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ORIGINAL ARTICLE

A cross-sectional study on activity impairment in primary Sjogren's syndrome

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Abstract

Objective: The aim of this cross-sectional study was to show relations between activity impairment and salivary gland involvement for patient empowerment in primary Sjogren's syndrome (pSS).

Methods: In the study, 86 patients with pSS were included. The data were collected through clinical examinations and a questionnaire regarding Work Productivity and Activity Impairment (WPAI), EULAR Sjogren's syndrome patient-reported index (ESSPRI) and Oral Health Impact Profile-14 (OHIP-14). Relations were analysed by using mediation and moderation analyses. In simple mediation analysis, an independent variable (X) influences outcome variable (Y) through a mediator variable (M) whereas a moderator variable (W) affects the direction of the relationship between the dependent (Y) and independent variables (X).

Results: Increases in ESSPRI-Dryness score (X) ($p=0.0189$) and OHIP-14 score (M) ($p=0.0004$) were associated with the poor WPAI activity impairment score (Y) in the first mediation analysis. The WPAI activity impairment score was mediated by the elevated ESSPRI-Fatigue score (X) ($p=0.03641$) and low U-SFR (M) ($p=0.0000$) in the second mediation analysis. In addition, ESSPRI-Pain score (W) was the significant moderator for WPAI activity impairment (Y) in patients without hyposalivation in the moderation analysis ($p=0.0010$).

Conclusion: WPAI activity impairment was affected by both ESSPRI-Dryness with OHRQoL and ESSPRI-Fatigue with SFR in glandular involvement.

KEYWORDS
ESSPRI, hyposalivation, OHIP-14, WPAI-daily impairment

1 | INTRODUCTION

Primary Sjogren's Syndrome (pSS) is a chronic systemic autoimmune disorder characterized by immune-mediated glandular dysfunctions and systemic extra-glandular involvement. Genetic and environmental factors are implicated in the disease pathogenesis. The disease is more frequently seen in females of middle age. The diagnostic criteria of pSS include oral and ocular symptoms, evidence of oral signs and ocular dryness, evidence of salivary gland involvement, a positive salivary gland biopsy and presence

of autoantibodies (SSA/SSB) (Negrini et al., 2022; Ramos-Casals et al., 2020; Shiboski et al., 2016; Vitali et al., 2002). Disease activity is assessed using the EULAR Sjogren Syndrome Disease Activity Index (ESSDAI) and EULAR SS patient-reported index (ESSPRI), which evaluate cardinal symptoms regarding dryness, pain, and fatigue in pSS (Negrini et al., 2022; Ramos-Casals et al., 2020; Seror et al., 2010, 2011, 2015) and reflect the negative impact of the disease on patient's life (Ramos-Casals et al., 2020; Seror et al., 2010, 2011, 2015, 2016).

Oral dryness is an essential problem for oral health, oral health-related quality of life (OHRQoL) and patients' life (Negrini et al., 2022; Plemons et al., 2014; Ramos-Casals et al., 2020; Rusthen et al., 2017; Shiboski et al., 2016; Vitali et al., 2002; Yalcinkaya et al., 2020) because saliva is a special fluid with multifunctional roles in the oral environment. The parotid glands contribute 20–25% of whole saliva at rest and almost 60% after stimulation, whereas submandibular glands produce 60%–65% of whole saliva at rest and sublingual salivary glands secrete almost 10% at rest (Roblegg et al., 2019). A decrease in salivary flow rate leads to difficulties in eating, chewing, speaking, digestion, moistening, swallowing, bolus formation and cleaning of oral surfaces. Moreover, the lack of salivary mucins as lubricating agents does not form a protective layer on teeth and mucosa. Local immune system also gets affected by oral dryness (Christensen et al., 2001; Kapourani et al., 2022; Plemons et al., 2014; Roblegg et al., 2019).

Improvement in patients' lives is achieved by patient empowerment strategies in chronic disease management (Hackett et al., 2014, 2018). Therefore, health professionals focus on what patients need or experience to clarify the burden of the disease on patients' lives for treatment protocols in pSS (Hackett et al., 2018; Lackner et al., 2017). In this perspective, arthritis, xerostomia and depression are key factors in daily life for patients with pSS (Bejarano et al., 2021). Complex associations are available among salivary gland involvement, OHRQoL and ESSPRI and patients' daily lives (Dias et al., 2021; Hackett et al., 2018; Lackner et al., 2017; Rusthen et al., 2017; Sandoval-Flores et al., 2021; Yalcinkaya et al., 2020). At this point, both mediation analysis and moderation analysis are good options to show complex relationships. A mediation analysis describes possible causal relationships by which an independent variable (X) influences outcome variable (Y) through a third variable known as a mediator variable (M). This method clarifies the underlying mechanism between the independent and dependent variables. Besides, a moderator variable (W) is defined as a third variable affecting the direction of the relationship between the dependent (Y) and independent variable (X) (Hayes, 2018; Hayes & Rockwood, 2017). In our previous studies, these analyses are used to understand associations among symptoms in Behcet's disease (BS) (Karacayli et al., 2021; Mumcu et al., 2020; Yay et al., 2019) and Takayasu arteritis (TAK) (Erdal et al., 2021). The aim of this cross-sectional study was to show relations between activity impairment and salivary gland involvement for patient empowerment in patients with primary Sjogren's syndrome (pSS).

