Primary dental care treatment in primary Sjögren's syndrome: a possible role in improving salivary flow rate

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Abstract

Objective

Primary Sjögren's syndrome (pSS) is an inflammatory chronic disorder that mainly affects exocrine glands. Additionally, oral infections can aggravate the glandular dysfunction. However, data on primary dental care (PDC) treatment in pSS are scarce. This study aimed to appraise the impact of PDC on the Xerostomia Inventory (XI), unstimulated/stimulated salivary flow rates and salivary cytokine profile in pSS.

Methods

Fifty-two pSS patients and 52 sex- and age-matched control participants without systemic autoimmune diseases were included in a prospective study. At inclusion, all participants were assessed through a standardised protocol, measurement of salivary pro-inflammatory cytokines, and underwent PDC. Dental procedures included: oral hygiene guidance, restorative treatment of caries, surgical removal of residual roots and impacted or partially erupted teeth, cysts, supra and subgingival periodontal scaling and treatment of soft tissue disorders (removal of lesions and treatment of opportunistic infections). After 3 months, the clinical/laboratorial assessments were repeated.

Results

At inclusion, the Decayed, Missing and Filled Teeth (DMFT) index was higher in the pSS patients than in the control group (13.3±8.2 vs. 8.6±6.2, p=0.002), whereas periodontal parameters were comparable in both groups (p>0.05). After PDC, 26.9% of pSS patients showed a reduction of at least 6 points (clinical improvement) in XI, but mean XI remained unchanged (p=0.285). PDC resulted in an increase in mean unstimulated (p<0.001) and stimulated (p=0.001) salivary flow rates in pSS, with no change in salivary cytokine profile (p≥0.05).

Conclusion

PDC promoted improvement in unstimulated and stimulated salivary flow rates in pSS. This novel finding reinforces the recommendation of this strategy for pSS patients. Clinicaltrials.gov (Identifier: NCT03711214).

Key words

primary Sjögren's syndrome, primary dental care, xerostomia, salivary flow, dental caries

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Introduction

Primary Sjögren's syndrome (pSS) is an immune-mediated inflammatory chronic sickness that mostly affects exocrine glands, leading to reduction of the lacrimal and salivary flow rates and, consequently, dry eye and mouth (sicca syndrome). Several organs and systems may also be involved, mostly manifesting with polyarthralgia/polyarthritis, cutaneous vasculitis, bronchiolitis/pneumonitis, tubulointerstitial nephritis and peripheral neuropathy, as well as an augmented risk of developing lymphoma (1). Various serological markers are associated with the phenotypic expression of this disease, principally anti-Ro (SS-A) and anti-La (SS-B) antibodies (2). pSS is currently considered the most prevalent systemic autoimmune rheumatic illness after rheumatoid arthritis (1), with an estimated prevalence of 60.82 cases per 100,000 inhabitants (3). This disease predominantly affects women (≅ 10:1), with an incidence peak between 40 and 60 years old (3).

pSS pathophysiology is not fully understood, however abnormal functions of plasmacytoid dendritic cells, B and T lymphocytes and activated salivary gland epithelial cells promoting the production of numerous cytokines and autoantibodies are cardinal findings (4). Pro-inflammatory cytokines, such as tumour necrosis factor-α (TNF-α), interleukin-1 (IL-1) and IL-6, can have a role in pSS development (4). Moreover, the exacerbated regulation of interferon-α (INF-α) coding genes in the peripheral blood and salivary gland cells stimulates the B-cell activating factor (BAFF) production, a TNF family ligand that stimulates the maturation and differentiation of B lymphocytes (1, 4).

The most frequent pSS symptoms are xerophthalmia and xerostomia: ≅ 92% and 93% at presentation, respectively (5). Hyposalivation has important consequences for the oral health (6). In this regard, pSS patients have decreased salivary flow rate, pH and buffering capacity of saliva, and increased salivary sodium and chloride concentrations compared to age-matched healthy individuals (7). These quantitative and qualitative salivary abnormalities can lead to multiple caries with tooth loss and oral candidiasis (6-8). Of note, a recent study showed that pSS patients have a higher risk of caries than individuals with other causes of hyposalivation (9).

On the other hand, available data on a possible clinical association between pSS and periodontitis are conflicting (10-15). Despite this, it is interesting that murine periodontitis can cause major salivary gland damage and hyposalivation, and the alleviation of this experimental condition leads to improvement of the glandular function (16). Similarly, reduction of unstimulated and stimulated salivary flow rates was reported in adult individuals from the general population with chronic periodontitis, which may be due to the injury of salivary glands induced by inflammatory mediators and free radicals produced in this disorder (17).

Nonetheless, data on the impact of the primary dental care (PDC) treatment on symptoms and disease activity parameters, as well as on quality of life in pSS are scarce. Treatment of chronic periodontitis in a small sample of pSS patients (n=7) provided an increase in salivary flow rate and improvement of xerostomia (18). However, the small number of patients included, as well as the lack of a complete evaluation including a specific questionnaire on xerostomia and measurement of unstimulated and stimulated salivary flow rates limit the interpretation of their findings (18).

Hence, the objectives of this study were to appraise the impact of PDC treatment on xerostomia using a specific questionnaire, unstimulated and stimulated salivary flow rates and salivary cytokine profile in pSS.

Materials and methods

Study design, pSS patients and control individuals

This is a prospective study that assessed fifty-two adult pSS patients (according to the ACR (American College of Rheumatology)/EULAR (European League Against Rheumatism) classification criteria (19)) under regular follow-up at the Sjögren's Syndrome Outpatient Clinic of the Rheumatology Division, Hospital das Clinicas

HCFMUSP, Faculdade de Medicina, Universidade de São Paulo, Brazil. In addition, 52 volunteers without systemic autoimmune diseases matched with pSS patients for sex and age and with a comparable socioeconomic classification (20) were enrolled as a control group. Control individuals were recruited from hospital staff and their family members. All participants were recruited from June 29, 2018 to November 13, 2020.

Exclusion criteria were: other systemic autoimmune rheumatic diseases, sarcoidosis, amyloidosis, graft *versus* host disease, B and C hepatitis, HIV, history of head or neck radiotherapy, current use of drugs that can cause xerostomia such as tricyclic antidepressants (19, 21), pregnancy, breastfeeding and periodontal treatment up to 6 months prior to study entry. All participants were evaluated at baseline prior to PDC treatment (D0) and 3 months after PDC treatment (D90) using a standardised clinical protocol (Fig. 1). Fifty-four patients were recruited, however two of them were excluded due to meeting classification criteria for other systemic autoimmune rheumatic diseases (one case of systemic lupus erythematosus and another of antisynthetase antibody syndrome).

