

Article

Co-Existence of Dry Mouth, Xerostomia, and Focal Lymphocytic Sialadenitis in Patients with Sjögren's Syndrome

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Abstract: Background: Some patients with Sjögren's syndrome (SS) do not develop xerostomia despite advanced involvement of the salivary glands and the presence of focal lymphocytic sialadenitis (FLS). The aim of the study is to determine possible correlations between xerostomia, symptoms of sicca syndrome, FLS, and other features in SS patients. Methods: The study group comprised 50 patients with SS. The comprehensive assessment of patients included clinical, laboratory, and serological examinations. All patients underwent labial salivary gland biopsies. Dry mouth and dry eyes were assessed by unstimulated whole salivary flow rate (USWSF) and Schirmer's test, respectively. Results: Xerostomia and xerophthalmia are closely related components of sicca syndrome. Xerostomia did not correlate with any serological or laboratory values, including ANA titers, SSA, SSB, Ro52 antibodies, rheumatoid factor, C-reactive protein, and Erythrocyte Sedimentation Rate. There were no correlations between xerostomia and FLS or Focus score. USWSF results correlated with xerostomia reported by patients, contrary to Schirmer's test, which did not correlate with xerophthalmia. Conclusions: Dry mouth in SS is independent of any serological or inflammatory parameters. The occurrence of FLS does not determine xerostomia and its severity. Dry mouth in SS is influenced by other undetermined factors and mechanisms independent of salivary gland involvement.

Keywords: Sjögren's syndrome; xerostomia; focal lymphocytic sialadenitis; labial salivary gland biopsy; sialometry



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1. Introduction

Sjögren's syndrome (SS) is a chronic autoimmune disease affecting exocrine glands such as the salivary and lacrimal glands. Although it can trigger systemic manifestations, its typical feature is a local predominance of symptoms limited to the salivary and lacrimal glands. SS is termed primary SS (pSS) if it occurs alone, and is not associated with other diseases or secondary SS (sSS) if it occurs in association with autoimmune connective tissue disorders such as rheumatoid arthritis, lupus erythematosus, and systemic sclerosis. Secondary SS coexists less frequently with multiple sclerosis and autoimmune hepatitis [1–4]. The term “secondary” does not refer to a chronological sequence of disease manifestations. Underlying connective tissue diseases may initially present with sicca symptoms and only later reveal themselves over the course of the disease. Therefore, differentiation between pSS and sSS is challenging in patients with overlapping disease entities [4]. One of the most common clinical complaints of SS patients is xerostomia and xerophthalmia. Both xerostomia and xerophthalmia result from decreased salivation and lacrimation [1,2]. However, xerostomia is a clinically broader and more comprehensive concept because it refers to the negative effects of decreased salivation and is usually chronic and persistent [5,6]. Xerostomia and hyposalivation are often treated as synonyms. However, xerostomia describes a more subjective experience of oral dryness. In turn, hyposalivation refers to objective confirmation of oral dryness [7]. Previous studies reported that at 50% of normal salivary function, even healthy individuals can experience xerostomia [7,8]. Xerostomia may also occur without a reduction in salivary flow resulting from a change in saliva composition.

