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Oral Aspects of Sjögren’s Syndrome

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1. Introduction

1.1 General aspects of Sjögren’s syndrome

1.1.1 Definition

Sjögren’s syndrome (SS) is a chronic autoimmune disease associated with the production of autoantibodies and characterized by a progressive lymphocytic and plasma cell infiltration of the salivary and lacrimal glands leading to xerostomia and keratoconjunctivitis sicca (1). A Danish ophthalmologist named Henrik Sjögren in 1932 was the first one, who reported the triad of keratoconjunctivitis sicca, xerostomia, and rheumatoid arthritis and then Sjögren introduced the term keratoconjunctivitis sicca for this syndrome, to distinguish it from dry eyes caused by lack of vitamin A (2). It is characterized by lymphocytic infiltration and subsequent destruction of the exocrine glands (3–5) including those found in the nose, ears, skin, vagina, respiratory and gastrointestinal systems (6).

1.2 Diagnosis

1.2.1 Differential diagnosis

The diagnosis of SS is not straightforward as many of the symptoms are subjective (Figure 1) (5).

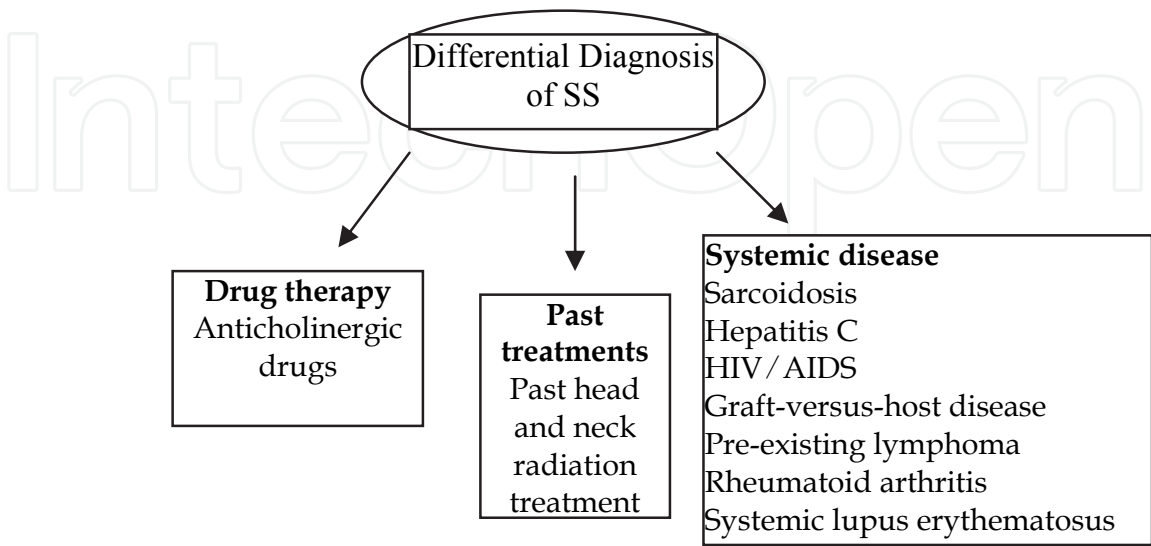


Fig. 1. Differential Diagnosis of SS (5)

1.2.2 Diagnostic criteria

The criteria for diagnosis of SS remain controversial, and different diagnostic criteria have been proposed. The syndrome can present primary or secondary. Generally, SS is classified as secondary (SS-2) when it is associated with other autoimmune diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis and polymyositis and as primary (SS-1) when there is no other connective tissue disease (7, 8). There are at least 6 international diagnostic criteria, such as Fox criteria, San Diego criteria, San Francisco criteria, European criteria (EEC), American-European Consensus Group (AECG) criteria, and Copenhagen criteria. San Diego criteria requires evidence for an autoimmune process associated with destruction of salivary and lacrimal gland tissues while the Copenhagen and EEC study group have based their diagnostic criteria on clinical findings of dry eyes and mouth with no absolute requirement for gland biopsy or presence of autoantibodies.

On the other hand, Sjögren's Syndrome Foundation (SSF) stressed that the classification criteria for Sjögren's syndrome currently used by clinicians and researchers around the world is the American-European Consensus Classification Criteria (Table 1). Because many different criteria previously were used both within the U.S. and in other countries, the Sjögren's Syndrome Foundation and members of the European Study Group on Classification Criteria brought international leaders in Sjögren's together to develop consensus on one set of guidelines (9). SSF mentioned that that classification criteria is the strictest criteria available to prove a definitive diagnosis of Sjögren's for research purposes. Physicians usually diagnose SS for clinical purposes on a more individual, medically intuitive and broader basis. However, none of them was approved by the World Health Organization, which suggested better diagnostic criteria should be established.

1.3 Prevalance

Sjögren's syndrome occurs worldwide and in all ages. The peak incidence is in the fourth and fifth decades of life, with a female : male ratio of 9:1 (13). A number of studies have shown great variation in the frequency of Sjögren's syndrome (14). Prevalence studies have demonstrated that sicca symptoms and primary Sjögren's syndrome affects a considerable percentage of the population, with precise numbers dependent on the age group studied and on the criteria used (15). A cautious but realistic estimate from the studies presented thus far is that primary Sjögren's syndrome is a disease with a prevalence not exceeding 0.6% of the general population (15).

