

The assessment of hyposalivation and its impact on mouth disability in systemic sclerosis patients

Sistemik skleroz hastalarında hiposalivasyon ve hiposalivasyonun oral yetersizliğe olan etkisinin değerlendirilmesi

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Abstract

Objective: This study aimed to evaluate the reduction in salivary flow rate (SFR) and the effect of hyposalivation on mouth disability of SSC patients and to the relationship between Sjogren's syndrome (SS) related, SSC-related autoantibodies and hyposalivation in SSC patients

Methods: SSC patients who fulfilled American College of Rheumatology/European Alliance of Associations for Rheumatology 2013 criteria of SSC, were included in this cross-sectional study. Unstimulated whole SFR (UWSFR) was performed for the sialometric assessment. The mouth handicap in SSC (MHSS) scale was used for the evaluation of mouth disability.

Results: Seventy-two SSC patients (91.7% female) were included in the study. The mean age of patients was 52.2±13 years with 65.3% limited cutaneous SSC (lcSSc). Subjective xerostomia was presented in 44% of patients and reduced UWSFR (≤ 0.1 mL/min) was detected in 39% of patients. A significant difference was not displayed in terms of the presence of xerostomia and hyposalivation between lcSSc and diffuse cutaneous SSC (dcSSc) patients. Patients with hyposalivation had significantly higher MHSS total and subscale 2 scores compared to patients with normal SFR ($p=0.04$ and $p=0.01$, respectively). Decreased saliva production was related to the presence of dysphagia [odds ratio (OR): 2.86, 95% confidence interval (CI): 1.01-8.13; $p=0.045$], anti-Ro60/SSA autoantibody (OR: 3.7, 95% CI: 1.08-12.55; $p=0.036$), xerophthalmia symptom (OR: 4.3, 95% CI: 1.56-11.77; $p=0.005$), positive Schirmer's test (OR: 20.7, 95% CI: 6.02-71.08; $p<0.001$), higher MHSS total (OR: 1.05, 95% CI: 1.00-1.09; $p=0.043$), and higher MHSS domain 2 scores (OR: 1.13, 95% CI: 1.02-1.24; $p=0.02$).

Conclusion: Hyposalivation and xerostomia are commonly observed in SSC. Patients with hyposalivation had significantly higher mouth disability. The risk factors for hyposalivation in SSC were the presence of anti-Ro60/SSA autoantibody, dysphagia, subjective and objective xerophthalmia, higher MHSS total, and higher MHSS domain 2 scores.

Keywords: Disability, mouth, salivary flow rate, systemic sclerosis, xerostomia

Öz

Amaç: Bu çalışmanın amacı sistemik skleroz (SSc) hastalarında uyarılmamış tüm tükürük akış hızının (UWSFR) değerlendirilmesi, hiposalivasyonun ağız yetersizliği üzerine etkisini ve Sjögren sendromu (SS) ve SSc ilişkili antikörler ile azalmış tükürük miktarı arasındaki ilişkiyi değerlendirmektir.

Yöntem: Bu kesitsel çalışmaya Amerikan Romatoloji Cemiyeti/Avrupa Romatizma Birliği 2013 SSc kriterlerini karşılayan hastalar dahil edildi. Sialometrik değerlendirmede UWSFR kullanıldı. Hastalığın ağız ilişkili etkilerini değerlendirmek için SSc ağız engeli (MHSS) skalası kullanıldı.

Bulgular: Çalışmaya yetmiş iki SSc hastası (%91,7'si kadın) dahil edildi. Hastaların ortalama yaşı 52,2±13 yıldır ve %65,3'ü sınırlı kutanöz SSc (lcSSc) hastasıydı. Hastaların %44'ünde kserostomi semptomu mevcutken; azalmış UWSFR ($\leq 0,1$ mL/dk) hastaların %39'unda saptandı. Hastalık alt tiplerine göre hastalar karşılaştırıldığında, kserostomi ve hiposalivasyon görülme sıklığı açısından anlamlı bir fark saptanmadı. Hiposalivasyonu olan ve olmayan hastalar karşılaştırıldığında, SSc ilişkili klinik özellikler, hastalık ciddiyeti ve sağlık yetersizlikleri benzerdi. Tükürük akım hızı azalmış hastalarda normal tükürük akış hızı olan hastalara göre anlamlı derecede MHSS toplam ve MHSS alt ölçek 2'nin puanları yüksekti ($p=0,04$ ve $p=0,01$, sırasıyla). SSc hastalarında düşük tükürük üretimi ile disfaji, [risk oranı (RO): 2,86, %95 güven aralığı (GA): 1,01-8,13; $p=0,045$], anti-Ro60/SSA antikoru (RO: 3,7, %95 GA: 1,08-12,55; $p=0,036$), kseroftalmi (RO: 4,3, %95 GA: 1,56-11,77; $p=0,005$), Schirmer's testi pozitifliği (RO: 20,7, %95 GA: 6,02-71,08; $p<0,001$), MHSS toplam ölçek puanında (RO: 1,05, %95 GA: 1,00-1,09; $p=0,043$), ve MHSS alt ölçek 2 puanında artış (RO: 1,13, %95 GA: 1,02-1,24; $p=0,02$) arasında ilişki saptanmıştır.