Therefore, xerostomia may or may not be associated with salivary gland hypofunction. Sometimes, xerostomic complaints can be poor predictors of objective measures of salivary flow [7,8]. In the study conducted by Chávez et al., older adults including diabetic patients and healthy subjects with the lowest parotid saliva flow rates did not have more subjective xerostomic complaints than subjects with normal flow rates [8]. Their findings prove that reported oral dryness depends on an individual's sensitivity to changes in salivation, blood and nerve supply of salivary glands, and their inability to detect xerostomia and distribution of receptors in oral mucosa. Therefore, patients who cannot detect salivary hypofunction could be even more vulnerable to the adverse oral and systemic effects of diminished salivary flow. Oral dryness results from insufficient salivation or a complete lack of saliva. One of the most common examples of salivary gland malfunction resulting in xerostomia is hyposalivation induced by radiotherapy to the head and neck [5]. Radiotherapy to the head and neck irreversibly damages the glandular tissue of the salivary glands. Contrary to xerostomia induced by radiotherapy to the head and neck, some patients experience a subjective impression of oral dryness despite the normal secretory function of the salivary glands. Differences in xerostomia perception may result from various sources of dry mouth and other unidentified mechanisms of adaptation to dryness. Xerostomia may be observed in patients with autoimmune diseases. Possible consequences of impaired saliva secretion include dysphagia, decreased lubricative function of saliva, higher susceptibility to bacterial, fungal, and viral infections, mechanical irritations, and increased periodontitis. The lack of lubricative and protective salivary properties may lead to the development of oral mucosal lesions, including non-specific ulceration, cheilitis angularis, recurrent aphthous stomatitis, denture stomatitis, simple and exfoliative cheilitis, and aphthae [9,10]. Reduced saliva secretion is associated with a decreased amount of antibacterial, antiviral, and antifungal salivary proteins including histatins, defensins, cystatins, and mucins. Most of these proteins play overlapping antibacterial, antiviral, and antifungal functions. A lack of sufficient amount of these proteins that fight oral infections may lead to higher susceptibility to this kind of oral infection. One of the most common opportunistic infections in patients with dry mouth is oral candidiasis. Xerostomic patients are at higher risk for oral *Candida* growth than controls and are at higher risk for developing oral candidiasis than controls [11,12]. Patients with pSS presenting oral lesions have lower unstimulated and stimulated whole salivary flow rates than those without oral lesions [12]. Moreover, disturbed calcium-phosphate homeostasis and enamel demineralization resulting from decreased salivation cause increased caries rate [10]. The opposite salivary disturbance to xerostomia is sialorrhea defined as an increased amount of retained saliva in the oral cavity. It occurs either due to salivary overproduction or impaired clearance of saliva. Sialorrhea is commonly caused by swallowing impairment. It is a frequently reported non-motor symptom affecting 30–80% of patients with Parkinson's disease (PD) [13]. In these cases, there is a direct relationship between salivary gland malfunction and oral health. Moreover, chronic and persistent dry mouth significantly reduces patients' quality of life [14]. Unbearable dry mouth, especially at night, makes sleeping and resting difficult. The frequent occurrence of xerostomia in SS patients led to its inclusion in previous diagnostic criteria [15–17]. On the other hand, xerostomia was argued to be a subjective symptom and not included in the diagnostic criteria for SS. This realization has led to a gradual evolution of diagnostic criteria toward more objective symptoms and diagnostic tests. One such objective test for assessing salivation in current SS diagnostic criteria is sialometry in the form of the unstimulated whole salivary flow rate (USWSF) [17].

Another unresolved issue in SS is the source of hyposalivation. Traditionally, decreased saliva secretion in SS is attributed to morphological changes in the salivary glands resulting from the presence of lymphocytic infiltrations and severe fibrotic rebuilding. These morphological tissue changes are representative of all salivary glands, and their typical microscopic pattern in labial salivary glands, termed focal lymphocytic sialadenitis (FLS), is the basis for confirming histological SS and is one of the diagnostic criteria for SS.

FLS damages glandular tissue and results decreases saliva secretion [18,19]. Labial salivary gland biopsy sensitivity ranges from 79% to 91.4% and specificity from 81.8% to 100% [20].