2 | MATERIALS AND METHODS

In this cross-sectional study, 86 patients (M/F: 5/81; mean age: 52.4 ± 11.6 years) who fulfilled the 2002 AECG classification criteria for pSS (Vitali et al., 2002) and followed-up in Sjogren syndrome outpatient clinic in Rheumatology department, Medical School, Marmara University were included. Data were collected from September 2019 to March 2020 due to the onset of the COVID-19 pandemic.

The sampling was drawn from the patients with pSS registered in the clinic ($N = 222$) using the simple random sampling method to ensure the homogeneity of the group. Each patient was given an equal chance of being included in the sample, thereby preventing bias. Before starting the study, a pilot study ($n = 30$) was conducted to determine the sample size. The mean and standard deviation of WPAI score were found to be 40.66 ± 27.78 in the pilot study ($n = 30$). The significance level was taken as 0.05 with 90% test power. The effect size (d) was obtained as 0.34 by using G-Power 3.1 free software program. The sample size to be drawn from the population was obtained as $n = 95$. Then, patients were included in the study protocol weekly. Since 86 patients were included in the study due to COVID pandemic, the response rate was found as 91% in the study.

The mean disease duration was 8.25 ± 6.3 years in the group. Patients were mainly treated with hydroxychloroquine ($n = 70$, 81.4%). The other treatment protocols were methotrexate ($n = 10$, 11.6%), *azathioprine*, *steroids*, *colchicine* and rituximab ($n = 3$, 3.5%). Muscarinic agonists and/or artificial saliva were prescribed to patients who needed it according to their salivary flow rates (NI, KA, GM) in each visits.

The study was performed according to the principles of the Declaration of Helsinki and received approval from the Ethical Committee of Marmara University Institute of Health Sciences Ethics Committee (20.06.2019–151). Written informed consent was obtained from all patients in the study.

The inclusion criteria for the study were: being adult patients (≥18 years of age), willing to participate in the study and under medical supervision for pSS. On the other hand, the exclusion criteria included the presence of other rheumatic diseases, uncontrolled chronic diseases, sarcoidosis, known hepatitis infection, acquired immune deficiency disease, graft versus host disease, history of lymphoma and radiotherapy on head and neck.

Patients were examined and their clinical data were collected by both rheumatologists (NI, KA) and a dentist (GM) in the clinic. The following data were collected in the clinic: socio-demographic properties (age and gender), disease-related factors (ocular and salivary glandular involvement, autoantibody positivity, systemic involvement and symptoms), smoking habits, alcohol consumption, frequency of daily tooth brushing, oral health-related problems, treatment protocols and access to healthcare of patients (rheumatology outpatient clinic, family medicine clinic, and dental clinic). A trained interviewer (YY) informed patients about the study protocol and assisted them in filling out the PROMs that were Work Productivity and Activity Impairment (WPAI), Oral Health Impact

Profile-14 (OHIP-14), EULAR Sjogren's syndrome patient-reported index (ESSPRI) and Hospital Anxiety and Depression Scale (HADS). As patients were willing to share their disease-related experiences while waiting for their clinical examinations, there was no missing data in the questionnaires.

2.1 | Salivary flow rates and hyposalivation

Measurements of unstimulated (U-SFR) and stimulated salivary flow rate (S-SFR) were performed in the morning (9–11 a.m.) by a dentist (GM) in accordance with standard procedures. Patients did not eat, drink, or smoke for the last 2 h before saliva collection. Patients were asked to lean forward and spit all their saliva into a graduated test tube for 15 min. Then, U-SFR was calculated as millilitres per minute (mL/min) (Navazesh & Kumar, 2008). In the second stage, the patients chewed a piece of paraffin until it softened and swallowed their saliva at that time. Then, while continuing to chew, they spat their saliva into a tube at short intervals for S-SFR during 5 min (Plemons et al., 2014). Saliva flow rates were calculated as mL/min (IT, FTÖ). Hyposalivation was defined as a U-SFR of ≤0.1 mL/min based on established criteria (Navazesh & Kumar, 2008; Plemons et al., 2014; Shiboski et al., 2016). Patients were then grouped based on the presence or absence of hyposalivation (≤0.1 mL/min for U-SFR) or not (Shiboski et al., 2016).

2.2 | The Sjögren's syndrome disease activity index (ESSDAI)

The systemic activity was measured by ESSDAI with 12 domains: lymphadenopathy, renal, pulmonary, constitutional, glandular, articular, cutaneous, muscular, biological, haematological central nervous system, peripheral nervous system. Each domain was scored as low: <5 points; moderate: 5–13 points; high: ≥14 points based on the severity of the activity (Ramos-Casals et al., 2020; Seror et al., 2010, 2011, 2015, 2016).