1.4 Aetiology and pathogenesis

The etiology of Sjögren's syndrome remains unidentified (16). Interactions between environmental contributors such as viruses or stress in conjunction with genetic susceptibility factors and hormonal effects are currently believed to result in disease development (16, 17). Intrinsic activation of epithelium in various target organs was demonstrated (18), based on inappropriate expression of MHC molecules, overexpression of costimulatory molecules and capacity for cytokine production, and the term "autoimmune epithelitis" was proposed (19). In the context of SS, Epstein Barr, HTLV-1, Hepatitis-C and enteroviruses have been previously proposed as potential initiating factors of the SS

I. Ocular Symptoms (at least one) <ul style="list-style-type: none">- Dry eyes >3 months?- Foreign body sensation in the eyes?- Use of artificial tears >3x per day?
II. Oral Symptoms (at least one) <ul style="list-style-type: none">- Dry mouth >3 months?- Recurrent or persistently swollen salivary glands?- Need liquids to swallow dry foods?
III. Ocular Signs (at least one) <ul style="list-style-type: none">- Schirmer's test, (without anesthesia) ≤5 mm/5 minutes- Positive vital dye staining (van Bijsterveld ≥4)
IV. Histopathology Lip biopsy showing focal lymphocytic sialoadenitis <ul style="list-style-type: none">- focus score ≥1 per 4 mm²)²
V. Oral Signs (at least one) <ul style="list-style-type: none">- Unstimulated whole salivary flow (≤1.5 mL in 15 minutes)- Abnormal parotid sialography³- Abnormal salivary scintigraphy⁴
VI. Autoantibodies (at least one) <ul style="list-style-type: none">- Anti-SSA (Ro) or Anti-SSB (La)
For a primary Sjögren's syndrome diagnosis: <ul style="list-style-type: none">a. Any 4 of the 6 criteria, must include either item IV (Histopathology) or VI (Autoantibodies)b. Any 3 of the 4 objective criteria (III, IV, V, VI)
For a secondary Sjögren's syndrome diagnosis: <p>In patients with another well-defined major connective tissue disease, the presence of one symptom (I or II) plus 2 of the 3 objective criteria (III, IV and V) is indicative of secondary SS.</p>
Exclusion Criteria <p>Past head and neck radiation treatment Hepatitis C infection Acquired immunodeficiency syndrome (AIDS) Pre-existing lymphoma Sarcoidosis Graft versus host disease Current use of anticholinergic drugs</p>

Table 1. American-European Consensus Classification Criteria accepted by Sjögren's Syndrome Foundation (9-12)

(16, 20) However, the mechanisms that account for the epithelial activation remain still unclear (16). Recent data suggest the central role of the type I interferon (IFN) system in the pathogenesis of many autoimmune disorders including SS (16).

A genetic predisposition to SS has been suggested because of multiple reports of two or more members of the same family developing the syndrome (21). A family history of the disease puts people at an increased risk of developing SS compared to the general population (22). This is also supported by the development of SS in twins (22). A genetic

susceptibility may be required for the development of autoantibodies which are found in SS (22) and this may be associated with a link between polymorphic major histocompatibility complex (MHC) genes and the development of autoimmune diseases (21).

High cDNA levels in patients with SS may result with a disease at worst prognosis which should the clinician let to follow-up the patients with SS both, clinically and serologically (23). The study of Alevizos *et al.* revealed that microRNA are promising candidate biomarkers of inflammation and salivary gland dysfunction in patients with SS (24). Further exploration of the predicted pathways associated with decreased salivary flow in this study will provide insight into the pathophysiology of SS and may identify novel therapeutic targets (24-25).

1.5 Complications

SS systemic disease may affect many other body systems. The most serious complication of SS could be accepted as the increased incidence of malignant lymphoma (26). This phenomenon was first reported in patients with SS in 1963 (26) and has been shown to be 44 times higher than the general population in some studies (27). Additionally, multiple case reports supported the association of lymphoma with Sjögren syndrome and stressed lymphoma as the major complication in the progression of the disease (28, 29). When it occurs, patients with SS are accepted as they are in stage 3 who consist of %5 of the general SS population.

Severael studies have shown different involvements in patients with SS such as hematological system, respiratory system, cardiac, liver, pancreatic, renal, thyroid and finally exocrine glands involvements. Bayetto and Logan have summerized extraglandular manifestations of SS in a table perfectly (Table 2) (27, 57).

Malaise Peripheral neuropathy Primary biliary cirrhosis
Fatigue Autoimmune thyroiditis GI symptoms
Fibromyalgia Renal tubular acidosis Respiratory diseases
Fever Myositis Psychosis
Arthralgia Chronic hepatitis Lymphadenopathy
Synovitis Purpura Splenomegaly
Raynaud’s phenomenon Vasculitis Lymphoma

Table 2. Symptoms associated with extraglandular manifestations of Sjögren’s syndrome by (27, 57)

Briefly, leucopenia (approximately 45% of all SS cases), thrombocytopenia (approximately 25% of all SS cases), hemolytic anemia (approximately 5% of all SS cases) and lower thrombopoietin levels (approximately 20% of all SS cases) are accepted as hematological system involvement of the disease. Respiratory system involvement of the disease reveals interstitial lung disease (approximately 20% of all SS cases), pulmonary hypertension (approximately 12% of all SS cases) and multiple nodules (approximately 5% of all SS cases). pericardial effusion (approximately 15% of all SS cases) and atrioventricular conduction block (approximately 5% of all SS cases) are the cardiac complications of the disease. The liver damage could be seen almost one third of the patients with SS. Likewise approximately

one third of the patients with SS revealed hepatosplenomegaly. Elevated gamma-glutamyl transpeptidase, alanine transferase and alkaline phosphatase levels are seen approximately in one fifth of the patients with SS. Renal involvement in SS are relatively common. Proteinuria (approximately 20% of all SS cases), Renal tubular acidosis (approximately 15% of all SS cases) and kidney stones and/or renal calcification (approximately 10% of all SS cases) are the most important renal complications of the disease. Thyroid disorders are also common among the patients with SS (33% of all cases). Abnormal thyroid function was seen in one fourth of the whole SS population (30).

