and treatments. SS is a chronic

autoimmune disorder most commonly present in middle age women. BMS isa chronic disorder characterized by burning sensation of the oral mucosa in the absence of any apparent clinical abnormalities or local and/or systemic etiology. Similarto SS, BMS affects women more commonly than men and patients may report oral dryness, but the xerostomia is often perceived rather than actual. The diagnostic challenges are evidenced by the fact that both SS and BMS patients typically experience symptoms for years prior to achieving a diagnosis (56). Halitosis (or oral malodour, defined as an unpleasant breath odour of oral or extraoral origin), is another common oral complaint that canbe associated with low salivary secretion or chemosensory disorders (57).

Recent study demonstrated poorer olfactory and gustatory function, more often reported dysguesia, BST and halitosis, lower salivary secretion rates and poorer OHRQoL in 31 patients with pSS in comparison with healthy subjects(58). Interestingly, authors have not observed correlationsbetween saliva secretion rates and the presence of dysgeusia, BST, halitosis or olfactory and gustatory scores. For OHRQoL assessment the short-form Oral Health Impact Profile (OHIP-14) was used in this study. The OHRQoL was found to be associated with dysgeusia, BST and halitosis and no associations with saliva secretion rates. Thereare conflicting results whether hyposalivation causes smelland taste impairments as well as burning sensation in the mouth, since no correlation between low salivary flow andtaste performance was observed (59).

Burning sensation in the mouth, dysgeusia and halitosis are common complaints among SS patients and the important notion is that the intensity of discomfort cannot be associated to clinical symptoms (54, 57). Current findings show that pSS patients' OHRQoL was more influenced by dysgeusia, BST, and halitosis, rather than by impaired smell and taste functions. Oral malodour was present in almost half of the patients in the study, but the question remains whether they had a genuine halitosis. The presence of chemosensory disorders such as smell andtaste dysfunction in these patients may be an alternative explanation for this complaint. This study shows that there were no associations between dysgeusia, BST, halitosis, orchemosensory dysfunction with patient's age, the number of medications taken or the disease duration. Presumably, a questionnaire better designed to detect taste and smell dysfunction is needed to gain more specific insight into the patients' chemosensory experiences and oral healthrelated quality of life.

Possible underlying cause of the olfactory and gustatory dysfunctions in pSS patients could be immunopathological mechanisms operating in pSS. Systemic chronic inflammation in primary Sjögren's syndrome is associatedwith overexpression of interferon-inducible genes (60) and higher response of B cells and monocytes to stimulation with IFN-α and IFN-γ (61). Proinflammatory pathways mediated by Toll-like receptors and interferons in taste tissue may interfere with normal taste transduction and turnover of taste bud cells (62). Further studies of inflammatory pathways in the peripheral taste and smell organs at the cellular and molecular level are warranted in order to gain more knowledge regarding the pathogenesis of oral disorders in pSS patients.

The oral manifestations in pSS could present as higher number of decayed, missing and filled teeth; and higher plaque index, gingival index and papillary bleeding index. Thus, it is very common that these patients require dentalimplants to rehabilitate any extractions arising from decayor periodontal disease. In addition, such patients are often treated with immunomodulators (hydroxychloroquine, methotrexate) and sometimes with immunosuppressivedrugs that affect patient's immune response. Results ofthe studies suggest that the dental implant therapy in SS patients seems to present high implant survival rate, low marginal bone loss (MBL) and low biological complications. In addition, an increase in the quality of life of SS patients who were rehabilitated through dental implants isdocumented (63, 64).

## CONCLUSION

In conclusion, patients with Sjögren's syndrome commonly experience many oral complications including impaired olfactory and gustatory functions and a higher occurrence of oral disorders such as dysgeusia, BST and halitosis. Due to their predominant oral symptomatology patients are often firstly seen by dental professionals who must recognize the signs and symptoms of xerostomia. Early diagnosis, prevention and treatment are crucial to maintaining oral health in patients with SS. Health care professionals have to work together to improve patient outcomes and quality of life for the patient diagnosed withSjögren's syndrome.

## CONFLICTS OF INTEREST

The authors declare no financial or commercial conflicts of interest.

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