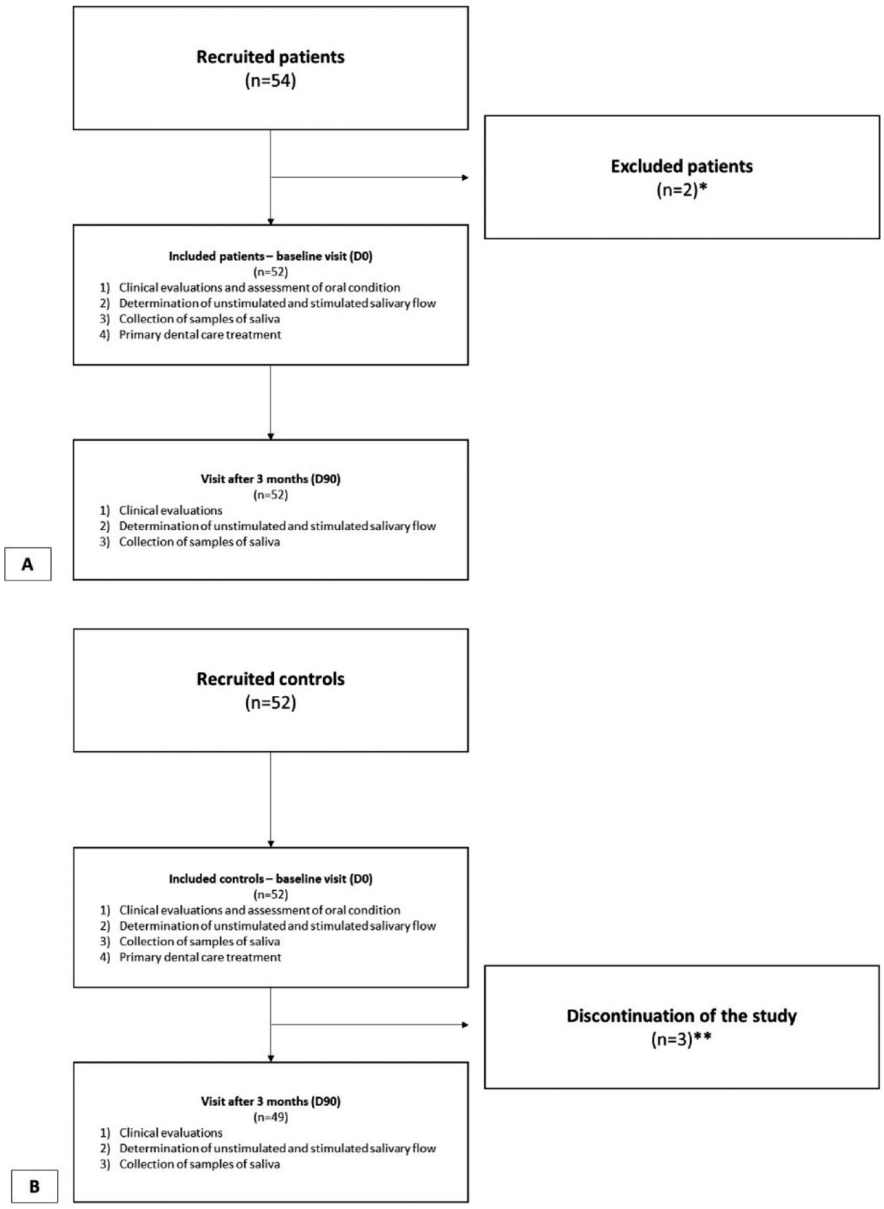

Fig. 1. Flow chart for pSS patients (A) and control individuals (B).
*Two patients were excluded due to meeting classification criteria for other systemic autoimmune rheumatic diseases (one case of systemic lupus erythematosus and another of antisynthetase antibody syndrome).
**Three control individuals discontinued the study because they were unable to attend their last visit.
pSS: primary Sjögren's syndrome.

Ethics approval and consent

All procedures carried out in the present study were in agreement with the ethical guidelines of the institutional review board and with the Helsinki declaration, and it was approved by the institutional review board (Comissão de Ética para Análise de Projetos de Pesquisa (CAPPesq)) (39705014.6.0000.0068, report: 2.676.161). All participants signed the informed consent form before study inclusion. The study was also registered in *Clinicaltrials.gov* (Identifier: NCT03711214).

Procedures

On D0, all participants were submitted to: 1) clinical evaluations and assessment of oral condition; 2) determination of unstimulated and stimulated salivary flow rates; 3) collection of samples of saliva; and 4) PDC treatment. After 3 months (D90), the clinical and laboratorial assessments were repeated (Fig. 1).

PDC treatment, Decayed, Missing and Filled Teeth (DMFT) index and unstimulated and stimulated salivary flow rates

On D0 (right after clinical assessments), all participants were submitted to PDC treatment, which was performed by the same investigator (VAOM). This treatment aims to resolve foci of oral infections (mucosal and dental conditions) to avoid systemic and local complications. The main foci of oral infections considered were: caries, periodontitis, apical periodontitis, impacted or partially erupted teeth, not completely protected by bone or exhibiting radiolucency, dental pulp necrosis, ulcerations, mucosal infections and other possible lesions (22). The dental procedures included: oral hygiene guidance, restorative and preventive treatment of caries, surgical removal of residual roots and impacted or partially erupt-

ed teeth, cysts, supra and subgingival periodontal scaling and treatment of soft tissue disorders (removal of lesions and treatment of opportunistic infections) (22, 23). For the dental data collection (carious and non-carious lesions), the clinical examination was conducted with a dental exploratory probe. Assessment of the DMFT index was also made for all participants (24). Unstimulated and stimulated salivary flow rates were measured as previously described (25). Participants with clinical indications had dental restorative treatment (22, 23).

Patients and controls were assessed for periodontitis according to the latest classification of periodontal diseases and conditions (26). To assess periodontal status, a conventional North Carolina periodontal probe was used, with the exclusion of third molars. Six periodontal sites from all teeth were evaluated (mesio-buccal, mid-buccal, disto-buccal, mesio-lingual, mid-lingual and disto-lingual) regarding probing depth, clinical attachment level and bleeding on probing (10). When the presence of dental calculus was identified, it was removed using manual periodontal curettes (supra and subgingival). Treatment consisted of periodontal scaling, in addition to root planing when indicated (18).

Patients with pericoronitis had their third molars extracted. Those with candidiasis were treated with topical antifungal drugs (1, 23). Participants who exhibited inflammatory fibrous hyperplasia had hyperplastic tissue removed, and the irritative factor corrected. In cases of leucoplakia, an excisional biopsy was performed.

Clinical evaluations

Xerostomia was assessed for all participants using a specific questionnaire, the Xerostomia Inventory (XI) (27). This questionnaire is composed of 11 items evaluating oral dryness and mouthfeel, ranging from 11 - no xerostomia to 55 - extreme xerostomia (27). Clinically meaningful improvement of xerostomia was defined as a reduction of at least 6 points in XI score (28). The quality of life was appraised through the general questionnaire Short-Form 36 (SF-36) (29). Systemic disease activity in pSS patients was measured by the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) (30), and the symptom index was assessed by the EULAR Sjögren's Syndrome Reported Index (ESSPRI) (31). Concerning ESSDAI, a decrease of at least three points was considered as a relevant improvement (32). Regarding ESSPRI, a reduction of at least one point was considered as a clinically relevant improvement (32). Clinical evaluations of all participants were conducted by investigators not involved in the PDC treatment (TFF and LEBV). At both time points of the study (D0 and D90), the investigators recorded all treatments in current use through face-to-face interviews with patients. A questionnaire on comorbidities, hypertension, dyslipidemia, diabetes and smoking was also applied to pSS patients and controls, since the last two conditions can influence oral health (33, 34).