Sonuç: SSc'de hiposalivasyon ve kserostomi sık rastlanmaktadır. Hiposalivasyonu olan hastalarda artmış ağız yetersizliği mevcuttur. Anti-Ro60/SSA antikoru, disfaji, kseroftalmi (subjektif semptom veya tanısız Schirmer's testi), MHSS toplam ve alt ölçek 2'nin artan puanları SSc hastalarında hiposalivasyon için risk faktörleridir.

Anahtar Kelimeler: Hiposalivasyon, kserostomi, sistemik skleroz, tükürük akış hızı, yetersizlik

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Introduction

Systemic sclerosis (SSc) is a complex autoimmune disease characterized by pathogenic mechanisms including the dysregulated immune system, vasculopathy, and proceeding fibrosis, which mainly affect the skin and internal organs.^[1] SSc is related to significant morbidity and mortality.^[2,3] Moreover, in SSc, more than half of the death is directly related to disease-specific causes, the most common of which are pulmonary fibrosis, pulmonary arterial hypertension (PAH), and cardiac causes, respectively.^[4]

In SSc, frequently observed manifestations such as orofacial involvement might have deleterious effects on the life of patients with social, psychological, and functional aspects; however, these involvements might be underdiagnosed or neglected due to being overshadowed by life-threatening complications and the complex nature of the disease.^[5] One of the most common findings among orofacial involvement is sicca syndrome (xerostomia, xerophthalmia) in SSc patients with a high prevalence ranging from 64% to 75%.^[6,7] Xerostomia, a sensation of dry mouth, is frequently reported by SSc patients due to decreased saliva production of salivary glands.^[8] When considering the etiology of hyposalivation in SSc there have been two actual reasons; the exact known cause is higher concomitance of Sjogren syndrome (SS) marked by lymphocytic sialadenitis with SSc, and, in the light of recent histologic evidence, SSc leads to fibrosis of salivary gland, which might result in impairment of saliva production and excretion.^[7,8] Moreover, the multi-center study supporting the latter hypothesis has reported that approximately two-thirds of SS patients have sicca symptoms and half of patients have fibrotic lesions while only twenty percent of patients fulfilled the criteria for primary SS.^[6]

The salivary flow rate (SFR) of patients with SSc is prominently low compared to the general population, and it is demonstrated that the presence of SSc is an independent predictor for saliva production. Besides, SS patients have markedly impaired oral health-related quality of life (HRQoL).^[9] The mouth handicap in Systemic Sclerosis scale (MHISS) is a specific tool developed to evaluate SS patients on the mouth disability associated with reduced mouth opening, sicca syndrome, and aesthetic concerns and independent predictor of disability and HRQoL.^[10,11] The primary aim of this study was to demonstrate reduced saliva production in SSc and its impact on oral disability evaluated by the MHISS scale. The secondary objective was to investigate the association between SS/SSc-related specific autoantibodies and hyposalivation.

Materials and Methods

Study Design and Participants

This cross-sectional, single-center study included patients who fulfilled the American College of Rheumatology/European League Against Rheumatism 2013 criteria of SSc from the Department of Rheumatology in Gazi University Hospital.^[12] Exclusion criteria for patients were active smoking, the concomitance of other diseases, which could affect salivary glands (hepatitis C virus infection, lymphoma, sarcoidosis, immunoglobulin-G4 related disorders, adult immune-deficiency syndrome, graft-versus-host disease), and prior radiotherapy of head or neck. Patients who gave informed and written consent in accordance with the Declaration of Helsinki were included in this study, which was approved by the Ethics Committee of Gazi University Hospital (reference number: 456, date: 17.05.2021).