However, there is no direct relationship between the severity and perception of xerostomia and the severity of morphological changes and inflammation of the salivary glands. Moreover, this does not consider other lesions such as acinar atrophy, epithelial cell proliferation, fibrosis, and small focal infiltrates [20]. Clinical observations have revealed that some SS patients present significant symptoms of xerostomia compared to a relatively low degree of inflammation in the salivary glands and tissue damage to a minor extent. Furthermore, some SS patients do not develop a more severe disease state or full-blown SS manifestation, only presenting symptoms of unbearable dry mouth [21]. In the previous study, some genes were recognized as responsible for differences in dry mouth severity in SS patients. Significant correlations were observed between Transmembrane P24 Trafficking Protein 10 (TMED10), Protein Disulfide Isomerase Family A Member 4 (PDIA4), and Calnexin (CANX) gene expression in SS patients suffering from sicca symptoms compared to controls. Among the genes changed in SS and responsible for saliva secretion, there is also a set of genes involved in ER function and the loss of cholinergic stimulation. It appears that xerostomia in SS has a multifactorial origin and may be independent of the tissue morphological changes in the salivary glands specific to SS [22]. Moreover, there is no consensus on the mutual occurrence of FLS, experienced xerostomia, real hyposalivation, and other phenotypic features specific to SS. For seronegative patients manifesting symptoms of sicca syndrome, detecting these correlations may help determine whether labial salivary gland biopsy is indicated.

The aim of the study was to find possible correlations between the existence of xerostomia, symptoms of sicca syndrome, FLS, and other phenotypic features in SS patients. It also explored the relationship between lymphocytic infiltration severity in salivary glands, as expressed by a focus score, and real saliva secretion assessed by sialometric tests.

2. Materials and Methods

The study group comprised 50 patients (female:male ratio 43:7, age range 30–82 years), who were diagnosed with primary Sjögren's syndrome (pSS) and met SS diagnostic criteria according to the 2016 American–European Consensus Group (AECG) [23–25]. Exclusion criteria included the presence of IgG4 syndrome, previous radiotherapy to the head and neck, lymphoma, sarcoidosis, graft-versus-host disease, and infections with hepatitis C virus, human T-lymphotropic virus type I, and HIV (Table 1). Current and former smokers were included in the sample group. Smoking was not an exclusion criterion.

Table 1. Inclusion and exclusion criteria.

Inclusion Criteria	Exclusion Criteria
Adult participants	IgG4 syndrome
Patients who signed the patient's consent	Previous radiotherapy to head and neck
Patients who meet SS diagnostic criteria of the 2016 AECG [23–25]	Lymphoma
	Sarcoidosis
	Graft versus host disease
	Hepatitis C virus
	Human T-lymphotropic virus type I
	HIV

Patients' comprehensive health assessment included a complete medical history and physical examination. Laboratory tests comprised routine blood count, erythrocyte sedimentation rate (ESR, Westergren method), C-reactive protein (CRP), rheumatoid factor (RF), and antinuclear antibody detection (ANA, Euroimmun, Medizinische Labordiagnostika AG, 23560 Lübeck, Germany) using a blot-type test (Euroimmun, Germany) in the case of ANA positivity. The reference ranges for standard values in our laboratory were

4×10^3 – $10 \times 10^3/\text{mm}^3$ for white blood cell count (WBC), less than 5 mg/L for CRP, and 1–10 mm/h for ESR. For dry eye assessment, Schirmer’s test was performed on all patients for both eyes simultaneously. Special paper strips were placed under the lower eyelids of each eye. After 5 min, the paper was removed and measured for moisture. Lacrimation in Schirmer’s test ≤ 5 mm in one eye was marked as a positive result [26]. All patients who reported xerostomia or xerophthalmia experienced daily sicca symptoms for longer than 3 months. Duration of dry mouth and dry eye was not considered in this study. Hyposalivation was assessed by an unstimulated whole salivary flow rate (USWSF). Volumes of ≤ 1.5 mL/15 min in USWSF were marked as abnormal saliva secretion and as a diagnostic criterion for hyposalivation [27]. USWSF lasting for 15 min was carried out 2 h after a meal based on a standardized collection procedure. Saliva sampling was performed in the morning between 9:00 and 11:00 in all patients. Saliva was collected in a graduated tube via a funnel every 2 min. Microscopic confirmation of SS was based on the presence of focal lymphocytic sialadenitis (FLS) in the labial salivary glands. Labial salivary gland biopsy was performed on all patients under local anesthesia from the lower lip at the level of the mandibular premolars as described [18,28–30]. Harvested labial salivary gland samples obtained by scalpel biopsy were fixed in 10% buffered formalin and assessed by the same pathologist. Besides confirming or excluding FLS in all labial salivary gland specimens, a focus score (FS) was conducted. An FS ≥ 1 per 4 mm² of glandular tissue was a microscopic confirmation of SS. FS was defined as a focus of 50 or more mononuclear cells adjacent to normal-appearing mucous acini in salivary gland lobules [18,28].