Primary outcome measures

The primary outcome was the reduction in xerostomia assessed by the mean XI values after PDC treatment (*i.e.* on visit D90 compared to visit D0) (27, 28).

Cytokine profile in saliva

Saliva samples were centrifuged under refrigeration at 3,000 rpm for 15 minutes, and they were stored at -80°C until use. Levels of pro-inflammatory cytokines were determined at D0 and D90 using the Luminex method (35). Salivary concentrations of cytokines implicated in pathophysiology of periodontitis (35) and pSS (4, 36), TNF-α, IL-1b, IL-6, BAFF and resistin, were determinated, as well as metalloproteinase (MMP-9) (35). Salivary concentrations of TNF-α, IL-1b, IL-6 and resistin were determined using the MAGPIX - Millipore/Luminex system (CA, USA) with commercially available kits (MILLIPLEX MAP KIT, HUMAN ADIPOCYTE MAGNETIC BEAD PANEL, MILLIPORE CORPORATION, Billerica, MA, USA), as manufacturer's guidelines. Salivary levels of BAFF and MMP-9 were measured by the Enzyme-Linked Immunosorbent Assay (ELISA) technique using commercially available kits (R&D SYSTEMS - Minneapolis, USA), according to the manufacturer's recommendations. Coefficients of intra-assay and inter-assay variation (CV%) for each analyte were: TNF-α (<10, <20), IL-1b (<15, <20), IL-6 (<10, <20), resistin (<10, <15), BAFF (7.2, 11.6) and MMP-9 (2.9 and 7.9), respectively.

Statistical analysis

Data were gathered on REDCap web-platform (Vanderbilt University, Nashville, TN, USA). Statistical analyses were done through the SigmaStat software, version 3.1, 2004. The normal distribution of each continuous parameter was appraised using Kolmogorov-Smirnov test. pSS and control groups were compared regarding continuous and categorical parameters through Student's t-test or Mann-Whitney U-test, and Chi-square or Fisher's exact tests, when recommended. pSS patients at baseline (D0) and 3 months after PDC treatment (D90) were evaluated for continuous variables through paired t test or Wilcoxon test, and using McNemar's test for categorical parameters, when applicable. Pearson product moment correlation (r) or Spearman rank order correlation (r_s) were used to assess the possible correlations between disease parameters such as XI, ESSPRI (total score and ocular/oral dryness scale of ESSPRI) and unstimulated/stimulated salivary flow rates at baseline (D0) and after three months of dental treatment (D90). Further analyses appraised baseline characteristics (at D0) that could influence the stimulated salivary flow rate after three months of dental treatment (at D90). Multivariate regression analysis was performed using stimulated salivary flow rate at D90 as the dependent variable and, as independent variables, all baseline characteristics (at D0) with $p<0.20$ in the univariate analysis. Data were presented as mean (±) standard deviation (SD), median (interquartile interval 25–75%), or n (%). Only two-tailed tests were used. It was considered significant $p<0.05$. The pSS group consisted of a convenience sample. The

Table I. Comparative analysis of pSS patients and control individuals regarding demographic characteristics and comorbidities.

	pSS n=52	Controls n=52	*p*-value
Demographic characteristics			
Age, years	51.2 ± 11.5	51.9 ± 13.0	0.800
Female sex	51 (98.1)	51 (98.1)	1.000
Ethnicity			
White	34 (65.4)	34 (65.4)	1.000
African-Latin American	16 (30.8)	16 (30.8)	
Asian	2 (3.8)	2 (3.8)	
Socioeconomic status			
A/B/C1*	38 (73.1)	40 (76.9)	0.821
C2/D/E*	14 (26.9)	12 (23.1)	
Comorbidities			
Hypertension	15 (28.9)	16 (30.8)	0.999
Diabetes	4 (7.7)	5 (9.6)	1.000
Dyslipidaemia	7 (13.5)	9 (17.3)	0.787
Current smoking	2 (3.9)	2 (3.9)	1.000

Data are presented as n (%) or mean ± standard deviation (SD).
*A/B/C1/C2/D/E: socioeconomic classes according to the Socioeconomic Classification of the Brazilian Association of Research Companies (ABEP) (20). pSS: primary Sjögren's syndrome.

post-hoc power was 90.9% with alpha 0.05, considering the mean DMFT index of 13.3±8.2 in pSS patients and 8.6±6.2 in control individuals.

Results

Demographic and clinical features of pSS patients

Fifty-two pSS patients were enrolled. There was predominance of females (98.1%), and the mean age was 51.2 ± 11.5 years. The mean time of diagnosis was 9.5±7.9 years, and of symptom onset was 11.8±8.6 years. At study inclusion, these patients had the following previous pSS clinical manifestations: dry eye (94.2%), dry mouth (94.2%), history of parotitis (76.9%), fatigue (75%), arthralgia (73.1%), arthritis (67.3%), cutaneous vasculitis (28.8%), Raynaud's phenomenon (17.3%), lung involvement (23.1%), renal tubular acidosis (5.8%), peripheral nervous system involvement (9.6%) and lymphoma (2%). Positive anti-Ro (SS-A) and anti-La (SS-B) antibodies were observed in 90.4% and 53.9%, respectively. Thirty-six patients (69.2%) had undergone minor salivary gland biopsy, which revealed focal lymphocytic sialadenitis with focus score ≥1 in 35/36 (97.3%) of them. The unstimulated salivary flow rate was ≤0.1 mL/min in 51.9% of the patients, and changes in salivary gland scintigraphy were observed in 77.8% of the cases. The Schirmer test was positive in 47.7% of the patients and 58.8% had positive Ocular Staining Score or van Bijsterveld score on at least one eye. Additionally, antinuclear antibodies and rheumatoid factor were positive in 88.5% and 67.3% of patients, respectively. Hypergammaglobulinaemia was observed in 80.4% of them, as well as 7.7% and 17.3% had low levels of C3 and C4 complement fractions, respectively. Of note, all patients were negative for anti-dsDNA and anti-Sm antibodies.

Comparative analysis of pSS patients vs. control participants at baseline (D0)

pSS patients and control participants had similar age (p=0.800), sex (p=1.000) and ethnicity (p=1.000). Moreover, both groups were comparable regarding socioeconomic status (p=0.821) (Table I). The comorbidity profile, including current smoking, was also similar in both groups (Table I).

Unstimulated and stimulated salivary flow rates at D0, as well as XI values, as expected, were quite different between pSS patients and control individuals (p<0.05) (Table II). The number per individual and the percentage per individual per present tooth of decayed teeth, number per individual of missing teeth previous to clinical examination and the percentage of filled teeth per individual per present tooth were higher in the pSS group than in control participants (p<0.05) (Table II). In accordance, DMFT index was higher in the first group: 13.3±8.2 *vs.* 8.6±6.2 (p=0.002). The frequency of non-carious cervical lesions (NCCLs) per individual per present tooth (p=0.008) and also their number per individual (p=0.012) in pSS patients were higher than in control participants. Periodontal parameters were comparable between pSS and control groups (p>0.05) (Table II). Otherwise, salivary concentrations of TNF-α, IL-6 and resistin, as well as MMP-9 were higher in the pSS group than in control participants (p<0.05) (Table III).