Data Collection

Demographic data, clinical features of SSc, and ongoing treatments were obtained from patients' interviews and medical records. Clinical features were evaluated and recorded as such, the disease duration [time between the onset of first non-Raynaud's Phenomenon (RP) symptoms and the last evaluation], disease subsets [classified as limited cutaneous SSc (lcSSc) and diffuse cutaneous SSc (dcSSc) according to the distribution of skin involvement by LeRoy et al.^[13], history/active of digital ulcers (DUs), musculoskeletal involvement (presence of arthralgia, arthritis, myositis, or joint contractures), gastroesophageal involvement (presence of gastroesophageal reflux symptoms with evidence of esophageal dysmotility detected by esophageal manometry or barium esophagogram), interstitial lung disease (ILD) (presence of ILD findings on high resolution computed tomography), PAH (suspected findings on echocardiography and confirmed by right heart catheterization), cardiac involvement (presence of diastolic dysfunction, arrhythmias, pericardial effusion, pericarditis or myocarditis), and scleroderma renal crisis.

Laboratory tests were Rheumatoid Factor by nephelometry (positivity >20 IU/mL), presence of hypergammaglobulinemia, anti-nuclear antibody (ANA) by indirect immunofluorescence (positivity was accepted as titers >1/160), anti-Ro 60 and 52 (SS-A), anti-La (SS-B), anti-topoisomerase I, and anti-centromere antibodies by enzyme-linked immunosorbent assay.^[13]

Xerophthalmia and xerostomia symptoms were evaluated using American College of Rheumatology/European Alliance of Associations for Rheumatology

inclusion criteria sicca questionnaire in all participants. Objective xerophthalmia was confirmed by Schirmer's test (positivity was the wetness of the paper ≤ 5 mm after 5 min.) in all participants. An unstimulated whole saliva collection test, an objective indicator of xerostomia, was used for the assessment of the hypofunction of salivary glands in SSc patients. UWSFR is equal to or less than 0.1 mL/min as accepted decreased SFR or hyposalivation.^[14] Microstomia was considered less than 40 mm of interincisal distance.^[5]

The mouth disability was evaluated by the MHISS scale questionnaire validated in the Turkish language.^[15] MHISS contains 12 item questionnaires, each of which is scored ranging from 0 (never) to 4 (always). MHISS is divided into three domains: handicap related to reduced mouth opening (score range: 0-20), mouth dryness (score range: 0-20), and aesthetic concerns (score range: 0-8). Higher scores of MHISS express more handicaps of mouth.^[10] HRQoL of patients was assessed by the Health Assessment Questionnaire (HAQ) and Scleroderma HAQ (SHAQ) visual analog scale of overall disease severity, validated in the Turkish version.^[16-19] SSc disease severity of participants was examined with the Physician's Global Assessment (PGA) on the numeric rating scale, ranging from 0 to 10 (no severity to extremely severe disease).

Statistical Analysis

All statistical analyses of data were performed using Statistical Package for the Social Sciences software v16.0 (SPSS Inc, Chicago IL). P-values of less than 0.05 were considered statistically significant. Demographic data, clinical features, and assessments of disease severity and disability were compared according to disease subsets (lcSSc and dcSSc) and hyposalivation. Categorical variables were analyzed using the chi-square or Fisher's exact tests. The distributions of numeric variables were examined by visual (histogram and probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). Based on the distribution of data, analyses were reported using the median with interquartile range (IQR) and mean with standard deviation (SD). The Student's t-test and Mann-Whitney U test were used for the comparison of variables between groups, as appropriate. Univariate regression analyses were performed and calculated odd ratios (ORs) with 95% confidence intervals (95% CI) to determine the risk factors of hyposalivation in SSc patients.

Results

Seventy-two patients (91.7% female) were included in the study. The mean age of patients was 52.2 ± 13 years. The median duration of the disease was 5 years and almost two-

thirds of patients (65.3%) had lcSSc. The characteristics of the disease in participants were demonstrated in Table 1.