2.2.1 | Patient-reported outcome measures

EULAR Sjogren's syndrome patient-reported index (ESSPRI)

The severity of symptoms regarding Dryness, Pain, and Fatigue was evaluated using ESSPRI with a scoring range of 0 point (absence of symptom) to 10 points (the highest intensity of symptoms) during the preceding 2 weeks. A higher score indicates a worse outcome during the last 2 weeks (Ramos-Casals et al., 2020; Sandoval-Flores et al., 2021; Seror et al., 2010, 2011, 2015, 2016).

Work productivity and activity impairment (WPAI)

Activity impairment was evaluated by using The Work Productivity and Activity Impairment (WPAI) scale during the last 7 days. A high score on the scale indicates greater *Activity Impairment* ((Q6/10)*100) (http://www.reillyassociates.net/wpai_general.html). However due to a limited number of employed patients ($n=6$), subgroups of WPAI absenteeism, presenteeism and overall impairment were not evaluated in this study. The WPAI scale was validated in previous studies for patients with BD (Karacayli et al., 2021; Mumcu et al., 2017), RAS (Karacayli et al., 2021) and TAK (Erdal et al., 2021) in our previous studies.

The Cronbach-alpha value for the internal consistency was 0.900 for last two items of WPAI because same scoring method was used for both items (Q5 and Q6). Test–retest results of WPAI were evaluated at an interval of 4-weeks in clinically stable patients ($n=8$) for the external reliability.

In construct validity analysis, patients were asked to evaluate whether their symptoms had improved or not compared to the previous visit (0: symptoms were healed/decreased vs. 1: symptoms were worsen/stable). The question was: 'How would you describe your symptoms during this visit compared to those on the previous visit'? Furthermore, the study also assessed the correlation between WPAI-Daily impairment and two patient global assessments: PGA-Health status and PGA-Disease activity in pSS. Patients were asked two questions about their opinions on their health status and disease activity during the past week. The responses were scored on a scale from 0 point to 100 points, where '0 point' indicated very poor health status or disease inactivity and '100 points' indicated very good health status or severe disease activity.

Oral health impact profile-14

The Oral Health Impact Profile-14 (OHIP-14) scale is used to evaluate the oral health-related quality of life of the patients. The total score ranges from 0 to 56 points with a higher score indicating a worse oral health-related quality of life status (Slade, 1997). The Turkish validity and reliability study of this scale was conducted by Mumcu et al. (2006).

Hospital anxiety and depression scale (HADS)

The scale includes both anxiety dimension with seven items (*HADS-A*) and depression dimension (*HADS-D*) with seven items (Snaith, 2003). Scores between 0 and 7 are accepted as normal whereas the over 7 points are coded as abnormal in both dimensions (Covic et al., 2012). In this study, the validated Turkish version of the scale (Aydemir et al., 1997).

2.3 | Statistical analysis

The data were analysed using SPSS 28.0 statistic program (SPSS Inc). As the data were not normally distributed, non-parametric tests such as the Mann–Whitney *U* test, Kruskal–Wallis test, and Spearman Correlation test were used. The Cronbach-alpha values for the internal consistency were found to be 0.961 for OHIP-14, 0.703 for ESSPRI, 0.823 for HADS-A and 0.800 for HADS-D in the study group.

2.4 | Mediation analysis and moderation analysis

After preliminary analysis, U-SFR, S-SFR, OHIP-14 score and ESSPRI-Dryness, -Fatigue and -Pain were used as variables in conceptual models of the mediation and moderation analyses. Both analyses were performed with the adaptation of PROCESS macro in SPSS 28.0 statistic program (Hayes, 2018; Hayes & Rockwood, 2017).

ESSPRI-Dryness (continuous data) as an independent variable (X), OHIP-14 (continuous data) as a possible mediator (M) and WPAI activity impairment (continuous data) as a dependent variable (Y) were used in the first simple mediation analysis.

ESSPRI-Fatigue (continuous data) as an independent variable (X), U-SFR (continuous data) as a possible mediator (M) and WPAI activity impairment (continuous data) as a dependent variable (Y) were used in the second simple mediation analysis.

In moderation analysis, ESSPRI-Pain (continuous data) as possible moderator variable (W), Hyposalivation (X) (absent: 0 vs. present:1) as an independent variable (X) and WPAI activity impairment (continuous data) as an outcome variable (Y) were defined in the analysis.

3 | RESULTS

Eighty-six pSS patients (F/M: 81/5; 52.4 ± 11.6 years) were included in this cross-sectional study with a mean disease duration 8.25 ± 6.32 years (Table 1). Two patients reported current smoking while none reported alcohol use. The ESSDAI score for the group was calculated as 2.5 ± 1.0 ($n = 12$; ≥1 point), which was only associated with PGA-Health status (r: −0.86 $p = 0.000$).

The mean frequency of visits during the previous year was 2.47 ± 1.48 in Rheumatology outpatient clinic and 4.02 ± 4.08 in Family Medicine clinic. The duration since the last dental visit was 15.8 ± 20.1 months in the group (Table 1). When patients experienced oral health problems ($n = 35$) during the past years, they primarily consulted their problems with Rheumatologists ($n = 21$, 60%).