The protocol of this study was approved by the Institutional Review Board at Poznan University of Medical Sciences (number 403/17). Informed consent was obtained from all subjects before any study procedure was carried out. This study was performed in accordance with the ethical standards laid down in the appropriate version of the World Medical Association Declaration of Helsinki.

The calculations were carried out with Microsoft Excel 2016 and STATISTICA software (v.13 TIBCO, Palo Alto, CA, USA). Patients’ demographic data were analyzed using descriptive statistics. The Shapiro–Wilk test was used to assess the normal distribution of variables. To examine the differences between the two groups, if a normal distribution and equal variances were present, the Student’s *t*-test was used for unrelated samples. If the normal distribution was not present, the Mann–Whitney test was used. To compare sialometry between a large number of groups, the Kruskal–Wallis test was used due to the lack of a normal distribution. To examine the relationship between continuous variables, Spearman’s rank correlation coefficient (*R*_s) was used due to the lack of a normal distribution. The Chi-squared test of independence, Fisher’s exact test, or the Fisher–Freeman–Halton test were calculated for categorical variables. For qualitative variables, numbers (*n*) and proportions (%) were calculated and collected in cross tables. Categorical variables were presented in contingency tables. For normally distributed data, results were presented as mean $\pm$ standard deviation (SD), and non-normally distributed data were expressed as median (interquartile range, IQR). Differences were considered statistically significant at $p < 0.05$.

3. Results

The comprehensive demographic, laboratory, and clinical characteristics of SS patients are presented in Table 2.

Table 2. Demographic, clinical, and laboratory characteristics of SS patients.

Parameter	SS Criteria	Study Group (n = 50)
Age mean $\pm$ SD years		52 $\pm$ 10.86
Gender Female/Male, <i>n</i>		43/7
BMI median (IQR)		25.67 (8.36)
Disease duration, (range), years		(3 months–12 years)
<1 year, <i>n</i>		33
$\geq$ 1 year, <i>n</i>		17
Xerostomia, yes/no <i>n</i>		31/19
Xerophthalmia, yes/no <i>n</i>		31/19
Arthralgia, yes/no <i>n</i>		42/8
Arthritis yes/no <i>n</i>		13/37
Fatigue yes/no <i>n</i>		9/41
Laboratory tests:		
median (IQR)		
Erythrocyte Sedimentation Rate (mm/h)		16 (16)
CRP (mg/dL)		0.53 (2.95)
Anemia yes/no <i>n</i>		3/47
Leukopenia yes/no <i>n</i>		4/46
ANA positive, <i>n</i> (%):		36 (70)
+ (<1:160), <i>n</i>		10
++ (1:320), <i>n</i>		4
+++ (<1:320), <i>n</i>		22
ANA negative, <i>n</i> (%):		14 (30)
–(<1:160)		
	ANA profile, <i>n</i> (%):	
	anti-Ro/SSA antibodies, <i>n</i> (%)	27 (54)
	anti-Ro52 antibodies, <i>n</i> (%)	8 (16)
	anti-La/SSB antibodies, <i>n</i> (%)	9 (18)
Rheumatoid factor (RF) positive, <i>n</i> (%)		13 (26)
	Focal lymphocytic sialadenitis (FLS)	
	positive, <i>n</i> (%)	50 (100)
	Focus score (FS), <i>n</i> :	
	<0	3
	1	19
	2	11
	3	11
	4	6
	USWSF positive, <i>n</i> (%)	23 (46)
	median (IQR)	2 (2.5)
	Schirmer's test positive, <i>n</i> (%)	35 (70)
	Right eye median (IQR)	5 (7)
	Left eye median (IQR)	5 (7)
Organ involvement:		
Fever yes/no <i>n</i>		0/50
Skin involvement yes/no, <i>n</i>		14/36
Weight loss yes/no, <i>n</i>		1/49
Raynaud's phenomenon yes/no, <i>n</i>		1/49
Salivary gland inflammation yes/no, <i>n</i>		2/48