1.6 Pediatric cases

SS is very rare in childhood and is frequently undiagnosed (31). Literature search revealed 200 pediatric cases of SS. The most important clinical manifestations in children with SS is the recurrent parotid swelling (31). Pathologic and laboratory findings are similar to those found in adults, with characteristic lymphocytic infiltration of exocrine glands, the presence of hypergammaglobulinemia, elevated erythrocyte sedimentation rate, and positive anti-SS antigen A, anti-SS antigen B, antinuclear antibody, and rheumatoid factor (32-34). Inflammation characterized by recurrent episodes of painful unilateral or bilateral parotid enlargement associated with swelling, fever, redness, and reduction in salivary flow (35-39).

1.7 Management

Sicca symptoms of the disease could be treated by using topical agents whereas extraglandular features are managed with glucocorticoids and immunosuppressive drugs (40). But, literature search revealed no evidence based therapeutic guidelines for the management of primary Sjögren syndrome which is also universally accepted (41). The results of one excellent systematic review about the treatment of SS shows that B cell targeted agents seem to be the most promising future therapy, especially rituximab, which has been used in more than 100 reported cases. Agents that block B cell-activating factor of the tumor necrosis factor family may also be a promising therapy (41, 42). Advances in knowledge of the molecular mechanisms involved in the etiopathogenesis of Sjögren's syndrome may allow the development of more effective, highly selective therapies without the adverse effects often associated with standard, less-selective drugs (41). Today, current treatment options are decided upon a mix of personal experience, expert opinion, and reported studies (41).

2. Oral aspects of Sjögren's syndrome

2.1 Saliva, glandular involvement, xerostomia and treatment

2.1.1 Saliva

Saliva is secreted from three major paired glands which are parotid, submandibular and sublingual glands and from hundreds of minor salivary glands which are localized over most parts of the oral mucosa (43). About 90% of mixed saliva is derived from three pairs of major salivary glands (parotid, submandibular and sublingual) and the remaining 10% is from numerous minor salivary glands distributed in the oral mucosa (43). In healthy humans, the daily production of whole saliva (mixed saliva) normally ranges from 0.5 to 1.5 L (43).

The salivary secretion is mainly induced during eating (43). Stimulated saliva which is also called as reflex salivation helps the chewing of food, formation and swallowing of a food bolus and digestion of starch and lipids (43). Saliva takes also part in the detection of food taste through the diffusion of taste substances to taste receptors, chemical interaction with taste substances and changes in the sensitivity of taste receptors (43). On the other hand, resting saliva, which is a lesser amount of saliva, covers the surface of the oral and pharyngeal cavities (43). When compared to the stimulated saliva resting saliva is accepted as more important in the maintenance of oral health (43). Protection properties against bacteria / - viruses / fungi are based on the salivary anti-microbial action [such as lysozyme, peroxidase, secretory immunoglobulin A (IgA) and histatins] and also on adhesion (mucins) and rinsing properties (43). Saliva is also responsible by taking part in speech, denture holding, anticaries activity, controlling breath odour and maintaining the integrity of oral and gastrointestinal mucosa (43).

Acinar cells produce saliva at first (43). Two types of these cells have been detected: serous and mucous cells (43). The parotid gland has serous acinar cells and secretes a thin, watery and amylase-rich saliva through its main excretory duct which is called as Stenson ductus; it opens onto the buccal mucosa near the upper molar teeth (43). The submandibular gland produces a more viscous and mucin-rich saliva and it consists of serous and mucous acinar cells whereas the sublingual gland has mucous acinar cells and also produces a viscous mucin rich saliva (43).

The sympathetic and parasympathetic autonomic nervous systems control mainly the salivary secretion (44). The sympathetic nerve is mainly responsible for the secretion of proteins accompanied by exocytosis in acinar cells, while the parasympathetic nerve is mainly responsible for the secretion of water and electrolytes (44). These are adequate stimuli for salivation, and secreted saliva is called stimulated saliva (43). Saliva secreted in the absence of apparent sensory stimuli related to eating refers to resting or unstimulated saliva (43). This saliva may have two components; one is spontaneous secretion, which is the continuous production of small amounts of saliva without any extraneous stimuli (43). There are prominent differences between stimulated and resting salivary secretions in their flow rate and viscosity (43). The flow rate of resting whole saliva is far less than that of stimulated whole saliva, whereas the viscosity of resting whole saliva is 2–3 times that of stimulated whole saliva in healthy adults which implies that resting whole saliva is rich in mucins mainly secreted by sublingual, submandibular and palatal glands (45). Resting whole saliva contains a higher concentration of high-molecular-weight mucin (MG1) than stimulated whole saliva, whereas low-molecular weight mucin (MG2) shows similar concentrations under resting and stimulated conditions (46).

One of two main roles of saliva in taste perception is the relatively short-term effect of saliva seen in the initial processes of taste perception (47). Taste substances should be dissolved in the salivary fluid layer to reach and stimulate taste receptors (43). The solubilization of taste substances in saliva, the chemical interaction between taste substances and salivary compositions, and the diffusion and dilution of taste substances in saliva are the ones which are responsible (43). Additionally, some components which can also stimulate taste receptors and / or change taste sensitivity by chemical interaction with the receptor are contained in the saliva (43). One other long-term effect of saliva is maintaining the health and function of the taste receptor site (43).

2.1.2 Glandular involvement

Garcio-Carrasco *et al.* summarized the mechanism of gland-induced dysfunction in primary SS in their excellent review article (Figure 2) (58).