3.1 | ESSPRI, patient global assessment and WPAI-activity impairment

The WPAI activity impairment score showed a significant correlation with ESSPRI-Dryness (6.31 ± 2.71; r: 0.42 $p = 0.000$), -Fatigue (5.41 ± 2.97; r: 0.32 $p = 0.004$) and -Pain (5.16 ± 3.12; r: 0.32 $p = 0.003$) in the group.

In term of construct validity, the WPAI activity impairment score (60.58 ± 31.12) was also associated with PGA-Disease activity (52.4 ± 23.29; r: 0.48 $p = 0.000$) and PGA-Health status (53.06 ± 20.17; r: −0.47 $p = 0.000$; Tables 1 and 2). Patients whose symptoms were worsened or remained stable (33.3%) had higher WPAI activity impairment compared to that of patients whose symptoms were healed/decreased (66.7%; 94.21 ± 13.46 vs. 54.73 ± 29.01; $p = 0.000$).

TABLE 1 The profile of patients with pSS.

	Mean ± SD
Age (years)	52.4 ± 11.6
Disease duration (years)	8.25 ± 6.32
Access to healthcare and frequency of tooth brushing	
Number of visits in rheumatology clinic/last year	2.47 ± 1.48
Number of visits in family medicine clinic/last year	4.02 ± 4.08
Duration from last dental visit (months)	15.8 ± 20.1
Frequency of daily tooth brushing	1.78 ± 0.70
Salivary flow rates	
Unstimulated SFR	0.42 ± 0.58
Stimulated SFR	1.02 ± 0.86
Disease activity	
ESSDAI ($n = 12$)	2.5 ± 1.0
Patient-reported outcome measures	
ESSPRI-Dryness	6.31 ± 2.71
ESSPRI-Fatigue	5.41 ± 2.97
ESSPRI-Pain	5.16 ± 3.12
WPAI-Activity impairment (%)	60.58 ± 31.52
OHIP-14	29.67 ± 18.23
Patient disease activity	52.04 ± 23.29
Patient general health	53.06 ± 20.17
HADS-A	10.36 ± 5.88
HADS-D	7.46 ± 4.49
	***n* (%)**
Female/Male (*n* %)	81/5 (94.2/5.8)
Disease-related factors	
Schirmer's test positivity (≤5 mm in 5 min)	81 (94.2)
ANA positivity/RF positivity	77 (89.5)/20 (23.3)
Anti-SSA/Anti-SSB positivity	43 (50)/23 (26,7)
Hypergammaglobulinemia	11 (12.9)
Arthralgia/Arthritis	59 (68,6)/23 (26,7)
Parotitis attacks	14 (16.3)
Reynaud	12 (14)
Venous thrombosis	12 (14)
Raynaud phenomenon	12 (14)
Fibromyalgia	12 (14)
Interstitial lung disease/Interstitial nephritis	2 (3.5)/4 (4.7)
Lymphadenopathies	20 (23.3)
Treatment protocols	
Hydroxychloroquine	70 (81.4)
Methotrexate	10 (11.6)
Azathioprine	3 (3.5)
Rituximab	3 (3.5)
Corticosteroids	3 (3.5)
Colchicine	3 (3.5)

Test–retest reliability ($n=8$) was found to be good for WPAI activity impairment (ICC: 0.819 $p=0.013$).

3.2 | Salivary gland involvement and WPAI-activity impairment

Both U-SFR (0.42 ± 0.58 mL/min) and S-SFR (1.02 ± 0.86) were correlated with scores of OHIP-14 (29.67 ± 18.23) and ESSPRI-Dryness (6.31 ± 2.71; $p<0.05$). In addition, OHIP-14 score was also related with ESSPRI-Dryness score ($r=0.39$ $p=0.000$; Table 2).

The WPAI activity impairment score was significantly correlated with U-SFR (r: −0.73 $p=0.000$), S-SFR (r: −0.44 $p=0.000$) and OHIP-14 score (r: 0.49 $p=0.000$). U-SFR was associated with ESSPRI-Dryness, -Fatigue, -Pain, PGA-Disease activity and PGA-Health status ($p<0.05$; Table 2).

Almost one third of the patients had hyposalivation ($n=31$, 36.04%). The mean U-SFR and S-SFR were 0.05 ± 0.04 mL/min and 0.39 ± 0.41 mL/min, respectively. The frequency of daily tooth brushing (1.78 ± 0.70) was similar according to presence of hyposalivation in patients (hyposalivation (+): 1.67 ± 0.68 vs. hyposalivation (−): 1.84 ± 0.72; $p=0.406$; Table 3).

Scores of WPAI activity impairment, OHIP-14 and ESSPRI-Dryness were higher in patients with Hyposalivation than the others ($p<0.05$; Table 3). Furthermore, HADS-A and HADS-D scores of patients with hyposalivation (9.1 ± 5.56 and 6.50 ± 3.96) were not different those without hyposalivation (11.24 ± 6.03 and 8.13 ± 4.77; $p>0.05$). In addition, ESSPRI-Fatigue and -Pain scores were found to be similar in both group ($p>0.05$).