Data presented as the median (interquartile range), mean $\pm$ standard deviation (SD), or as *n* (%); BMI, body mass index; CRP, C-reactive protein; ANA, antinuclear antibodies; FS, focus score; USWSF; unstimulated whole salivary flow rate.

There were no correlations between xerostomia reported by patients and FS ($p = 0.87$) or between FS and USWSF results ($p = 0.85$). Positive USWSF results were correlated subjective xerostomia experience ($p = 0.00$). In turn, there were no statistically significant differences between Schirmer's test results and xerophthalmia ($p = 0.40$). Xerostomia in SS is independent of demographic features such as age and gender. Xerostomia did not depend

on the patient's age ($p = 0.08$) or gender ($p = 0.40$). There were no differences between FS and ESR or between FS and CRP ($p = 0.48$ and $p = 0.83$, respectively). Xerophthalmia did not correlate with the patient's age or gender ($p = 0.22$ and $p = 0.40$, respectively). Dry eye did not correlate with ESR or CRP ($p = 0.51$ and $p = 0.43$, respectively). There was a statistically significant correlation between xerophthalmia and USWSF results ($p = 0.02$). There was no difference in FS between SS patients with dry eye and those without dry eye ($p = 0.27$). There were no differences in clinical symptoms, laboratory values, or serological values between patients with dry eye and those without dry eye. The detailed comparison between SS patients with xerostomia and without xerostomia is presented in Table 3.

Table 3. Comparison between SS patients with xerostomia and without xerostomia.

Parameter	SS Patients with Xerostomia ($n = 31$)	SS Patients without Xerostomia ($n = 19$)	p Value
Age, mean	54.48	49.10	$p = 0.08^a$
Gender, n			
Female/Male	28/3	15/4	$p = 0.40^b$
BMI			
median (IQR)	23.74 (8.59)	27.34 (7.88)	$p = 0.03^c$
CRP (mg/dL)	0.76	0.48	$p = 0.37^c$
ESR (mm/h)	0.80	0.90	$p = 0.05^c$
RF positive, n	9	4	$p = 0.74^b$
USWSF			
median (IQR)	1 (2.5)	3 (3)	$p = 0.00^c$
FS:			
median (IQR)	2 (2)	2 (2)	$p = 0.87^c$
FS ≤ 1 , n	22	11	
FS < 2 , n	9	8	$p = 0.34^d$
Xerophthalmia, n	24	7	$p = 0.00^d$
Schirmer's test positive, n	22	13	$p = 0.84^d$
Arthralgia, n	25	17	$p = 0.69^b$
Arthritis, n	8	5	$p = 1.00^b$
Fatigue, n	4	5	$p = 0.27^b$
Skin involvement, n	9	5	$p = 1.00^b$
Leukopenia, n	3	1	$p = 1.00^b$
ANA positive, n :			
+ ($<1:160$), n	6	4	
++ ($1:320$), n	3	1	
+++ ($<1:320$), n	13	9	$p = 0.83^d$
ANA negative, n :			
−($<1:160$)	9	5	
ANA profile, n :			
anti-Ro/SSA antibodies, n	17	10	$p = 1.00^b$
anti-Ro52 antibodies, n	5	3	$p = 1.00^b$
anti-La/SSB antibodies, n	6	3	$p = 1.00^b$

Data presented as the median (interquartile range) (IQR), mean $\pm$ standard deviation (SD) or as number, n ; BMI, body mass index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; USWSF, unstimulated whole salivary flow rate; FS, focus score; ANA, antinuclear antibodies; ^a, Student's t -test; ^b, Fisher's exact test; ^c, Mann–Whitney U test; ^d, Chi² Pearson's test.