On D0, pSS patients had worse results than controls in the physical health component of SF-36 [40.3 (33.9–51.1) *vs.* 54.4 (45.8–57.3), p<0.001], and in the mental health component [29.1 (13.7–52.4) *vs.* 47.8 (29.2–52.4), p<0.024], respectively.

Interventions in the groups of pSS patients and controls

The total number of restorations performed due to caries [1 (0-4) *vs.* 0 (0-1), p=0.011], as well as the percentage of restorations due to caries per individual per tooth present [9.7% (0-24) *vs.* 0% (0-5.2), p=0.003] were higher in the pSS group than in controls, respectively. Similarly, the total number of restorations due to NCCL [0 (0-3.5) *vs.* 0 (0-0.5), p=0.012) and the percentage of restorations due to NCCL [4.6% (0-19.1) *vs.* 0% (0-3.6), p=0.003] were higher in the first group, respectively. The cleaning procedure was offered to all participants, and 23.1% of pSS patients *vs.* 15.4% of controls underwent root planing and scaling (p=0.456).

Comparative analysis of pSS patients before (D0) and after PDC treatment (D90)

All 52 pSS patients completed the study (D0 and D90). At D90, 14/52 (26.9%) of pSS patients had a clinically meaningful improvement (reduction of at least 6 points) in XI score, but mean values of XI were comparable at these two moments (p=0.285) (Table IV). pSS patients had enhancement in unstimulated (p<0.001) and stimulated

Table II. Comparative analysis of pSS patients and control individuals regarding salivary flow rates, Xerostomia Inventory and odontological parameters at baseline (D0).

	pSS n=52	Controls n=52	*p*-value
Salivary flow rates (mL/min)			
Unstimulated	0.1 (0.04-0.2)	0.6 (0.3-0.8)	<0.001
Stimulated	0.5 (0.3-1.1)	2.0 (1.0-3.0)	<0.001
Xerostomia inventory	42.0 (33.0-46.5)	17.0 (13.0-21.5)	<0.001
Dental parameters			
Decayed teeth n per individual	1.0 (0-4.0)	0 (0-1.0)	0.020
% per individual per present tooth	6.1 (0-23.4)	0 (0-4.5)	0.009
Missing teeth previous to clinical examination n per individual	6.5 (2.0-16.0)	3.0 (0-11.5)	0.038
Teeth condemned by caries n per individual	0 (0-0)	0 (0-0)	0.761
% per individual per present tooth	0 (0-0)	0 (0-0)	0.860
Filled teeth n per individual	9.0 (4.5-14.0)	8.0 (1.5-12.0)	0.209
% per individual per present tooth	48.0 (19.9-64.7)	29.1 (1.8-51.0)	0.045
DMFT index	13.3 ± 8.2	8.6 ± 6.2	0.002
Non-carious cervical lesions n per individual	0 (0-3.5)	0 (0-0.5)	0.012
% per individual per present tooth	0 (0-18.1)	0 (0-1.8)	0.008
Periodontal parameters			
Mean clinical probing depth (mm)	1.8 (1.5-1.9)	2.0 (1.0-2.3)	0.809
Mean clinical attachment level (mm)	1.8 (1.7-2.0)	2.0 (1.0-2.8)	0.809
Bleeding on probing (%)	0 (0-1.0)	0 (0-1.8)	0.619
Number of periodontal pockets (≥4)	0 (0-4.0)	0 (0-0)	0.385
Periodontitis	12 (23.1)	8 (15.4)	0.456
Stage I	5/12 (41.7)	0	0.136
Stage II	4/12 (33.3)	2/8 (25.0)	
Stage III	2/12 (16.7)	5/8 (62.5)	
Peri-implantitis	1/12 (8.3)	1/8 (12.5)	
Grade A	9/11 (81.8)	5/7 (71.4)	1.000
Grade B	2/11 (18.2)	2/7 (28.6)	
Grade C	0	0	
Pericoronaritis	2 (3.9)	2 (3.9)	1.000
Inflammatory fibrous hyperplasia	2 (3.9) 0	(0) 0.495	
Clinical candidiasis	7 (13.5)	1 (1.9)	0.060
Oral leucoplakia	0 (0)	1 (1.9)	1.000

Data are presented as n (%), mean ± standard deviation (SD), or median (25th – 75th percentile).
pSS: primary Sjögren's syndrome; DMFT: Decayed, Missing and Filled Teeth index.

Table III. Comparative analysis of pSS patients and control individuals regarding levels of salivary cytokines at baseline (D0).

	pSS n=52	Controls n=52	*p*-value
TNF-α (pg/mL)	11.5 (6.1-27.3)	4.2 (1.8-8.4)	<0.001
IL-1β (pg/mL)	51.0 (15.1-131.9)	36.2 (10.5-74.6)	0.103
IL-6 (pg/mL)	41.2 (21.8-82.9)	22.4 (6.2-38.7)	0.007
Resistin (pg/mL)	51,421.0 (24,750.0-67,358.5)	25,970.0 (6,670.5-56,078.0)	0.004
MMP-9 (pg/mL)	4.8 (2.6-7.4)	2.4 (1.2-4.7)	<0.001
BAFF (pg/mL)	23.0 (9.5-53.0)	14.5 (8.0-29.0)	0.144

Data are presented as n (%) or median (25^{th} – 75^{th} percentile).
pSS: primary Sjögren's syndrome; BAFF: B-cell activating factor; IL: interleukin; MMP-9: Matrix Metalloproteinasis-9; TNF-α: tumour necrosis factor-alpha.

(p=0.001) salivary flow rates on D90 comparatively to D0. Median ESSPRI (p=0.072) and ESSDAI (p=0,111) values were comparable on D0 and D90 (Table IV). Salivary cytokine levels were also unchanged on D0 and D90 (p≥0.05) (Table IV). Of note, topical and oral treatments for dry mouth, as well as the use of hydroxychloroquine, prednisone, immunosuppressants and biological agents were similar on D0 and D90 (p>0.05) (Table IV). There were not ameliorations in SF-36 components after PDC treatment (p>0.05). Positive moderate to strong correlations between XI and ESSPRI were observed at D0 (r_s=0.577, p<0.001) and D90 (r_s=0.480, p<0.001). There were also positive moderate correlations between XI and ocular/oral dryness scale of ESSPRI at D0 (r_s=0.497, p<0.001) and D90 (r_s=0.415, p=0.002). In addition, a positive correlation between the occurrence of improvement in XI (decrease of at least 6 points) and improvement in ESSPRI (decrease of at least 1 point) (r_s=0.324, p=0.020) was observed. On the other hand, there were not correlations between XI and stimulated salivary flow rate at D0 (r_s=-0.249, p=0.074) and D90 (r_s=-0.012, p=0.934). Similarly, no correlations were observed between ESSPRI and stimulated flow rate at D0 (r_s=-0.204, p=0.147) and D90 (r_s=0.017, p=0.903); nor between ocular/oral dryness scale of ESSPRI and stimulated salivary flow rate at D0 (r_s=-0.196, p=0.163) and D90 (r_s=-0,074, p=0.602). Furthermore, there were no correlations between improvement in XI (decrease of at least 6 points) and stimulated salivary flow rate at D90 (r_s=0.013, p=0.927); nor between ESSPRI improvement (decrease of at least 1 point) and stimulated salivary flow at D90 (r_s=0.048, p=0.733).