In addition, hyposalivation was observed 35.8% ($n=29$) of patients with Schirmer test positive ($n=81$). Scores of ESSPRI-Dryness (7.38 ± 2.44 vs.5.74 ± 2.77) and WPAI activity impairment (91.72 ± 15.82 vs. 43.88 ± 25.35) were higher in patients with ocular dryness ($n=52$) accompanied with hyposalivation ($n=29$) than patients with isolated ocular dryness ($p=0.005$, $p=0.000$, respectively).

In systemic clinical manifestations, subgroup analysis was performed for WPAI activity impairment in patients with arthralgia ($n=59$) and arthritis ($n=23$) owing to the number of patients. Score of WPAI activity impairment in patients with arthralgia ($n=30$; 41.0 ± 24.26) was lower than those in patients with arthralgia and hyposalivation ($n=9$; 91.11 ± 13.64; $p=0.000$). Moreover, the WPAI activity impairment score was related to ESSPRI-Pain score (4.47 ± 2.92) in patients with arthralgia (r: 0.48 $p=0.007$). Similarly, patients with arthritis and hyposalivation ($n=11$; 90.0 ± 13.78) had elevated WPAI activity impairment score compared to that in patients with arthritis ($n=12$; 52.50 ± 21.37; $p=0.000$).

TABLE 2 WPAI activity impairment-related factors in pSS.

	Whole group	
	r	*p*
WPAI-daily impairment		
Unstimulated SFR	−0.73	**0.000**
Stimulated SFR	−0.44	**0.000**
ESSPRI-Dryness	0.42	**0.000**
ESSPRI-Fatigue	0.30	**0.004**
ESSPRI-Pain	0.32	**0.003**
OHIP-14	0.49	**0.000**
Patient disease activity	0.48	**0.000**
Patient general health	−0.47	**0.000**
ESSPRI-Dryness		
Unstimulated SFR	−0.47	**0.000**
Stimulated SFR	−0.37	**0.000**
OHIP-14	0.39	**0.000**
OHIP-14		
Unstimulated SFR	−0.59	**0.000**
Stimulated SFR	−0.35	**0.000**
Unstimulated SFR		
Patient disease activity	−030	**0.032**
Patient health status	0.30	**0.042**
ESSPRI-Dryness	−0.47	**0.000**
ESSPRI-Fatigue	−0.25	**0.023**
ESSPRI-Pain	−0.27	**0.013**

3.3 | Oral health problems

No significant differences were observed in the ratios of denture problems regarding irritations, infections and malodour, tooth filling problems, tooth mobility and halitosis according to presence of Hyposalivation in the group ($p<0.05$). However, patients with denture problems (52%) had elevated WPAI activity impairment (78.07 ± 29.93 vs. 61.60 ± 26.97) compared to those in patients without these problem (48%; $p=0.022$).

Increases in OHIP-14 score were also observed in patients with denture problems, (49.92 ± 15.11 vs. 26.7 ± 16.66) tooth filling problem (44.15 ± 15.83 vs. 29.13 ± 16.51), tooth mobility (45.0 ± 15.68 vs. 31.67 ± 17.25) and halitosis (39.45 ± 16.62 vs. 22.84 ± 15.21) than those without them ($p=0.002$; $p=0.005$, 0.030 and 0.007, respectively). However, similar relations were not observed between WPAI activity impairment score and problems regarding tooth filling, tooth mobility and halitosis ($p>0.05$).

3.4 | Mediation analyses and moderation analysis

After preliminary analyses, complex relations were examined by using mediation and moderation analyses. Two simple mediation models were obtained for WPAI-Daily impairment as dependent variables. In the first simple mediation analysis, rise in ESSPRI-Dryness score directly increased WPAI activity impairment score without a mediator (X) ($p=0.0189$). Indirectly, OHIP-14 score as a mediator (M)

($p=0.0004$) was associated with the poor WPAI activity impairment score (Table 4, Figure 1).

The WPAI activity impairment score (Y) was mediated by the elevated ESSPRI-Fatigue score (X) ($p=0.0364$) and low U-SFR (M) ($p=0.0000$) in the second simple mediation analysis (Table 4, Figure 1b).

ESSPRI-Pain score (W) was the only significant moderator variable for WPAI activity impairment (Y) in patients without hyposalivation (X) in the Moderation analysis ($p=0.0010$). Three cut-off points were defined as 2 points, 5.5 points and 9.08 points for ESSPRI-Pain score by the statistical analyse program in the study. The interaction plot showed gradual elevations in WPAI activity impairment scores (33.85 in 2 points; 45.84 in 5.5 points and 58.1 in 9.08 points) at these cut-off points in ESSPRI-Pain score in patients without hyposalivation ($p<0.05$; Table 4, Figure 1c).

4 | DISCUSSION

Since patient's empowerment is an essential part of chronic disease management (Marinello et al., 2021), it is necessary to understand what patients need to overcome disease-related problems or what patients experience in their life owing to disease burden (An et al., 2021; McCormick et al., 2019; Pekonen et al., 2020). Since salivary gland involvement is an essential problem for most of patients, the main goal of the current study was to show relations between Activity impairment and salivary gland involvement and their effects on patient empowerment in patients with pSS.