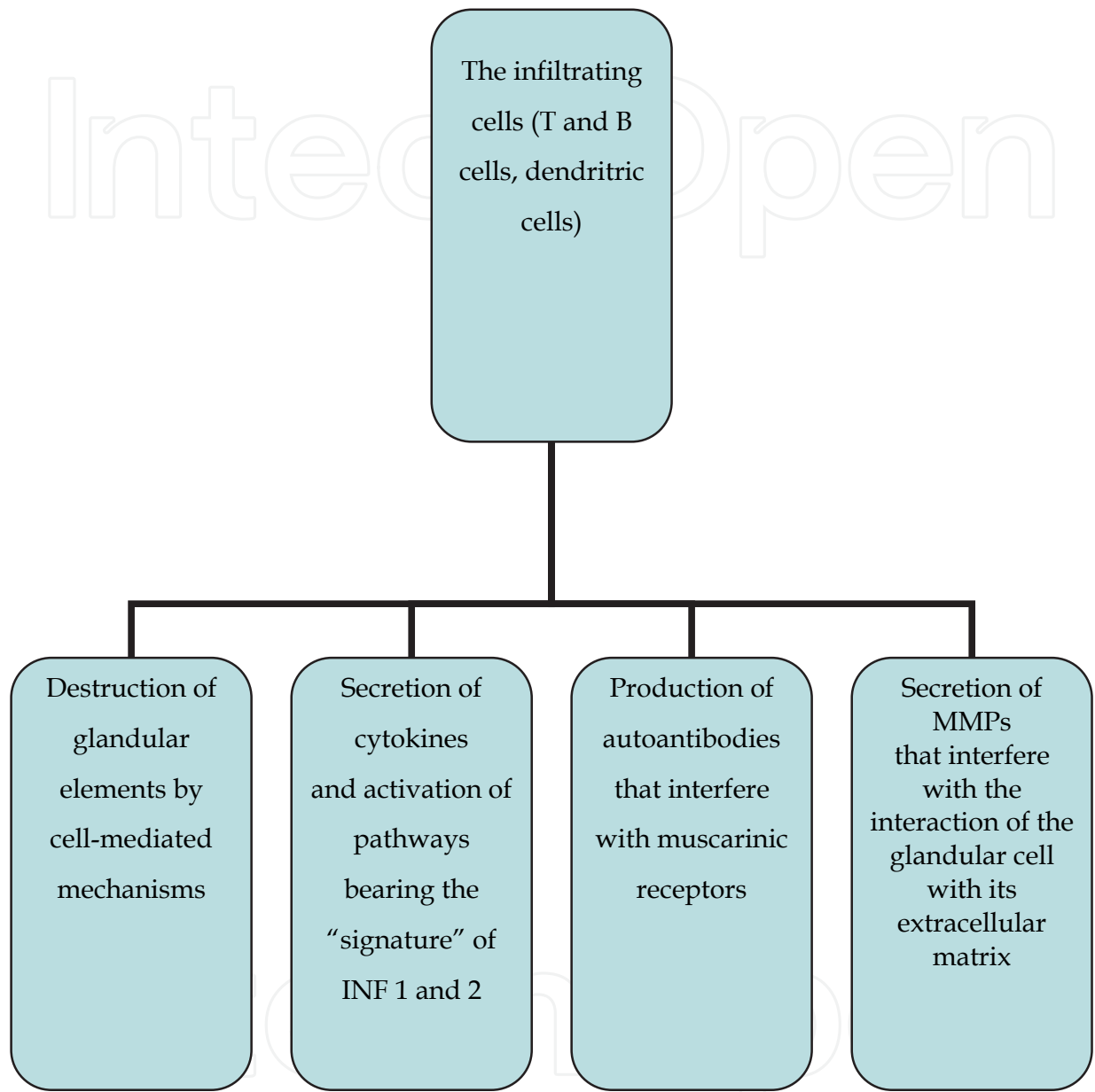


Fig. 2. Main mechanisms of gland-induced dysfunction in pSS. INF, interferon; MMP, metalloproteinase (58).

2.1.3 Xerostomia & treatment

Xerostomia is defined as a subjective complaint of dry mouth that may result from deficient production of saliva (48). Xerostomic patients complain mostly about burning mouth, loss of taste, difficulty in swallowing, unpleasant taste and odor, oral dryness, increased thirst, chewing, speaking, gastroesophageal reflux, oral breathing, malfunction of removable prosthesis and sensitive teeth (49-54). Allec *et al.* concluded in their prospective cross-

sectional descriptive observational study that patients with SS have voice, speech and swallowing abnormalities, not only associated with xerosis but perhaps also to neurological abnormalities, probably secondary to the syndrome (55). On the other hand, subjective xerostomia has been reported in higher percentages (75.18% to 91.84%) in patients with SS (56). In addition to that, Skopouli *et al.* showed that the rate of dry mouth increased from 41% of patients at initial diagnosis to 84% 10 years after diagnosis (57). Salivary gland dysfunction appears due to progressing lymphocytic infiltration in salivary acini, which in turn leads to inflammatory reaction causing acinar atrophy and proliferation of connective tissue (58). Sometimes such pathological changes originate in the minor salivary glands and may result in early symptoms of xerostomia, which are less intense than those in cases when the major salivary glands are affected (48).

Alcohol and smoking should be avoided and thorough oral hygiene is essential (40, 59). Saliva replacement products and sugarfree chewing gums may be effective for mild to moderate dry mouth (41). Oral pilocarpine and cevimeline are the treatment of choice for patients with SS (41). The doses that best balance efficacy and adverse effects are reported to be 5 mg every 6 hours for pilocarpine and 30 mg every 8 hours for cevimeline (41). In patients with contraindications or intolerance to muscarinic agonists, N-acetylcysteine may be an alternative (41).