Additional analyses assessed baseline characteristics (at D0) that could influence the stimulated salivary flow rate after three months of dental treatment (D90). Baseline characteristics evaluated in the univariate analysis included: age, sex, ethnicity, XI, ESSPRI (total score and ocular/oral dryness score), unstimulated and stimulated salivary flow rates, salivary levels of cytokines (TNF-α, IL-1b, IL-6, BAFF and resistin) and MMP-9, ESSDAI, as well as current treatments with prednisone (and current dose), hydroxychloroquine, immunosuppressive drugs (methotrexate, leflunomide, azathioprine, mycophenolate mofetil and cyclophosphamide), rituximab, pilocarpine, n-acetylcysteine, linseed oil and artificial saliva. Multivariate regression analysis was performed using stimulated salivary flow rate at D90 as the dependent variable and, as independent variables, all baseline characteristics (at D0) with p<0.20 in the univariate analysis, including age (p=0.001), unstimulated and stimulated salivary flow rates (p<0.001 and p<0.001, respectively), salivary levels of TNF-α (p<0.001), IL-

Table IV. Comparative analysis of pSS patients who completed clinical assessments at baseline (D0) and at 3 months after PDC treatment (D90).

	pSS – D0 n=52	pSS – D90 n=52	*p* value
Salivary flow rates (mL/min)			
Unstimulated[@]	0.1 (0.04-0.2)	0.3 (0.2-0.4)	<0.001
Stimulated[@]	0.5 (0.3-1.1)	0.7 (0.4-1.4)	0.001
Xerostomia inventory	39.7 ± 9.5	38.5 ± 8.6	0.285
Clinical improvement[*]	-	14 (26.9)	-
ESSPRI	5.8 (4.2-7.2)	6.2 (4.8-7.8)	0.072
Ocular and oral dryness	7.0 (5.0-8.0)	7.5 (5.0-8.0)	0.975
Fatigue	5.0 (4.5-7.5)	6.5 (4.5-8.0)	0.092
Pain	6.0 (2.0-8.0)	6.0 (2.5-8.0)	0.806
Clinical improvement[**]	-	6 (11.5)	-
ESSDAI	3.0 (1.0-7.0)	2.0 (0-6.5)	0.111
Clinical improvement[***]	-	6 (11.5)	
Salivary levels			
TNF-α (pg/mL)	11.5 (6.1-27.3)	11.8 (5.2-24.7)	0.362
IL-1β (pg/mL)	51.0 (15.1-131.9)	43.0 (16.9-123.9)	0.649
IL-6 (pg/mL)	41.2 (21.8-82.9)	34.5 (14.6-80.3)	0.469
Resistin (pg/mL)	51,421.0 (24,750.0-67,358.5)	35,727.5 (17,668.5-70,290.0)	0.052
MMP-9 (pg/mL)	4.8 (2.6-7.4)	4.5 (2.7-7.7)	0.964
BAFF (pg/mL)	23.0 (9.5-53.0)	28.0 (7.5-79.0)	0.297
Current treatments			
Sicca syndrome			
Topical			
Artificial saliva	28 (53.9)	25 (48.1)	0.371
Artificial tears	47 (90.4)	41 (78.9)	0.041
Oral route			
Pilocarpine	4 (7.7)	4 (7.7)	1.000
N-acetylcysteine	26 (50)	22 (42.3)	0.221
Linseed oil	22 (42.3)	19 (36.5)	0.371
Systemic manifestations			
Prednisone	21 (40.4)	20 (38.5)	1.000
Dose (mg/day)	5 (5-10)	5 (5-17.5)	0.240
Hydroxychloroquine	26 (50)	22 (42.3)	0.221
Immunosuppressants			
Methotrexate	6 (11.5)	4 (7.7)	0.617
Leflunomide	3 (5.8)	4 (7.7)	1.000
Azathioprine	8 (15.4)	9 (17.3)	1.000
Mycophenolate mofetil	9 (17.3)	5 (9.6)	0.134
Cyclophosphamide	0 (0)	1 (1.9)	1.000
Biological agents			
Rituximab	3 (5.8)	3 (5.8)	1.000

Data are presented as n (%), mean ± standard deviation (SD), or median (25th – 75th percentile).
[@]Values of unstimulated (≤0.1 mL/min) and of stimulated (<0.5-0.7 mL/min) salivary flow rates are considered hyposalivation (6).
[*]Reduction of at least 6 points. [**]Reduction of at least 1 point. [***]Reduction of at least 3 points.
pSS: primary Sjögren's syndrome; PDC: primary dental care; ESSPRI: EULAR Sjögren's Syndrome Reported Index; ESSDAI: EULAR Sjögren's Syndrome Disease Activity Index; BAFF: B-cell activating factor; IL: interleukin; MMP-9: matrix metalloproteinasis-9; TNF-α: tumour necrosis factor-alpha.

1b (p<0.001), IL-6 (p=0.047), resistin (p=0.073), BAFF (p=0.001) and MMP-9 (p=0.041), current treatments with azathioprine (p=0.113) and artificial saliva (p=0.088). This multivariate analysis revealed that age (p=0.003), unstimulated salivary flow rate (p<0.001), salivary levels of TNF-α (p=0.043) and use of artificial saliva (p=0.037) at D0 were independently associated with the stimulated salivary flow rate at D90. In this regard, age (r=-0.436, p=0.001), salivary levels of TNF-α at D0 (r_s=-0.619, p<0.001) and current use of artificial saliva (0.6 (0.3-1.2) *vs*. 0.9 (0.5-1.8) mL/min, p=0.088) were negatively associated with the stimulated salivary flow rate at D90. In contrast, the unstimulated salivary flow rate at D0 was positively correlated with the stimulated salivary flow at D90 (r_s=0.600, p<0.001).

Comparative analysis of control individuals before (D0) and after PDC treatment (D90)

During the study (D0 *vs*. D90), the mean XI (p=0.124), unstimulated (p=0.680) and stimulated (p=0.089) salivary flow rates remained stable in the control group (Table V). Similarly, control individuals did not have improvement in SF-36 components after PDC treatment (p>0.05).

Discussion

This study demonstrated that PDC treatment promoted improvement in unstimulated and stimulated salivary flow rates in pSS patients, however without mean XI reduction. Moreover, it confirmed a high frequency of dental caries and tooth loss in pSS patients compared to sex-, age- and race-matched control individuals without autoimmune systemic diseases and with comparable socioeconomic classification and comorbidity profile.