Close associations were observed among WPAI activity impairment, low U-SFR, elevated scores of OHIP-14 as OHRQoL and ESSPRI-Dryness in patients with pSS. The negative impacts of dryness on patients' life, social relations and quality of life are inevitable in pSS (Azuma et al., 2021; Enger et al., 2011; Rusthen et al., 2017; Stewart et al., 2008; Yalcinkaya et al., 2020). The other important point was that denture-related problems were associated with Daily impairment in pSS. Poor denture adaptation, denture-related stomatitis and halitosis are main denture-related problems. Dentures improve oral functions and facial appearance preventing patients from looking elderly individuals (Soto-Rojas & Kraus, 2002). When the tooth loss occurs, patients with SS have great difficulties in both wearing and retention of removable dentures due to lack of salivary output (Stewart et al., 2008). Implant could be a good option for patients with tooth loss (Bolstad & Skarstein, 2016). In addition to complaints of oral dryness (Ramos-Casals et al., 2020; Shiboski

TABLE 3 Scores of WPAI activity impairment, OHIP-14 and ESSPRI dryness according to presence of hyposalivation.

	Hyposalivation (+)		Hyposalivation (−)		
	Mean	SD	Mean	SD	*p*
WPAI-daily impairment	90.32	16.22	43.81	24.98	**0.000**
OHIP-14	45.37	12.99	18.19	11.58	**0.000**
ESSPRI-Dryness	7.39	2.44	5.71	2.69	**0.004**
Unstimulated SFR	0.05	0.04	0.64	0.63	**0.000**
Stimulated SFR	0.39	0.41	1.38	0.84	**0.000**
Frequency of tooth brushing	1.67	0.68	1.84	0.72	0.406

TABLE 4 Results of mediation analyses and moderation analysis for WPAI-activity impairment in pSS.

	B	SE	*t*	*p*	LLCI	ULCI
Mediation analysis model 1						
Constant	23.2583	7.7487	3.0016	**0.0035**	7.8465	38.6702
ESSPRI-Dryness	2.8296	1.1816	2.3947	**0.0189**	0.4794	5.1797
OHIP-14	0.6557	0.1762	3.7221	**0.0004**	0.3053	1.0061
Mediation analysis model 2						
Constant	62.0721	6.5468	9.4813	**0.0000**	49.0507	75.0935
ESSPRI-Fatigue	2.0212	0.9502	2.1271	**0.0364**	0.1313	3.9111
Unstimulated SFR	−28.8851	4.8493	−5.9565	**0.0000**	−0.3853	−19.2399
Moderation analysis						
Constant	27.0021	5.6889	4.7464	**0.0000**	15.6850	38.3191
Hyposalivation	64.5722	9.7284	6.6375	**0.0000**	45.2193	83.9251
ESSPRI-Pain	3.4255	1.0040	3.4120	**0.0010**	1.4283	5.4227
Interaction effect	−3.6245	1.4899	−2.4327	**0.0050**	−6.5884	−0.6606

Abbreviations: B, coefficient; LLCI, lower level confidence interval; SE, standard error; ULCI, upper level confidence interval.