4. Discussion

Current SS diagnostic criteria are based on selected clinical, laboratory, and histopathological features. The co-existence of all symptoms attributed to SS is rare, causing the exclusion of some patients with sicca symptoms who do not meet the criteria for SS. This discrepancy between clinical and either laboratory or microscopic symptoms makes it difficult to introduce an effective treatment policy. Furthermore, there are no strict guidelines indicating when to refer patients for labial salivary gland biopsy. Therefore, finding possible correlations between phenotypic features specific to SS is crucial.

One of the most common clinical manifestations of SS is dry mouth and dry eyes. Some patients with sicca symptoms are seronegative with simultaneously positive results of labial salivary gland biopsy. In the study, xerostomia corresponded with positive USWSF results and xerophthalmia. This finding proves that USWSF is a reliable test for confirming hyposalivation and correctly identifying patients with symptoms of sicca syndrome. Patients with xerostomia reported xerophthalmia. The co-occurrence of dry mouth and dry eye is an SS-specific manifestation and a feature of sicca syndrome. On the other hand, contrary to USWSF, there were no differences in Schirmer's test between patients with and without xerostomia. Therefore, it appears that Schirmer's test cannot confirm xerophthalmia properly.

In the study, there was no difference in FLS and FS occurrence between SS patients with and without xerostomia. In previous studies, dry mouth was treated as a predictor of FLS on labial salivary gland biopsy. However, these studies revealed divergent results depending on disease suspicion. The results of salivary gland biopsy were significantly higher in patients for whom a biopsy was requested by internists or rheumatologists compared to other departments due to a stronger suspicion of SS [31]. The findings obtained in the present study are consistent with those shown by Ayesha et al., who revealed that abnormal biopsies were more frequent in SS patients with serologic abnormalities than in patients with sicca symptoms or systemic illnesses [31]. Similar results were obtained by Daniels et al., who found that $FS \geq 1$ was strongly associated with positive serum anti-SSA and anti-SSB but not with symptoms of dry mouth [32]. Patients with positive anti-SSA/SSB were nine times more likely to have an $FS \geq 1$ than $FS < 1$. Patients with USWSF < 0.1 mL/min were only twice as likely to have an $FS \geq 1$ than $FS < 1$. Moreover, only a diagnosis of FSL with $FS \geq 1$ was associated with the ocular and serological components of SS. $FS < 1$ reflected a similar correlation to the serological symptoms of SS as other types of sialadenitis, such as nonspecific chronic sialadenitis and sclerosing chronic sialadenitis [32]. Dry eye as a component of sicca syndrome was a stronger predictor of FLS and $FS \geq 1$ than dry mouth. These findings are consistent with previous results that FLS and FS did not influence xerostomia occurrence or its severity, as assessed by USWSF. Furthermore, this possible correlation must be explored separately in seronegative and seropositive SS patients. The main indication for labial salivary gland biopsy appears to be the occurrence of sicca syndrome in seronegative patients.