2.2 Risk of dental caries and erosions & treatment

2.2.1 Risk of dental caries and erosions

The reduced salivary flow and its altered composition influence the bacterial clearance in the oral cavity as well as the accumulation of dental plaque on teeth surfaces (60). In addition to that, the saliva loses its ability to buffer, lubricate, and perform antimicrobial duties which leads to an increase in mucosal friability and oral infection (61). Increased incidence of cervical, incisal, decays in cusps tips and root caries has been reported in patients with SS as a major dental problem (62). These types of decays are accepted as atypical or unusual dental decays. This is constant demineralization, a rapidly progressing (rampant) and aggressive form of dental decay (43).

Mathews *et al.* mentioned in their excellent review article named 'Oral manifestations of Sjögren's syndrome' that dental plaque, consisting of more than 500 species of bacteria in a mature state, is a complex biofilm of microbes that adheres to the surfaces of teeth and provides a reservoir for oral microbial pathogens (61, 63, 64). Sjögren's syndrome increases a person's likelihood of contracting opportunistic infections and the proliferation of cariogenic micro-organisms (61, 65). Pederson *et al.* have reported that persons with primary Sjögren's syndrome have lower numbers of periopathogenic microorganisms and higher numbers of cariogenic and acidophilic micro-organisms in comparison with those found in control individuals (61, 66). Pederson *et al.* concluded in another study that patients with a labial salivary gland biopsy focus score of one or more (as per the American-European Classification Criteria) or the presence of Ro/SSA and La/SSB antibodies in serum, had a significantly higher DMFT/DMFS score than patients without these two factors (67).

Boutsi *et al.* mentioned in their study investigating dental and periodontal status of patients with SS that the number of cervical decay lesions correlated negatively with the salivary flow (56). It is known that because of reduced salivary flow, bacterial plaque accumulates

more rapidly on the tooth surface and especially at the marginal gingiva and crevicular areas which results in a higher prevalence of cervical caries (56). In patients with SS, an increased number of decayed and filled teeth surfaces have been referred previously by several investigators (62, 68). The very low salivary secretion rates, the decreased buffering effect and neutralization of bacterial acids as well as the high counts of lactobacilli and streptococci found in patients with SS, may be responsible for this effect (69). It is interesting that in their study, the number of cervical decay lesions correlated negatively with the salivary flow, while the number of distal or mesial decay lesions correlated negatively with age (56). It seems that the lack of salivary flow affects more extensively the cervical surfaces of the teeth, and predisposes them to a more rapid development of caries (56).

2.2.2 Treatment

Mese and Matsua stressed that patients should be advised to maintain impeccable hygiene, schedule frequent examinations and use topical fluoride regimens (43). The choice of the fluoride-delivery system varies with the clinical need and patient compliance (43). Common sources of fluoride in toothpaste are sodium monofluorophosphate and sodium fluoride (70-72). But Mathews *et al* reported that even with excellent oral hygiene, individuals with Sjögren's syndrome have elevated levels of dental caries, along with the loss of many teeth early in the disease (61). Pedersen *et al.* reported that persons who brushed their teeth with toothpaste containing fluoride and visited their dentist more frequently still had higher numbers of missing, filled, and decayed teeth, along with a higher gingival index (66).

2.3 Periodontal status & treatment

2.3.1 Periodontal status

The reduced salivary flow and its altered composition influence the bacterial clearance in the oral cavity, as well as the increased accumulation of dental plaque on tooth surfaces. Studies have demonstrated a higher gingival bleeding and plaque index in subjects with hyposalivation but without shown a correlation between salivary flow rate and gingival bleeding index or plaque index (73, 74).

Few studies have managed to report an increased risk of periodontal disease in Sjögren's syndrome (75-77). Ergun *et al.* had summarised the studies that evaluated the periodontal status of the patients with Sjögren's syndrome (78) (Table 3).

Number of the teeth (NT), bleeding on probing (BOP) (expressed as the % of sites which bled upon gentle probing), approximal plaque index (API) (expressed as the % of sites which presented plaque), probing pocket depth (PPD) were used in studies evaluating the periodontal status of patients with SS since they are easy to perform and produced adequate results for this kind of evaluation (78). Ergun *et al.* found out a significant difference between patients with SS and healthy controls in regard to API and BOP (78). This result is in agreement with the studies which have found that the API, PPD and BOP are significantly higher in SS patients than healthy subjects (75-77, 79). Other studies, however, have shown that SS patients are not at higher risk of having periodontitis (56, 79-83).

It is well known that BOP is strongly correlated to API and both are correlated with tooth brushing efficiency (84). Ergun *et al* concluded that as there was no statistically significant