Sicca symptoms were reported in fifty-seven percent of patients. Thirty-two patients (44%) had subjective xerostomia while hyposalivation was detected in twenty-eight patients (39%). Subjective xerophthalmia was observed in thirty-one patients (43.1%) concordant with the result of positivity of Schirmer's test. Thirty-five percent of the patients were using medications with xerogenic side effects, including calcium-channel blockers, beta-blockers, diuretics, angiotensin-converting enzyme inhibitors, and selective serotonin reuptake inhibitors. The use of xerogenic medications did not have a statistically meaningful effect on hyposalivation in SSc patients (28.6% in patients with reduced UWSFR and 38.6% in patients with normal UWSFR; $p=0.53$). The evaluation of mouth disability in all patients showed that the median total MHISS score was 14 (minimum-maximum: 0-43) and the median MHISS subscale 2, assessing dry mouth, was 6 (minimum-maximum: 0-19).

The comparison of patients according to the disease subset, subjective xerostomia and the reduction in UWSFR were similar ($p=0.35$; $p=0.52$, respectively). MHISS total and subscale 2 scores were significantly higher in patients with dcSSc ($p<0.001$ and $p=0.003$, respectively) (Table 2). Likewise, dcSSc patients had markedly higher MHISS subscales 1 and 3 scores than lcSSc patients ($p<0.001$). Besides, patients with lcSSc presented significantly lower HAQ and SHAQ-disease severity than dcSSc patients ($p=0.024$ and $p=0.04$).

The comparison of SSc-related features in terms of hyposalivation displayed that the disease duration and organ involvements were similar in both groups. Similarly, there was no statistically significant difference in disease severity evaluated by PGA and health disability measured by SHAQ and HAQ between the two groups. Furthermore, the frequency of dysphagia was prominently increased in patients with reduced USWFR than in patients with normal USWFR (75% vs 51%; $p=0.04$); however, the presence of gastroesophageal involvement and gastroesophageal reflux were similar between patients with reduced salivary production and patients with normal salivary production (85.7% vs 86%; $p=1.00$ and 55.6% vs 65%; $p=0.46$, respectively). Patients with reduced UWSFR had a statistically higher rate of sicca and xerophthalmia symptoms and positivity of Schirmer's test rather than patients with normal UWSFR (71.4% vs 47.7%; $p=0.04$, 64.3% vs 29.5%; $p=0.007$ and 82.1% vs 18.2%; $p<0.001$, respectively). Notwithstanding, xerostomia symptom was reported in sixteen patients with hyposalivation (57.1%)

and seventeen patients with normal SFR (38.6%) (p=0.15). Regarding serologic evaluation, the only positivity of anti-Ro60/SSA antibody was statistically frequent in patients with hyposalivation (p=0.03) (Table 3). The assessment of health and mouth disability of patients showed that a significant difference was detected in terms of total MHISS and MHISS subscale 2 between patients with reduced UWSFR and

patients with normal SFR (p=0.04 and p=0.01, respectively). The risk factors of hyposalivation in SSc patients were determined as the presence of dysphagia (OR: 2.86, 95% CI: 1.01-8.13; p=0.045), anti-Ro60/SSA autoantibody (OR: 3.7, 95% CI: 1.08-12.55; p=0.036), presence of subjective xerophthalmia (OR: 4.3, 95% CI: 1.56-11.77; p=0.005), positive Schirmer's test (OR: 20.7, 95% CI: 6.02-71.08;