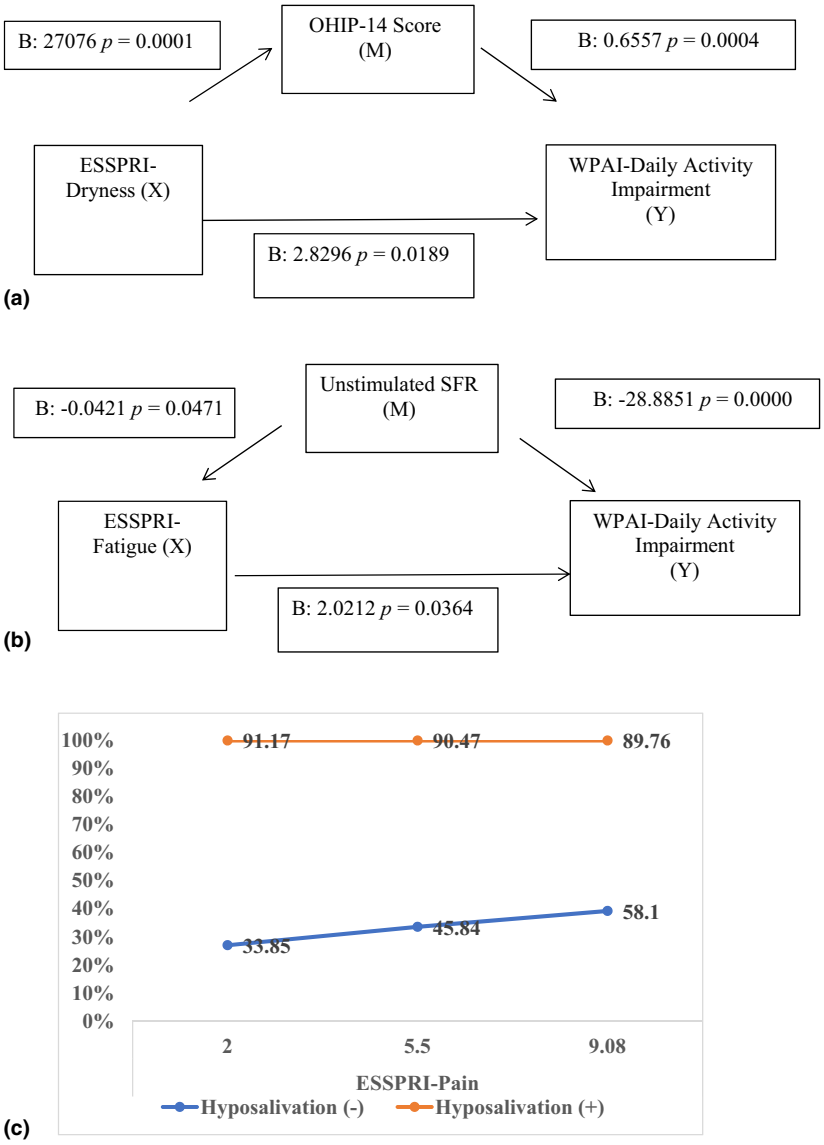

FIGURE 1 (a, b) Mediation analyses for WPAI-activity impairment in pSS. (c) Moderation analysis for WPAI-daily impairment in patients without glandular involvement.

et al., 2016; Vitali et al., 2002), problems in tooth filling and dentures, presence of halitosis and tooth mobility lead to poor OHRQoL of patients with pSS (Rusthen et al., 2017; Schmalz et al., 2020). An increase in tooth decay, periodontal diseases, tooth loss, oral mucosal changes and imbalance of oral microbiome as well as a decrease in soft tissue repair, buffer capacity, remineralization, immunity and defence mechanisms are the results of insufficient salivary flow rate and lack of regular dental visits (Christensen et al., 2001; de Goés Soares et al., 2018; Plemons et al., 2014; Soto-Rojas & Kraus, 2002; Stewart et al., 2008).

During the previous year, the number of visits was 4 for family practitioners and 2 for rheumatologists. The mean duration from last dental visits was almost 15 months. Surprisingly, patients contacted rheumatologists first for their oral complaints during the last year. Oral health is influenced by various factors including the dental care system, oral health behaviours and general health status (Ramraj et al., 2012). Patients should have access to oral health education programs focusing on the effects of the disease on oral health and the importance of regular dental visit. In addition, proactive dental management and preventive applications should be planned by dentists based on individual risk factors (Christensen et al., 2001; de Goés Soares et al., 2018; Plemons et al., 2014; Roblegg et al., 2019; Stewart et al., 2008; Yalcinkaya et al., 2020). Healthcare utilization is a key factor in evaluating the burden of the disease (Hackett et al., 2018), and thus strategies should be implemented to encourage regular dental visits for prevention, early diagnosis and treatment protocols designed for individual risk factors (Westhoff et al., 2012). Rheumatologists, as essential healthcare providers for patients with chronic disease can play a critical role in promoting oral hygiene practices and regular dental visits (Schmalz et al., 2020).

The study results showed that different associations were available for WPAI activity impairment. Firstly, an elevated ESSPRI-Dryness score directly increased WPAI activity impairment score without a mediator. Poor OHRQOL as a mediator was also associated with WPAI activity impairment indirectly in the first mediation analysis. Furthermore, a decrease in U-SFR was found to be a significant mediator for the relationship between increase in ESSPRI-Fatigue score and the WPAI activity impairment in the

second mediation analysis. ESSPRI-Dryness with OHRQoL in the first model and ESSPRI-Fatigue with low U-SFR in the second model were two clues for treatment plans. Salivary gland involvement was the main component of WPAI activity impairment, as mentioned in the previous study (Bejarano et al., 2021). As it is known that a decrease in saliva production leads to dysphagia, altered taste, burning sensation, limitation in social relations and difficulties in oral functions, digestion, lubrication, microbial homeostasis, moistening and protection of oral ecosystem in patients with pSS (Christensen et al., 2001; de Goés Soares et al., 2018; Negrini et al., 2022; Roblegg et al., 2019; Soto-Rojas & Kraus, 2002). At this point, topical and systemic treatment protocols are helpful to relieve dryness-related symptoms. The first-line treatment is to use non-pharmacological stimulation techniques including lozenges, sugar free candies, xylitol and sugar free chewing gum for the stimulation of salivary glands. In the second step, pharmacological stimulation with pilocarpine and cevimeline as muscarinic agonists, saliva substitutes mimicking the content of natural saliva and a removable electrostimulation device for the innervation of lingual nerve are considered to overcome oral discomfort in severe glandular involvement (Alajbeg et al., 2012; Negrini et al., 2022; Ramos-Casals et al., 2020; Strietzel et al., 2011). Moreover, patient education is thought to be a key component of patient empowerment strategy for the improvement of both quality of life and activities of daily life (Hackett et al., 2018; Schmalz et al., 2020).