The present work had some advantages, including its prospective design with a complete evaluation including measurement of unstimulated and stimulated salivary flow rates, as well as a specific xerostomia instrument. In addition, it included a homogeneous population of pSS patients, who were classified according to widely accepted criteria (19), and who had no other systemic autoimmune disorders as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). Indeed, RA and SLE can be associated with SS (secondary SS) (21), and they can affect the oral health (37). Another important aspect was the inclusion of a comparative control group without autoimmune systemic diseases matched for sex, age and race. In addition, both groups had comparable socioeconomic and comorbidity profiles, comprising current smoking, hypertension, diabetes and dyslipidemia. Indeed, demographic features and comorbidities are relevant for dental parameters, since age, ethnicity and socioeconomic status directly influence the frequency of caries (38), missing teeth (39) and DMFT values (40). Furthermore, age (41) and the socioeconomic factor may also influence some periodontal parameters (42). In the same way, current smoking (33) and diabetes (34) can influence the dental and gingival health status.

The number per individual and the per-

Table V. Comparative analysis of control individuals who completed clinical assessments at baseline (D0) and at 3 months after PDC treatment (D90).

	Controls – D0 n=49	Controls – D90 n=49	*p*-value
Salivary flow rates (mL/min)			
Unstimulated	0.6 (0.3-0.8)	0.6 (0.3-1.1)	0.680
Stimulated	2.2 ± 1.3	2.5 ± 1.4	0.089
Xerostomia inventory	18.6 ± 6.4	19.9 ± 7.0	0.124
Clinical improvement*	-	6 (12.3)	-
Salivary levels			
TNF-α (pg/mL)	4.3 (1.9-8.3)	4.7 (2.5-9.5)	0.861
IL-1β (pg/mL)	38.2 (10.9-74.5)	29.3 (13.6-56.0)	0.296
IL-6 (pg/mL)	23.0 (6.2-37.4)	14.9 (7.6-32.3)	0.249
Resistin (pg/mL)	32,965.8 ± 27,504.6	30,872.9 ± 27,116.9	0.480
MMP-9 (pg/mL)	2.3 (1.2-4.7)	2.5 (1.6-3.7)	0.846

Data are presented as n (%), mean ± standard deviation (SD), or median (25th – 75th percentile).
*Reduction of at least 6 points.
PDC: primary dental care; IL: interleukin; MMP-9: matrix metalloproteinasis-9; TNF-α: tumour necrosis factor-alpha.

centage per individual per present tooth of decayed teeth, number per individual of missing teeth previous to clinical examination and the percentage of filled teeth per individual per present tooth were higher in pSS patients than in control participants, showing the great challenge of dental caries in pSS patients, as observed in previous studies (9, 24, 43). We also calculated the DMFT index, which was higher in pSS patients than in control participants, as also reported in a previous study that evaluated Danish pSS patients (24).

An interesting observation of the present study is that NCCLs, which are clinically defined as loss of dental tissue around the cement-enamel not associated with dental caries (44), were also more frequent and numerous in pSS patients than in control individuals. To our knowledge, such finding was not reported previously in pSS. NCCLs are considered to have a multifactorial aetiology, with some important causal factors including age, acidified diet, oral health status and hygiene habits (44). In fact, the aetiology of these lesions has not yet been fully clarified, and its possible association with diminished unstimulated and stimulated salivary flow rates is controversial (45).

On the other hand, we observed that periodontal parameters were comparable in pSS patients and control participants. However, the convenience sample is a limitation of the present study that precludes a conclusive inference on the relative risk of periodontitis in pSS. In this regard, there are conflicting data on periodontal disease in pSS. While retrospective and observational studies have found a positive correlation between these two conditions (10, 14), other investigators have not confirmed this finding (11), including recent systematic review and meta-analyses studies that indicated no evidence of such an association (12, 13, 15).

Regarding PDC treatment, there are no data in the literature on its impact on XI in pSS. The present study did not reach its primary objective, as there was no relief of dry mouth symptoms evaluated through the mean values of XI. In this aspect, the low median value of stimulated salivary flow rate in the pSS group (0.5 mL/min) is associated with poorer outcome of dry mouth treatment in pSS (46).

Our correlation analyses demonstrated the consistency of XI and ESSPRI (total score and ocular/oral dryness scale of ESSPRI) in the assessment of dry mouth symptoms at both time points of the study. On the other hand, our results demonstrate a dissociation between the increase in stimulated salivary flow rate and oral dryness symptoms for which there was no relief, as previously described in pSS patients treated with rituximab (47). This dissociation could in part be explained by the progressive deterioration in saliva quality in pSS (48).

Despite this, the increase in unstimulated and stimulated salivary flow rates in pSS patients after PDC treatment is encouraging, since the decreased salivary flow may be associated with oral complications of this disease such as multiple dental caries (49) and candidiasis (8). Indeed, saliva contains glycoproteins, IgA, lipids and electrolytes that have a key function in preserving of the oral health, inhibiting bacterial growth, lubricating and protecting mucosa and teeth, participating in the processes of mastication, swallowing, taste and carbohydrate digestion (6). Corroborating this hypothesis, there is evidence that in the general adult population, reduced salivary flow rate is a risk factor for presence of dental caries, and can also influence the periodontal disease (6, 50).

The underlying mechanism for the increase in salivary flow rate after PDC treatment observed herein may be related to improvement of the inflammatory status of oral mucosa after resolution of oral infectious foci, which could decrease the damage of salivary glands, similarly to that described in experimental periodontitis (16). Indeed, considerable numbers of restorations of carious and non-carious lesions, cleaning, clinical treatment of periodontitis and topical treatment of candidiasis were performed in pSS patients in the present study, which could contribute to the improvement of the inflammatory status of the oral mucosa. We did not observe decrease in concentrations of salivary pro-inflammatory cytokines after PDC treatment in pSS patients. This finding is in accordance with a previous study of periodontitis treatment in a small sample of pSS patients (n=7) (18), and probably reflects the chronic inflammatory process located within salivary glands in these patients. Similarly, we observed no change in ESSPRI and ESSDAI after PDC treatment. In this regard, the treatment of glandular and systemic manifestations of pSS may be dissociated and there is no strong evidence of satisfactory results (46).

pSS patients also have an impaired quality of life (51), which was confirmed by this study. We did not ob-

serve enhancement in quality of life after PDC treatment, and the lack of relief of dry mouth symptoms, in spite of the increase in salivary flow rate, may account for this finding. Furthermore, the reduction in quality of life in pSS is attributed to several factors, including ocular and oral dryness, fatigue and pain (51, 52).

Our findings also suggest that patients with older age, lower unstimulated salivary flow rate at baseline and more prominent inflammation in the salivary glands were more likely to have a poor response to dental treatment assessed by the stimulated salivary flow at D90, a measure of glandular function (46). Corroborating with these findings, it was recently described in the large population of the Sjögren Big Data Consortium registry study that the frequency of altered objective oral tests, including unstimulated salivary flow rate, progressively increases with older ages at diagnosis (5). It was also recently described by Berman *et al*. that focus score >1 was associated with the number of caries, emphasizing the importance of the degree of inflammation in the salivary glands as a determinant of impaired oral status in pSS (9).

In conclusion, the present study brings the novel finding that PDC treatment promoted improvement in unstimulated and stimulated salivary flow rates in pSS that may be relevant for the reduction of oral complications of this disease, which needs to be confirmed in future studies. Our finding reinforces the recommendation of this important strategy for pSS patients.