Table 1. The baseline characteristics of SSc patients

	SSc (n=72)	lcSSc (n=47)	dcSSc (n=25)	p
Female, n (%)	66 (91.7)	43 (91.5)	23 (92)	1.00
Age, years, mean ± SD	52.24 (13.00)	52.62 (12.62)	51.52 (14.16)	0.75
Smoking, ever, n (%)	19 (26.4)	15 (31.9)	4 (16)	0.14
Disease duration, median (IQR) years	5 (8)	5 (9)	5 (7)	0.59
mRSS, median (IQR)	11 (10)	9 (6)	20 (10)	<0.001
Maximal mouth opening, mean (SD)	3.63 (0.65)	3.78 (0.6)	3.33(0.68)	0.005
Microstomia (interincisal distance <40 mm), n (%)	47 (65.3)	28 (59.6)	19 (76)	0.08
Digital ulcers, n (%)	30 (41.7)	14 (29.8)	16 (64)	0.006
Musculoskeletal involvement, n (%)	42 (58)	23 (48.9)	19 (76)	0.03
Gastrointestinal involvement, n (%)	62 (85.9)	38 (80.9)	24 (96)	0.46
Oesophageal involvement, n (%)	57 (79.2)	37 (78.2)	20 (80)	0.37
Cardiac involvement, n (%)	19 (26.4)	14 (29.8)	5 (20)	0.44
ILD, n (%)	38 (52.8)	19 (40.4)	19 (76)	0.04
PAH, n (%)	7 (10)	4 (8.5)	3 (12)	0.84
Renal crisis, n (%)	6 (8.3)	5 (10.6)	1 (4)	0.63
Autoantibodies, positivity n (%)				
ANA ≥1/160	70 (97.2)	46 (97.9)	24 (96)	1.00
Anti-centromere	16 (22.2)	13 (27.7)	2 (8)	0.46
Anti-Topoisomerase	39 (54.2)	20 (42.6)	19 (76)	0.007
Anti-Ro60/SSA	14 (19.4)	7 (14.9)	7 (28)	0.30
Anti-Ro52/SSA	11(15.3)	8 (17)	3 (12)	0.88
Anti-La/SSB	2 (2.8)	1 (2.1)	1 (4)	1.00
RF	16 (22.2)	11 (23.4)	5 (20)	0.74
Hypergammaglobulinemia, n (%)	15 (20.8)	8 (17)	7 (28)	0.23
Sicca Symptoms, n (%)	41 (56.9)	25 (53.2)	16 (64)	0.38
Xerostomia	32 (44.4)	19 (40.4)	13 (52)	0.35
Xerophthalmia	31 (43.1)	20 (42.7)	11 (44)	0.90
Schirmer's test ≤5 mm/5 min	31 (43.1)	19 (40.4)	12 (48)	0.53
UWSFR ≤ 0.1 mL/min, n (%)	28 (38.9)	17 (36.2)	11 (44)	0.52

ANA: Antinuclear antibody, dcSSc: Diffuse cutaneous systemic sclerosis, ILD: Interstitial lung disease, IQR: Interquartile range, lcSSc: Limited cutaneous systemic sclerosis, mRSS: Modified Rodnan skin score, PAH: Pulmonary arterial hypertension, RF: Rheumatoid factor, SD: Standard deviation, SSc: Systemic sclerosis, UWSFR: Unstimulated whole saliva flow rate

Table 2. The assessment of health and mouth disability in SSc patients

	SSc (n=72)	lcSSc (n=47)	dcSSc (n=25)	p
MHISS total, median (IQR)	14 (19)	9 (15)	27 (18)	<0.001
MHISS subscale 1, median (IQR)	4 (11)	2 (8)	11.5 (11)	<0.001
MHISS subscale 2, median (IQR)	6 (9)	4 (9)	8 (9)	0.003
MHISS subscale 3, median (IQR)	3 (6)	0 (3)	5.5 (4)	<0.001
PGA, mean±SD	4.91 (1.42)	4.27 (1.54)	5.21 (1.14)	0.20
HAQ, median (IQR)	0.62 (1)	0.5 (1.2)	1 (0.87)	0.024
SHAQ-disease severity, median (IQR)	1.4 (2.15)	0.6 (2.2)	1.45 (1.0)	0.040

IQR: Interquartile range, HAQ: Health assessment questionnaire, MHISS: Mouth handicap in Systemic Sclerosis, PGA: Physician's Global Assessment, SD: Standard deviation, SHAQ: Scleroderma HAQ, SSc: Systemic sclerosis

Table 3. The evaluation of disease-related autoantibodies profile, mouth, and health disability of SSc patients in accordance with salivary production

	UWSFR >0.1 mL/min n=44	UWSFR ≤0.1 mL/min n=28	p
Autoantibody positivity, n (%)			
ANA ≥1/160	42 (95.5)	28 (100)	0.52
Anti-centromere antibody	9 (20.9)	6 (21.4)	1.00
Anti-topoisomerase II antibody	23 (52.3)	16 (57)	0.8
Anti-Ro60/SSA antibody	5 (11.4)	9 (32)	0.03
Anti Ro52/SSA	8 (18.6)	3 (10.7)	0.57
Anti-SSB antibody	1 (2.3)	1 (3.6)	1.00
Double positive*	3 (6.8)	5 (17.9)	0.50
RF positivity, n (%)	8 (18.2)	8 (28.6)	0.38
Hypergammaglobulinemia, n (%)	9 (20.9)	6 (21.4)	1.00
MHIS total, median (IQR)	13 (17)	20 (21)	0.04
MHIS subscale 1, median (IQR)	3.5 (10)	7.5 (14)	0.20
MHIS subscale 2, median (IQR)	4 (9)	8 (7)	0.01
MHIS subscale 3, median (IQR)	1 (5)	4 (6)	0.45
PGA, mean ±SD	5 (1.5)	5 (1.3)	0.27
HAQ, median (IQR)	0.5 (1.12)	0.92 (1.1)	0.34
SHAQ-disease severity, median (IQR)	1 (2.1)	1.4 (1.3)	0.24