In the second step, fatigue was found to be risk factor for WPAI activity impairment without a mediator. Additionally, it was also found to be associated with HADS-D and HADS-A in the study. Fatigue, anxiety, depression and decrease in physical activity are main components of limitations in the daily life of most patients (Negrini et al., 2022). Moreover, fatigue is commonly observed (Meijer et al., 2009; Negrini et al., 2022) and is often affected by the depression that is highly prevalent in pSS (Westhoff et al., 2012). Fatigue has also significant impacts on physical exercise, gardening/shopping, performing and household chores as well as socializing with others and engaging in recreation/hobbies (Schoon et al., 2022). Therefore, it is thought be other target symptom along with depression, for treatment protocols to reduce the impact of the disease on the patient's life (Cui et al., 2018; Westhoff et al., 2012).

The other essential result was that rise in WPAI activity impairment score was associated with gradual increases of ESSPRI-Pain score in patients without hyposalivation according to the Moderation analysis. Pain as one of the essential symptoms in pSS (Sandoval-Flores et al., 2021; Seror et al., 2015) was found to be the third clue for treatment plans in patients without salivary gland involvement. Therefore, pain management is the essential factor for patient empowerment in these patients.

When arthralgia or arthritis were accompanied with hyposalivation, daily activities of patients were poorly affected in the study. In addition, ESSPRI-Pain was the reason of elevated WPAI-Daily impairment score in patients with arthralgias. Musculoskeletal involvement is seen in the majority of patients (Mandl et al., 2017; Negrini et al., 2022) and causes poor health-related quality of life (Meijer et al., 2009). Activities of daily living are also associated with xerostomia and arthralgia in pSS (Bejarano et al., 2021). Therefore, these results could have been predicted.

When oral dryness and ocular dryness were together in patients, this association affected Activity impairment negatively. Ocular dryness is most frequently observed in this patient group. Changes in qualitative and quantitative properties of tear film lead to chronic inflammation on ocular surface, photosensitivity, erythema, itching and foreign body sensation in lachrymal gland involvement (Hackett et al., 2018; Meijer et al., 2009; Negrini et al., 2022). At this point, presence of salivary and lacrimal gland involvement together could be thought as severe clinical spectrum for daily activities of patients (Negrini et al., 2022).

It is important to note that WPAI-Daily impairment is a valid and reliable tool that has been previously studies (Erdal et al., 2021; Karacayli et al., 2021; Mumcu et al., 2017). The current study also found that WPAI activity impairment was associated with self-reported general health status, disease activity, and symptom control. It is important to have evidence-based data regarding daily activities in order to inform treatment protocols in clinical practice, as unpaid work loss is an important factor in healthcare utilization and health policy (McCormick et al., 2019).

The strength of the study was to show key points for Daily activity impairment by using both mediation and moderation analyses in patients with pSS. These analyses helped to understand hidden relations on outcome variables in clinical practice (Mumcu et al., 2020; Yay et al., 2019). In previous studies, increase in oral ulcer-related pain in Behcet's disease (Karacayli et al., 2021) and HADS-D score in Takayasu arteritis (Erdal et al., 2021) are found to be significant mediators for WPAI-Daily activity impairment. Furthermore, the relationships identified through these mediation and moderation analyses offer important insights to rheumatologists and oral medicine specialists seeking to create personalized treatment strategies for daily activity impairment and empower patients with pSS. However, the study had some limitations. Firstly, limited number of patients were employee, so subgroups of WPAI regarding absenteeism, presenteeism and overall impairment were not evaluated. Secondly, data collection was terminated due to the onset of COVID-19 pandemic unfortunately. Therefore, the results should be interpreted with these limitations.

Consequently, it was found that WPAI activity impairment was affected by ESSPRI-Dryness with OHRQoL as well as ESSPRI-Fatigue with low U-SFR in glandular involvement. However, ESPRI-Pain was found to be the main factor for poor WPAI activity Impairment in patients without glandular involvement. In a holistic view, the minimizing the effects of the disease on daily life in pSS should be focused on patient-centred care according to individual needs. Therefore, these relationships are critical for treatment decisions during follow-up periods. In addition, rheumatologists monitoring patients with dry mouth together with the dentist and motivating their patients to go to the dentist regularly contributes to the chronic disease management.

AUTHOR CONTRIBUTIONS

Yıldız Yenissoy: Data curation; resources; methodology; writing – original draft; formal analysis; conceptualization. **Elif Naz Altıngöz:** Data curation; resources; methodology; writing – original draft. **Aysun Kapusuz:** Data curation; resources; writing – original draft; methodology. **Kerem Abacar:** Data curation; writing – review and editing; methodology. **Imren Tatlı:** Resources; writing – review and editing; methodology. **Filiz Türe-Özdemir:** Resources; methodology; writing – review and editing. **Umit Karacayli:** Visualization; supervision; writing – original draft. **Meral Yay:** Methodology; formal analysis; supervision; writing – original draft; visualization. **Haner Direskeneli:** Supervision; writing – original draft; validation. **Farida Fortune:** Writing – review and editing; supervision; methodology; conceptualization. **Nevsun Inanc:** Writing – review and editing; conceptualization; investigation; supervision; methodology; validation; project administration. **Gonca Mumcu:** Writing – review and editing; writing – original draft; project administration; conceptualization; methodology; supervision.

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DATA AVAILABILITY STATEMENT

The data is available from the corresponding author.

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