Author	Study group(s)	Control group(s)	Difference in approximal plaque index (API)	Difference in bleeding on probing (BOP)	Difference in periodontal probing depth (PPD)	Difference in attachment loss	Difference in supragingival calculus	Difference in subgingival calculus	Difference in alveolar bone loss	Difference in GCF volume	Difference in DMF-T	Conclusion: Higher risk of having periodontitis ?
Tseng (1991)	SS (n=14)	HS (n=14)	NS	NS	NS	NS	NS	NS	-	-	S	No
Celenligil et al (1994)	SS (n=17)	HS (n=14)	S	S	S	-	-	-	-	-	S (missing)	Yes
Najera et al (1997)	SS-1 (n=23) SS-2 (n=2)	HS (n=24)	S	NS	NS	S	-	-	S	-	S	Yes
Ravald and List (1998)	SS-1 (n=22)	HS (n=21)	NS	NS	NS	NS	-	-	-	-	S (decay)	No
Pedersen et al (1999)	SS-1 (n=16)	HS (n=13)	NS	NS	NS	-	-	-	-	-	S	No
Boutsi et al (1999)	SS-1 (n=8) SS-2 (n=16)	Patients with other autoimmune diseases (n=27) HS (n=29)	NS	NS	NS	NS	-	-	-	-	NS	No
Schiodt et al (2001)	SS-1 (n=57)	HS (n=75)	-	NS	NS	-	S	NS	-	-	-	No
Kuru et al (2002)	SS-1 (n=8) SS-2 (n=10)	HS (n=11)	NS	NS	NS	NS	-	-	-	-	-	No
Jorkjend et al (2003)	SS-2 (n=33)	HS (n=33)	-	-	-	S (mandibular teeth)	-	-	-	-	S (teeth) NS (fillings)	No
Leung et al (2004)	SS-1 (n=26) SS-2 (n=25)	HS (n=29)	-	-	-	-	-	-	-	-	S	-
Rhodus et al (2005)	SS-1 (n=10)	HS (n=10)	S	NS	NS	S	-	-	-	S	-	No (but more gingival recession)
Pers et al (2005)	SS-1 (n=9)	Patients with xerostomia (n=15) and with periodontal disease (n=10)	NS	NS	NS	-	-	-	-	-	NS	-
Marton et al (2006)	SS-1 (n=38)	HS (n=34)	-	S	S	-	-	-	-	-	S	Yes

Table 3. Studies which evaluated the periodontal status of the patients with Sjögren’s syndrome (GCF: gingival crevicular fluid, DMF-T: decayed, missing, and filled permanent teeth, HS: healthy subjects, S: statistical significant; NS: not statistical significant) (78).

difference between patients with SS and healthy controls regarding to their tooth brushing habits (p>0.05) it can be concluded that the significant difference in terms of API could have been occurred due to the low SFR levels of the subjects participated in the study group

which is in agreement with Marton *et al.* (75, 78). Their results indicate that patients with SS carry a higher risk of having periodontitis.

There is a limited number of the studies regarding evaluation of the periodontal status of the subgroups of SS patients in terms of plaque accumulation, gingival inflammation and pocket depth. Most of these studies did not find a statistically significant difference between primary and secondary SS patients in terms of their periodontal status (56, 75, 82, 83, 85, 86). Najera *et al.* (77) found a significant difference in plaque index, but they did not find a statistically significant difference in gingival bleeding and periodontal pocket depth between SS-1 and SS-2 patients. The lack of difference in periodontal status between SS-1 and SS-2 subjects may indicate that both types of SS do not play significant role in periodontal status (66, 78, 80).

2.3.2 Treatment

As mentioned before, the treatment of SS is palliative and turns to the xerostomia related complications. One of these is the increased periodontal damage seen in patients with SS as accepted as some authors who found out possible correlations between the disease and the periodontal status of this type of patients. The aim is to maintain impeccable hygiene by having regular follow-ups, teaching oral hygiene instructions and some topical applications. The treatment should be conservative aiming to reduce the bacterial clearance in the oral cavity, as well as the accumulation of dental plaque on tooth surfaces.

2.4 Oral mucosal lesions

Oral health status of patients with SS has been investigated in many studies, previously (56, 75, 87-91). Subjective xerostomia has been reported in higher percentages (75.18% to 91.84%) in the patients with SS (56, 75, 88, 91). Additional dryness-related signs in patients with SS are angular cheilitis, redness of the tongue, atrophy of filiform papillae (Figure 3 and 4), erythematous buccal mucosa (Figure 5), hardpalate and softpalate, difficulties and pain on swallowing, burning syndrome, sensitivity to acid and/or spicy food, dysgeusia and bitter taste (8, 87-93). Most of the subjective symptoms such as dry mouth feeling and dysphagia have been reported to be in direct correlation with the decreased salivary flow rate which could also affect the sensory process of swallowing that leads to pain and difficulties on swallowing (73, 94).

Ergun *et al* have shown that oral objective and subjective signs on oral clinical examination are very common among patients with SS regardless its type. Similarly, a recent study demonstrated that oral health related quality of life was poor in patients with SS (95). The reason why dysgeusia was a common subjective symptom of SS-2 when compared with that of SS-1, could be related to the use of D-penicillamine which has found as common drug-therapy for patients with RA. Dysgeusia was reported to be seen as a frequent problem of patients using D-penicillamine (96).

Ergun *et al* have shown that oral examination of the patients with SS revealed no statistically significant difference between SS-1 and SS-2 patients in regard to presence of angular stomatitis, oral ulcerations, atrophic, reddened and dry mucosa, dysgeusia and atrophy of filiform papilla (78). Similar percentage of the two subgroups of SS complained about