*Positivity of anti-topoisomerase and anti-SSA/SSB. ANA: Antinuclear antibody, IQR: Interquartile range, HAQ: Health assessment questionnaire, MHIS: Mouth handicap in Systemic Sclerosis, PGA: Physician's Global Assessment, RF: Rheumatoid factor, SD: Standard deviation, SHAQ: Scleroderma HAQ, SSc: Systemic sclerosis, UWSFR: Unstimulated whole saliva flow rate

$p < 0.001$), higher MHIS total scores (OR: 1.05, 95% CI: 1.00-1.09; $p = 0.043$), and higher MHIS domain 2 scores (OR: 1.13, 95% CI: 1.02-1.24; $p = 0.02$) by using univariate regression analyses.

Discussion

Sicca symptoms are one of the most frequent findings with a higher prevalence in SSc patient.^[6,7,20] Our study demonstrated the prevalence of sicca symptoms in 57% of SSc patients and tended to be increased in dcSSc. Besides, subjective xerostomia was observed in 44.4% of patients consistent with the results from previous reports.^[21,22]

Xerostomia can lead to numerous complications including dysphagia, mucosal infections, periodontal diseases, and denutrition, and eventually result in a reduction in quality of life.^[8,23] Several studies displayed that decreased SFR namely objective xerostomia was frequently observed in SSc patients and indeed, SSc was considered as an independent risk factor of saliva production.^[9,24] Recent histopathologic reports suggested that salivary gland involvement in SSc is not only caused by the presence of secondary SS but also progressive fibrosis, which is one of the hallmark mechanisms of SSc, might directly lead to impairment of salivary glands.^[6-8] In our study, hyposalivation (UWSFR ≤ 1 mL/min) was detected in 39% of SSc patients. A study assessing sicca symptoms and prevalence of SS in SSc patients reported 35% of patients with reduced salivary production, congruent with our finding. Furthermore, older age and positive SS-A

autoantibody were considered as predictors of SS in SSc patients.^[7] In addition, SSc-related clinical manifestations prominently observed in SSc patients with SS, were lcSSc subset and absence of ILD.^[6,25,26] According to our results, there were not any significant associations detected between the disease subsets, disease duration, organ involvements, disease severity scores measured with PGA, and decreased salivary production. However, the positivity of anti-SSA antibodies was frequently observed in SSc patients with decreased salivary production and considered as predictor for hyposalivation in SSc patients. Similarly, a recent study revealed the important association between reduced saliva production and the positivity of at least one SS-related antibody and reported that disease severity scores were not related to saliva production.^[27] On the other hand, the study with a small number of dcSSc patients without concomitant SS or SS-related antibodies displayed reduced SFR in dcSSc patients and a negative correlation between disease severity and SFR.^[24] In addition to the positivity of SS-A antibody, in our cohort, subjective xerophthalmia symptoms and objective xerophthalmia were predictors for decreased saliva production in SS patients as expected.

Dysphagia is one of the most common symptoms in SSc patients. SSc-related various causes are resulting in dysphagia such as esophageal dysmotility, gastroesophageal reflux, myositis, microstomia, or xerostomia.^[28] Our study showed that the dysphagia was significantly related to reduced saliva production. However, there was no significant association

observed between decreased saliva production and gastroesophageal involvement, which might be suggested that xerostomia might be one of the main contributors to dysphagia in our study.