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References

1. VIVINO FB, BUNYA VY, MASSARO-GIORDANO G *et al*.: Sjögren's syndrome: an update on disease pathogenesis, clinical manifestations and treatment. *Clin Immunol* 2019; 203: 81-121. https://doi.org/10.1016/j.clim.2019.04.009
2. BRITO-ZERÓN P, ACAR-DENIZLI N, NG WF *et al*.: How immunological profile drives clinical phenotype of primary Sjögren's syndrome at diagnosis: analysis of 10,500 patients (Sjögren Big Data Project). *Clin Exp Rheumatol* 2018; 36 (Suppl. 112): S102-12.
3. QIN B, WANG J, YANG Z *et al*.: Epidemiology of primary Sjögren's syndrome: a systematic review and meta-analysis. *Ann Rheum Dis* 2015; 74: 1983-89. https://doi.org/10.1136/annrheumdis-2014-205375
4. CHIVASSO C, SARRAND J, PERRET J *et al*.: The involvement of innate and adaptive immunity in the initiation and perpetuation of Sjögren's syndrome. *Int J Mol Sci* 2021; 22: 658. https://doi.org/10.3390/ijms22020658
5. RETAMOZO S, ACAR-DENIZLI N, HORVÁTH IF *et al*.: Influence of the age at diagnosis in the disease expression of primary Sjögren's syndrome. Analysis of 12,753 patients from the Sjögren Big Data Consortium. *Clin Exp Rheumatol* 2021; 39 (Suppl. 133): S166-74. https://doi.org/10.55563/clinexprheumatol/egnd1i
6. PEDERSEN AML, SØRENSEN CE, PROCTOR GB, CARPENTER GH, EKSTRÖM J: Salivary secretion in health and disease. *J Oral Rehabil* 2018; 45: 730-46. https://doi.org/10.1111/joor.12664
7. PEDERSEN AM, BARDOW A, NAUNTOFTE B: Salivary changes and dental caries as potential oral markers of autoimmune salivary gland dysfunction in primary Sjögren's syndrome. *BMC Clin Pathol* 2005; 5: 4. https://doi.org/10.1186/1472-6890-5-4
8. SERRANO J, LÓPEZ-PINTOR RM, RAMÍREZ L *et al*.: Risk factors related to oral candidiasis in patients with primary Sjögren's syndrome. *Med Oral Patol Oral Cir Bucal* 2020; 25: e700-5. https://doi.org/10.4317/medoral.23719
9. BERMAN N, VIVINO F, BAKER J *et al*.: Risk factors for caries development in primary Sjögren's syndrome. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2019; 128: 117-22. https://doi.org/10.1016/j.oooo.2019.04.011
10. ANTONIAZZI RP, MIRANDA LA, ZANATTA FB *et al*.: Periodontal conditions of individuals with Sjögren's syndrome. *J Periodontol* 2009; 80: 429-35. https://doi.org/10.1902/jop.2009.080350
11. LUGONJA B, YEO L, MILWARD MR *et al*.: Periodontitis prevalence and serum antibody reactivity to periodontal bacteria in primary Sjögren's syndrome: a pilot study. *J Clin Periodontol* 2016; 43: 26-33. https://doi.org/ 10.1111/jcpe.12485
12. DE GOÉS SOARES L, ROCHA RL, BAGORDAKIS *et al*.: Relationship between Sjögren's syndrome and periodontal status: a systematic review. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2018; 125: 223-31. https://doi.org/10.1016/j.oooo.2017.11.018
13. MAARSE F, JAGER DHJ, ALTERCH S *et al*.: Sjögren's syndrome is not a risk factor for periodontal disease: a systematic review. *Clin Exp Rheumatol* 2019; 37 (Suppl. 118): S225-33.
14. CHUANG CJ, HSU CW, LU MC *et al*.: Increased risk of developing dental diseases in patients with primary Sjögren's syndrome- a secondary cohort analysis of population-based claims data. *PLoS One* 2020; 15: e0239442. https://doi.org/10.1371/journal.pone.0239442
15. WU SY, WU CY, CHEN MH *et al*.: Periodontal conditions in patients with Sjögren's syndrome: a meta-analysis. *J Dent Sci* 2021; 16: 1222-32. https://doi.org/10.1016/j.jds.2020.11.015
16. NAKAMURA-KIYAMA M, ONO K, MASUDA W *et al*.: Changes of salivary functions in experimental periodontitis model rats. *Arch Oral Biol* 2014; 59: 125-32. https://doi.org/10.1016/j.archoralbio.2013.11.001
17. VALLABHAN CG, SIVARAJAN S, SHIVKUMAR AD *et al*.: Assessment of salivary flow rate in patients with chronic periodontitis. *J Pharm Bioallied Sci* 2020; 12: S308-12. https://doi.org/10.4103/jpbs.JPBS_92_20.
18. AMBRÓSIO LM, ROVAI ES, FRANÇA BN *et al*.: Effects of periodontal treatment on primary Sjögren's syndrome symptoms. *Braz Oral Res* 2017; 31: e8. https://doi.org/10.1590/1807-3107BOR-2017.vol31.0008
19. 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. *Ann Rheum Dis* 2017; 76: 9-16. https://doi.org/10.1136/annrheumdis-2016-210571
20. Brazilian Association of Research Companies, ABEP, 2016. http://www.abep.org/. Accessed April, 2018.
21. VITALI C, BOMBARDIERI S, JONSSON R *et al*.: Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheum Dis* 2002; 61: 554-58. https://doi.org/10.1136/ard.61.6.554
22. SPIJKERVET FKL, SCHUURHUIS JM, STOKMAN MA, WITJES MJH, VISSINK A: Should oral foci of infection be removed before the onset of radiotherapy or chemotherapy? *Oral Dis* 2021; 27: 7-13. https://doi.org/10.1111/odi.13329
23. LÓPEZ-PINTOR RM, FERNÁNDEZ CASTRO M, HERNÁNDEZ G: Oral involvement in patients with primary Sjögren's syndrome. Multidisciplinary care by dentists and rheumatologists. *Reumatol Clin* 2015; 11: 387-94. https://doi.org/10.1016/j.reuma.2015.03.010
24. CHRISTENSEN LB, PETERSEN PE, THORN JJ, SCHIØDT M: Dental caries and dental health behavior of patients with primary Sjögren's syndrome. *Acta Odontol Scand* 2001; 59: 116-20. https://doi.org/10.1080/000163501750266684
25. KALK WW, VISSINK A, SPIJKERVET FK, BOOTSMA H, KALLENBERG CG, NIEUW AMERONGEN AV: Sialometry and sialochemistry: diagnostic tools for Sjögren's syndrome. *Ann Rheum Dis* 2001; 60: 1110-16. https://doi.org/10.1136/ard.60.12.1110
26. CATON JG, ARMITAGE G, BERGLUNDT T *et al*.: A new classification scheme for periodontal and peri-implant diseases and conditions - introduction and key changes from the 1999 classification. *J Clin Periodontol* 2018; 45 Suppl 20: S1-S8. https://doi.org/10.1111/jcpe.12935
27. DA MATA AD, DA SILVA MARQUES DN, FREITAS FM *et al*.: Translation, validation, and