Similarly to serological and histopathological symptoms in SS, xerostomia did not correlate with other clinical or laboratory features. There were no statistically significant differences in positive RF, anemia, leukopenia, and clinical symptoms such as extraglandular manifestations, fatigue, and arthritis between SS patients with and without xerostomia. Previous studies showed divergent results related to the correlation between the coexistence of ANA positivity, FLS, and other phenotypic features in SS. According to Fauchais et al., a positive RF is more likely to be present in SS seropositive patients with FSL [33]. The co-occurrence of RF positivity, anti-SSA, and anti-SSB positivity is associated with a more active immunologic profile predisposed to systemic complications [34,35]. RF does not correlate with arthritis in SS patients. Previous studies revealed no correlation between elevated inflammatory markers, FLS, RF, or arthritis [31,36–38]. There was a group of SS patients with FLS and elevated inflammatory markers with negative RF and non-erosive inflammatory arthritis. In turn, there was a positive correlation between anti-CCP antibodies and arthritis in SS patients [36,37].

Although there were no statistically significant differences in ANA titer and seropositivity to SS-specific antibodies between patients with and without dry mouth, it proves that neither positive serology nor the presence of dry mouth predicts a positive labial salivary gland biopsy. However, previous studies found that sicca symptoms, ANA profile, and FSL must be included in comprehensive analysis. Ayesha et al. showed that among patients with FLS, seronegative patients had a significantly higher proportion of dry mouth than seropositive patients [31]. Furthermore, FSL and higher FS results more often correlate with serological components of SS, including positive anti-SSA/SSB, rheumatoid factor (RF)

serology, higher ANA titers, and IgG concentration than subjective and objective tests for diagnosing sicca syndrome [31,32]. This finding proves that FSL in salivary gland biopsy should not be treated as a synonym for xerostomia in SS. Other methods for defining the salivary component of SS and dry mouth must be introduced. These methods include defining whole salivary or parotid flow rates with and without stimulation, measuring technetium uptake and secretion with salivary scintigraphy, and ultrasound images of the salivary glands. Although FSL does not reflect xerostomia severity in SS, it appears that FSL and FS are good markers for assessing the autoimmune activity of salivary glands. Moreover, positivity to anti-SSA might differ from positivity to anti-SSB. It is postulated that patients with isolated anti-SSB antibodies form a different phenotype among SS patients characterized by more severe systemic manifestations [39]. Similar phenotypic differences were found for SS patients with both anti-Ro60 and anti-Ro52 co-occurrence and patients with anti-Ro60 alone and anti-Ro52 alone. Patients with both anti-Ro60 and anti-Ro52 had a significantly increased prevalence of FLS with $FS \geq 1$, $ANA \geq 1:320$, RF, and parotid gland ultrasound scores compared to patients with either anti-Ro60 or anti-Ro52 alone. Although these serologic profiles are predisposed to some phenotypic features of SS and are markers of glandular inflammation, there was no correlation between the anti-Ro60/Ro52 profile and dry mouth [40]. Contrary to these results, Yang et al. detected that SS patients with combined anti-Ro52 and anti-Ro60 antibodies were more likely to suffer from xerophthalmia and xerostomia than patients with isolated anti-Ro52 or anti-Ro60 antibodies. The proportion of patients with glandular involvement was significantly higher in patients with combined anti-Ro52 and anti-Ro60 antibodies than in patients with isolated anti-Ro60 antibodies [41,42]. However, after division into smaller serology subgroups, the small sample size may have prevented a possible correlation from being found between anti-SSA/SSB positivity and the occurrence of dry mouth.

Another research finding was the correlation between xerostomia and xerophthalmia. SS patients who reported dry mouth also complained of dry eyes. There was a statistically significant difference in xerophthalmia between SS patients with and without xerostomia. Although there was no difference in Schirmer's test between patients with and without xerostomia, it appears that both dry mouth and dry eye coexist and are components of sicca syndrome in SS patients. This finding is consistent with previous findings, which showed that xerostomia and dry eye symptoms are both relatively common in the older adult population. In addition, they are associated and moderately concurrent. Patients with symptomatic dry eye had higher Summated Xerostomia Inventory–Dutch Version scores than those without [43]. The routine evaluation of xerostomia symptoms should be part of the assessment of dry eye patients and vice versa [43]. Furthermore, parasympathetic drugs used to increase salivary secretion can improve lacrimal secretion and reduce overall symptoms of sicca syndrome [44]. This positive correlation is typical of exocrinopathies such as SS. The symptoms of ocular and oral sicca are closely related. A previous study conducted among patients with rheumatic diseases showed that the majority (85.7%) of xerostomic patients were also xerophthalmia positive [45].