Fig. 3. Atrophy of filiform papillae



Fig. 4. Redness of the tongue

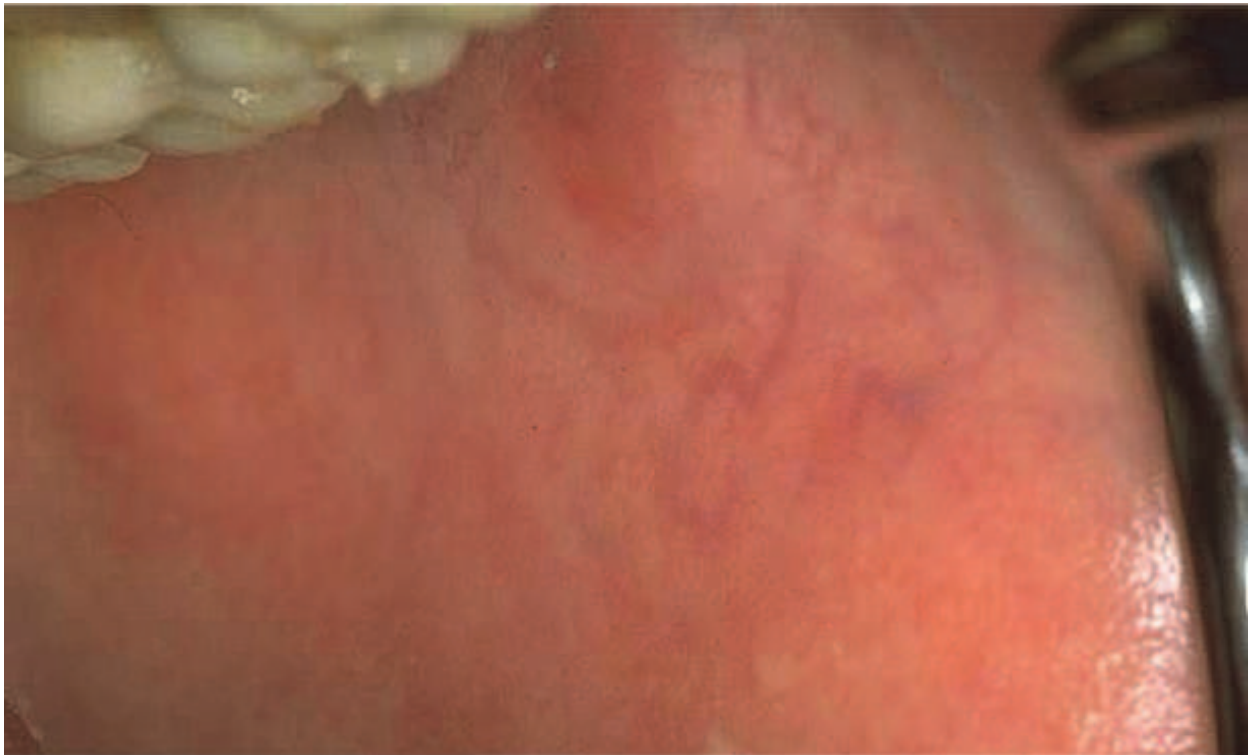


Fig. 5. Erythematous buccal mucosa

subjective xerostomia, burning sensation, pain on swallowing and hypersensitivity. They observed significant differences between patients with SS and healthy subjects in terms of the clinical oral findings associated with SS (Table 4).

	SS (n=37) N, %,	HS (n=37) N, %,	p
Angular Chelitis	8 (21.62%)	0 (0%)	0.005 (S)
Oral Ulcerations	13 (35.13%)	0 (0%)	0.0001 (S)
Atrophic Mucosa	28 (75.67%)	3 (8.10%)	0.0001 (S)
Dry Mucosa	23 (62.16%)	1 (2.70%)	0.0001 (S)
Reddened Mucosa	23 (62.16%)	5 (13.51%)	0.0001 (S)
Atrophy of Filiform Papilla	18 (48.65%)	4 (10.81%)	0.001 (S)
Xerostomia	32 (86.49%)	5 (13.51%)	0.0001 (S)
Burning Sensation	29 (78.38%)	5 (13.51%)	0.0001 (S)
Pain on Swallowing	23 (62.16%)	4 (10.81%)	0.0001 (S)
Dysgeusia	30 (81.08%)	3 (8.10%)	0.0001 (S)
Hypersensitivity	22 (59.46%)	0 (0%)	0.0001 (S)

Table 4. Positive objective and subjective signs on oral clinical examination of the patients with SS (78)

2.5 Oral flora & treatment

2.5.1 Oral flora

A continuous flow of saliva is important in preventing oral colonization by *Candida*, as the constant flushing action of saliva may remove the unattached or loosely attached *Candida* from the oral cavity (86). It has been shown that high *Candida albicans* counts in saliva are associated with clinical signs of candidiasis (97). Also there has also been shown an inverse association between salivary flow rate and *C. albicans* counts in saliva (98-100). Various investigators have reported a high prevalence of oral *Candida* species in patients with SS when compared with those of healthy controls (90, 101-104), while others have found that there is no significant difference between patients with SS and healthy controls in terms of presence of candidiasis (86, 101). Most reports indicate that *C. albicans* is the predominant yeast isolated in gingival crevicular fluid and in periodontal pockets of the periodontal patients as well as in healthy subjects, although *Candida glabrata* and *Candida tropicalis* have also been found, albeit infrequently (33, 86, 100, 102, 104). Additionally, one study showed that *C. albicans* was detected in gingival crevicular fluid at one measurement site in one of the SS-1 subjects but not in the control group (79).

Saliva has antibacterial, remineralizing, digestive, soft tissue reparative, lubricative, buffering, and cleansing properties. Therefore, decreased saliva production, which occurs in SS, can directly contribute to the oral and dental complications experienced by these patients. An inverse relationship between salivary flow rates and the level of *Candida* infection has been described, previously (86). Additionally, infection by *C. albicans* has been reported more frequently in individuals with SS than in the general population (87). While an even higher proportion of the total population (up to 60%) carry *C. albicans* in their mouths without clinical symptoms. The amount of the candidal load is important for development of candidiasis (105). As the quantification is essential for candidal assessment, we have detected the salivary *Candida* levels of the study population. Ergun *et al* have found out that *Candida* counts in saliva were statistically higher either in SS-1 or SS-2 patients as compared with that of the healthy control, which is in agreement with the results of other similar studies (78, 89, 99).