Recent evidence has revealed that SSc has a detrimental impact on the oral health of patients, which eventuates in significant oral disabilities. The Canadian SSc oral health study demonstrated that SSc patients had impaired oral HRQoL assessed by the Oral Health Impact Profile which is widely used for the evaluation of oral health disability whereas it is not a specific instrument for SSc.^[9] Moreover, another Canadian SSc oral health study reported that oral HRQoL was related to global HRQoL. However, there was not any significant relationship detected between disease subset, disease duration, PGA disease severity, and oral HRQoL.^[29] Our study showed that SSc patients with decreased SFR had prominently worse oral HRQoL evaluated with the MHISS scale and MHISS subscale 2 scores reflecting disabilities related to mouth dryness were significantly higher in these patients. Furthermore, an increase in MHISS total and MHISS subscale 2 scores were considered as risk factors for reduction in saliva production in SSc patients.

Study Limitations

This study had a few limitations. First, there was not a control-healthy group to confirm the increased risk of hyposalivation in SSc. Another important limitation was that secondary SS has not been diagnosed due to the requirement of histopathologic evaluation which needs invasive procedure, that is why, the prevalence of secondary SS has been not demonstrated. Despite all limitations, the most important strength of the study was the first report to assess the effect of hyposalivation on oral health and disability with MHISS which is the SSc-specific instrument developed for orofacial involvement of SSc.

Conclusion

In conclusion, our study demonstrated that the prevalence of xerostomia and reduction in salivary production were frequently observed in SSc patients. It was founded that risk factors for the presence of hyposalivation in SSc were the positivity of anti-Ro60/SSA antibody, xerophthalmia, and dysphagia symptom. Besides, SSc patients with hyposalivation had markedly poorer oral HRQoL assessed by MHISS. Moreover, a significant relationship between hyposalivation and higher MHISS scores was thought that MHISS might be more commonly used for follow-up for salivary gland hypofunction or salivary gland involvement of SSc patients.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of Gazi University Hospital (reference number: 456, date: 17.05.2021).

Informed Consent: Informed consent was obtained from patients.

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Authorship Contributions

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References

1. Allanore Y, Simms R, Distler O, et al. Systemic sclerosis. *Nat Rev Dis Primers* 2015;1:15002.
2. Pagkopoulou E, Arvanitaki A, Daoussis D, Garyfallos A, Kitas G, Dimitroulas T. Comorbidity burden in systemic sclerosis: beyond disease-specific complications. *Rheumatol Int* 2019;39:1507-17.
3. Elhai M, Meune C, Avouac J, Kahan A, Allanore Y. Trends in mortality in patients with systemic sclerosis over 40 years: a systematic review and meta-analysis of cohort studies. *Rheumatology* 2011;51:1017-26.
4. Tyndall AJ, Bannert B, Vonk M, et al. Causes and risk factors for death in systemic sclerosis: a study from the EULAR Scleroderma Trials and Research (EUSTAR) database. *Ann Rheum Dis* 2010;69:1809-15.
5. Smirani R, Poursac N, Naveau A, Schaefferbeke T, Devillard R, Truchetet ME. Orofacial consequences of systemic sclerosis: A systematic review. *J Scleroderma Relat Disord* 2018;3:81-90.
6. Avouac J, Sordet C, Depinay C, et al. Systemic sclerosis-associated Sjögren's syndrome and relationship to the limited cutaneous subtype: results of a prospective study of sicca syndrome in 133 consecutive patients. *Arthritis Rheum* 2006;54:2243-9.
7. Can G, Sarioğlu S, Birlik M, et al. The prevalence of Sjögren's syndrome and sicca symptoms in patients with systemic sclerosis and alpha-smooth muscle actin expression in biopsy specimens from minor salivary glands. *Turk J Med Sci* 2021;51:1875-82.
8. Zimmermann F, Robin F, Caillault L, et al. Sicca syndrome in systemic sclerosis: a narrative review on a neglected issue. *Rheumatology (Oxford)* 2023;62:Si1-11.
9. Baron M, Hudson M, Tatibouet S, et al. The Canadian systemic sclerosis oral health study: orofacial manifestations and oral