Another possible explanation for the lack of correlations between FS and phenotypic features of SS and xerostomia is the modifying effect of tobacco smoking on focal lip sialadenitis [46,47]. Although previous studies revealed that present or past smoking does not disturb salivary gland function and does not change unstimulated or stimulated whole salivary flow, cigarette smoking is negatively associated with FLS and FS in SS patients. Cigarette smoking reduces glandular FS, and this correlation is dose-dependent. FS decreases with the number of cigarettes smoked per week [40]. Manthorpe et al. found that current smokers have a reduced frequency of abnormal FS in the labial salivary gland biopsy compared to patients who never smoked. The frequency of non-focal sialadenitis or normal biopsy findings is increased in smokers [47]. From this perspective, not considering smoking could have significantly impacted the final results of the study. These findings show that present and former cigarette smokers suffering from SS should not be referred for a labial salivary gland biopsy. Therefore, abnormal FS in present and former cigarette

smokers should be approached with great caution in SS diagnosis. This protective mechanism is observed in other immunological disorders such as ulcerative colitis, extrinsic alveolitis, aphthous stomatitis, and sarcoidosis [46,47]. Smoking protects against disease-associated humoral and cellular autoimmunity [46]. Moreover, Stone et al. showed that current smoking protects against SS classification, FLS, FS, and SS-specific autoantibodies, including SSA [46]. Smokers are less likely to present with FLS and $FS \geq 1$; they also have significantly more non-specific chronic inflammation. On the other hand, smoking does not affect saliva and tear production according to the USWSF and Schirmer's test, respectively. Its immunomodulatory function results in reduced organized lymphocytic infiltration of the salivary glands and a predominance of non-specific inflammation.

The limitations of this study are mainly due to the small sample size. The obtained findings should be verified in a larger SS population. In the study, a few patients suffered from other systemic diseases such as hypertension, hypothyroidism, hyperthyroidism, and depression. Among these systemic diseases, hypertension was the most common. Moreover, a few patients took methylprednisolone, non-steroidal anti-inflammatory drugs (NSAIDs), and immunosuppressive drugs. These drugs may influence CRP and ESR values as well as labial salivary gland biopsy results. The patients enrolled in the study were not taking any anticholinergic drugs, psychotropic, neuroleptic, or antihistamine drugs. However, a few patients took antihypertensive drugs. The drugs administered in hypertension therapy can reduce salivary secretion. Therefore, current and previous therapies, as well as co-existing diseases and therapies, may have interfered with the obtained results. Similarly, a few patients were either present or former cigarette smokers. There were distinct differences in the number of cigarettes smoked per week and per day. Therefore, cigarette smoking was not treated as an exclusion criterion in this study. Nevertheless, smoking can be considered a limitation of the study. Other limitations include the absence of assessment of oral mucosa condition and diagnosis of possible fungal infections in the oral cavity. Candidiasis and local oral inflammation can interfere with saliva secretion and worsen xerostomia. It appears that local bacterial and fungal infections should be considered significant factors associated with salivation.

5. Conclusions

Xerostomia severity is independent of morphological changes and inflammatory involvement in salivary glands typically seen in SS. Inflammation in salivary glands, reflected by FS, is an insufficient factor for inducing and worsening xerostomia in SS. Xerostomia and xerophthalmia are closely related conditions that are concurrent components of sicca syndrome. The lack of SS-specific antibodies in serologic examination is not an indication for labial salivary gland biopsy. Confirmation of FLS in labial salivary gland biopsy should be treated as a diagnostic criterion in comprehensive clinical, serological, and microscopic assessments.

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