For successful colonization and infection, adhesion to oral surfaces is necessity. *C. albicans* can adhere to epithelial cells of buccal mucosa, the tongue, tooth surfaces, various oral prostheses such as dentures, and other oral micro-organisms that have already colonized these surfaces. Clinically, *C. albicans* can be cultured from swabs of the buccal mucosa, tongue, teeth, denture surfaces, and dental plaque samples. The flushing effect of saliva and anti-candidal salivary components such as lysozyme, histatins, lactoferrin, and calprotectin are the innate host defenses which act to remove or kill invading yeasts (106). The decreased salivary flow means the decreased host defense. Ergun *et al.* showed that candidal colonization on the buccal epithelial and the dorsal tongue was found to be in higher in SS patients than in healthy controls. In colonized individuals with no clinical symptoms of candidiasis, *C. albicans* is most frequently found on the dorsum of the tongue. Although Almståhl & Wikström (107) did not find an increase of frequency of *Candida* in subjects with hyposalivation, those authors did not analyse *Candida* colonization on the tongue's dorsal surface, which is the main ecological niche for *Candida* in the oral cavity.

Denture wearing is one of the major predisposing factor in humans for oral candidiasis. In denture wearers, the fitting surface of the denture is the main reservoir of the yeasts (108). Angular cheilitis is commonly associated with denture-induced stomatitis. Ergun *et al.* stressed that no statistically significant difference was found between SS and healthy subjects on the prevalence of *C. albicans* colonization on dentures, palatal and angular areas who use dentures with similar cleaning habits. Absence of normal salivary flow results with candidal colonization on the denture surfaces, palatal mucosa and angular area in denture wearers even with normal or decreased salivary flow rate.

As there is limited findings in healthy subjects, yeasts especially *C. albicans* have been recovered from periodontal pockets of patients with chronic periodontitis in different rates (7.1-19.6%) (104, 109-112). Brill considered gingival crevicular fluid a transudate, a passage of fluid from bloodstream (113). But it's also known that amount of gingival crevicular fluid increases with periodontal disease and decreases during health (114). According to Cimasoni, gingival crevicular fluid flow rate in slightly inflamed gingiva is about 0.1mg in 3 minutes, which leads us to think that gingival crevicular fluid renews itself continuously (115). Ergun *et al* concluded that population it is found that the subjects showed slight to moderate signs of inflammation (78). Finding only one subject (2.70%) in each group who has *C. albicans* colonization in the gingival crevicular fluid, might be because of this continuous flow despite high scores of positive *candida albicans* colonization in different areas of the mouth. Rhodus and Michalowicz (25) found almost the same result in their pilot study, in which they compared the periodontal status and prevalence of sulcular *C. albicans* between subjects with SS-1 and healthy control subjects.

Ergun *et al* have found out that there were direct correlations between positive *candida albicans* colonization on buccal area and dry mucosa, hypersensitivity and pain on swallowing with no specific reason (78). Additionally, they have shown a weak correlation between *Candida* carriage in saliva and pain on swallowing (78). Volter *et al.* and Logemann *et al.* reported that xerostomia affects the sensory process of swallowing (94, 116). It is well known that positive *Candida* carriage in saliva is mostly the result of the lower levels of salivary flow rate. From this available evidence, it can be assumed that difficulties and pain on swallowing could occur due to positive *Candida* carriage in saliva. But more studies with higher number of patients with SS are needed to confirm or refute this association.

2.5.2 Treatment

Reduced saliva predisposes patients to an overgrowth of *Candida albicans* (43). This may be augmented by the use of dentures, smoking and diabetes (43, 51). Recurrent oral candidiasis can be treated with topical anti-fungal medications. Oral rinses with anti-fungal medications such as nystatin and fluconazole are effective in the treatment of oral candidiasis and for relieving oral discomfort (43, 117, 118). Management of chronic erythematous candidiasis and angle cheilitis can be based on the prescription of nystatin in tablets or solution (100,000 IU 4-6 times a day), or miconazole gel 4 times a day (119). Removable dental prostheses should be treated separated by soaking in anti-fungal medication. Angular cheilitis can be treated with nystatin ointment or clotrimazole cream. Milillo *et al.* recently reported that 5% amorolfine anti-fungal varnish was effective for *Candida*-related denture stomatitis (120).

As mentioned before dentures may not be suitable for patients SS; however, dentures could be the only restorative choice (43). The tongue adheres to and dislodges the denture, causing decreased retention of partial and totally removable prosthesis and resulting in abrasions, sore spots, ulceration and irritation, all unpleasant and painful experiences for the patient (4, 43). Despite this, an implant-supported denture may be successful; however, the high cost of this denture could represent a problem for patients. If dryness is a continuous problem, the manufacture of dentures with reservoirs or chambers for artificial saliva is suggested for continuous delivery of saliva, although these dentures should not be worn during eating (43, 121-123).

3. References

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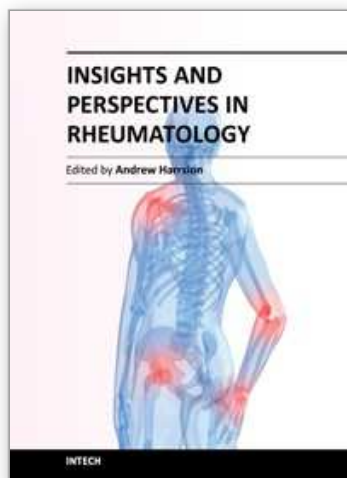
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This book offers a range of perspectives on pathogenesis, clinical features and treatment of different rheumatic diseases, with a particular focus on some of the interesting aspects of Sjögren's syndrome. It contains detailed and thorough reviews by international experts, with a diverse range of academic backgrounds. It will also serve as a useful source of information for anyone with a passive interest in rheumatology, from the genetic and molecular level, through to the psychological impact of pain and disability.

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