- health-related quality of life in systemic sclerosis compared with the general population. *Rheumatology (Oxford)* 2014;53:1386-94.
10. Mouthon L, Rannou F, Bérezné A, et al. Development and validation of a scale for mouth handicap in systemic sclerosis: the Mouth Handicap in Systemic Sclerosis scale. *Ann Rheum Dis* 2007;66:1651-5.
 11. Maddali-Bongi S, Del Rosso A, Mikhaylova S, et al. Impact of hand and face disabilities on global disability and quality of life in systemic sclerosis patients. *Clin Exp Rheumatol* 2014;32(Suppl 86):S-15-20.
 12. van den Hoogen F, Khanna D, Fransen J, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. *Arthritis Rheum* 2013;65:2737-47.
 13. LeRoy EC, Black C, Fleischmajer R, et al. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. *J Rheumatol* 1988;15:202-5.
 14. Shiboski CH, Shiboski SC, Seror R, et al. 2016 American College of Rheumatology/European League Against Rheumatism Classification Criteria for Primary Sjögren's Syndrome: A Consensus and Data-Driven Methodology Involving Three International Patient Cohorts. *Arthritis Rheumatol* 2017;69:35-45.
 15. Tore NG, Sarı F, Tunà Z, Kucuk H, Haznedaroglu S, Oskay D. Translation, validation and cross-cultural adaptation of the mouth handicap in systemic sclerosis questionnaire into the Turkish language. *Int J Rheum Dis* 2020;23:669-73.
 16. Bruce B, Fries JF. The Health Assessment Questionnaire (HAQ). *Clin Exp Rheumatol* 2005;23(Suppl 39):S14-8.
 17. Steen VD, Medsger TA, Jr. The value of the Health Assessment Questionnaire and special patient-generated scales to demonstrate change in systemic sclerosis patients over time. *Arthritis Rheum* 1997;40:1984-91.
 18. Temiz Karadag D, Karakas F, Tekeoglu S, Yazici A, Isik OO, Cefle A. Validation of Turkish version of the Scleroderma Health Assessment Questionnaire. *Clin Rheumatol* 2019;38:1917-23.
 19. Küçükdeveci AA, Sahin H, Ataman S, Griffiths B, Tennant A. Issues in cross-cultural validity: example from the adaptation, reliability, and validity testing of a Turkish version of the Stanford Health Assessment Questionnaire. *Arthritis Rheum* 2004;51:14-9.
 20. Swaminathan S, Goldblatt F, Dugar M, Gordon TP, Roberts-Thomson PJ. Prevalence of sicca symptoms in a South Australian cohort with systemic sclerosis. *Intern Med J* 2008;38:897-903.
 21. Bajraktari IH, Kryeziu A, Sherifi F, Bajraktari H, Lahu A, Bajraktari G. Oral manifestations of Systemic Sclerosis and Correlation with anti-Topoisomerase I Antibodies (SCL-70). *Med Arch* 2015;69:153-6.
 22. Crincoli V, Fatone L, Fanelli M, et al. Orofacial Manifestations and Temporomandibular Disorders of Systemic Scleroderma: An Observational Study. *Int J Mol Sci* 2016;17.
 23. Mortazavi H, Baharvand M, Movahhedian A, Mohammadi M, Khodadoust A. Xerostomia due to systemic disease: a review of 20 conditions and mechanisms. *Ann Med Health Sci Res* 2014;4:503-10.
 24. Parat K, Radić M, Perković D, Lukenda DB, Kaliterna DM. Reduced salivary flow and caries status are correlated with disease activity and severity in patients with diffuse cutaneous systemic sclerosis. *J Int Med Res* 2020;48:300060520941375.
 25. Kobak S, Oksel F, Aksu K, Kabasakal Y. The frequency of sicca symptoms and Sjögren's syndrome in patients with systemic sclerosis. *Int J Rheum Dis* 2013;16:88-92.
 26. Salliot C, Mouthon L, Ardizzone M, et al. Sjogren's syndrome is associated with and not secondary to systemic sclerosis. *Rheumatology (Oxford)* 2007;46:321-6.
 27. Baron M, Hudson M, Tatibouet S, et al. Relationship between disease characteristics and orofacial manifestations in systemic sclerosis: Canadian Systemic Sclerosis Oral Health Study III. *Arthritis Care Res (Hoboken)* 2015;67:681-90.
 28. Kadakuntla A, Juneja A, Sattler S, et al. Dysphagia, reflux and related sequelae due to altered physiology in scleroderma. *World J Gastroenterol* 2021;27:5201-18.
 29. Baron M, Hudson M, Tatibouet S, et al. The Canadian systemic sclerosis oral health study II: the relationship between oral and global health-related quality of life in systemic sclerosis. *Rheumatology (Oxford)* 2015;54:692-6.