construct reliability of a Portuguese version of the Xerostomia Inventory. *Oral Dis* 2012; 18: 293-98. https://doi.org/10.1111/j.1601-0825.2011.01879.x
28. THOMSON WM: Measuring change in dry-mouth symptoms over time using the Xerostomia Inventory. *Gerodontology* 2007; 24: 30-5. https://doi.org/10.1111/j.1741-2358.2007.00137.x
29. CICONELLI RM, FERRAZ MB, SANTOS W *et al*.: Tradução para a língua portuguesa e validação do questionário genérico de avaliação de qualidade de vida SF-36 (Brasil SF-36) [Brazilian-Portuguese version of the SF-36. A reliable and valid quality of life outcome measure.] *Rev Bras Reumatol* 1999; 39: 143-50.
30. SEROR R, RAVAUD P, BOWMAN SJ *et al*.: EULAR Sjögren's syndrome disease activity index: development of a consensus systemic disease activity index for primary Sjögren's syndrome. *Ann Rheum Dis* 2010; 69: 1103-09. https://doi.org/10.1136/ard.2009.110619
31. SEROR R, RAVAUD P, MARIETTE X *et al*.: EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI): development of a consensus patient index for primary Sjögren's syndrome. *Ann Rheum Dis* 2011; 70: 968-72. https://doi.org/10.1136/ard.2010.143743
32. SEROR R, BOOTSMA H, SARAUX A *et al*.: Defining disease activity states and clinically meaningful improvement in primary Sjögren's syndrome with EULAR primary Sjögren's syndrome disease activity (ESSDAI) and patient-reported indexes (ESSPRI). *Ann Rheum Dis* 2016; 75: 382-89. https://doi.org/10.1136/annrheumdis-2014-206008
33. JIANG X, JIANG X, WANG Y, HUANG R: Correlation between tobacco smoking and dental caries: a systematic review and meta-analysis. *Tob Induc Dis* 2019; 17: 34. https://doi.org/10.18332/tid/106117
34. BARUTTA F, BELLINI S, DURAZZO M, GRUDEN G: Novel insight into the mechanisms of the bidirectional relationship between diabetes and periodontitis. *Biomedicines* 2022; 10: 178. https://doi.org/10.3390/biomedicines10010178
35. EBERSOLE JL, NAGARAJAN R, AKERS D, MILLER CS: Targeted salivary biomarkers for discrimination of periodontal health and disease(s). *Front Cell Infect Microbiol* 2015; 5: 62. https://doi.org/10.3389/fcimb.2015.00062
36. BOSTRÖM EA, D'ELIA HF, DAHLGREN U *et al*.: Salivary resistin reflects local inflammation in Sjögren's syndrome. *J Rheumatol* 2008; 35: 2005-11.
37. IRWANDI RA, KUSWANDANI SO, HARDEN S, MARLETTA D, D'AIUTO F: Circulating inflammatory cell profiling and periodontitis: a systematic review and meta-analysis. *J Leukoc Biol* 2022; 111: 1069-96. https://doi.org/10.1002/JLB.5RU1021-524R
38. DE CASTRO MENEGHIM M, KOZLOWSKI FC, PEREIRA AC *et al*.: Classificação socioeconômica e sua discussão em relação à prevalência de cárie e fluorose dentária [A socioeconomic classification and the discussion related to prevalence of dental caries and dental fluorosis]. *Cien Saude Colet* 2007; 12: 523-9. https://doi.org/10.1590/s1413-81232007000200028
39. BORGES CM, CAMPOS AC, VARGAS AM *et al*.: Perfil das perdas dentárias em adultos segundo o capital social, características demográficas e socioeconômicas [Adult tooth loss profile in accordance with social capital and demographic and socioeconomic characteristics]. *Cien Saude Colet* 2014; 19: 1849-58. https://doi.org/10.1590/1413-81232014196.02332013
40. BALDANI MH, VASCONCELOS AG, ANTUNES JL: Associação do índice CPO-D com indicadores sócio-econômicos e de provisão de serviços odontológicos no Estado do Paraná, Brasil [Association of the DMFT index with socioeconomic and dental services indicators in the state of Paraná, Brazil]. *Cad Saude Publica* 2004; 20: 143-52. https://doi.org/10.1590/s0102-311x2004000100030
41. CLARK D, KOTRONIA E, RAMSAY SE: Frailty, aging, and periodontal disease: basic biologic considerations. *Periodontol 2000* 2021; 87: 143-56. https://doi.org/10.1111/prd.12380
42. BOING AF, PERES MA, KOVALESKI DF *et al*.: Estratificação sócio-econômica em estudos epidemiológicos de cárie dentária e doenças periodontais: características da produção na década de 90 [Social stratification in epidemiological studies of dental caries and periodontal diseases: a profile of the scientific literature in the 1990s]. *Cad Saude Publica* 2005; 21: 673-8. https://doi.org/10.1590/s0102-311x2005000300002
43. FOX PC, BOWMAN SJ, SEGAL B *et al*.: Oral involvement in primary Sjögren syndrome. *J Am Dent Assoc* 2008; 139: 1592-601. https://doi.org/10.14219/jada.archive.2008.0101
44. PENONI DC, GOMES MIRANDA MEDSN, SADER F, VETTORE MV, LEÃO ATT: Factors associated with noncarious cervical lesions in different age ranges: a cross-sectional study. *Eur J Dent* 2021; 15: 325-31. https://doi.org/10.1055/s-0040-1722092
45. KOLAK V, PEŠIĆ D, MELIH I, LALOVIĆ M, NIKITOVIĆ A, JAKOVLJEVIĆ A: Epidemiological investigation of non-carious cervical lesions and possible etiological factors. *J Clin Exp Dent* 2018; 10: e648-56. https://doi.org/10.4317/jced.54860
46. RAMOS-CASALS M, BRITO-ZERÓN P, BOMBARDIERI S *et al*.: EULAR recommendations for the management of Sjögren's syndrome with topical and systemic therapies. *Ann Rheum Dis* 2020; 79: 3-18. https://doi.org/10.1136/annrheumdis-2019-216114
47. AL HAMAD A, LODI G, PORTER S, FEDELE S, MERCADANTE V: Interventions for dry mouth and hyposalivation in Sjögren's syndrome: a systematic review and meta-analysis. *Oral Dis* 2019; 25: 1027-47. https://doi.org/10.1111/odi.12952
48. AZUMA N, KATADA Y, SANO H: Deterioration in saliva quality in patients with Sjögren's syndrome: impact of decrease in salivary epidermal growth factor on the severity of intraoral manifestations. *Inflamm Regen* 2018; 38: 6. https://doi.org/10.1186/s41232-018-0062-0
49. WU AJ: Optimizing dry mouth treatment for individuals with Sjögren's syndrome. *Rheum Dis Clin North Am* 2008; 34: 1001-10. https://doi.org/10.1016/j.rdc.2008.08.013
50. SHIMAZAKI Y, FU B, YONEMOTO K *et al*.: Stimulated salivary flow rate and oral health status. *J Oral Sci* 2017; 59: 55-62. https://doi.org/10.2334/josnusd.16-0372
51. CORNEC D, DEVAUCHELLE-PENSEC V, MARIETTE X *et al*.: Severe health-related quality of life impairment in active primary Sjögren's syndrome and patient-reported outcomes: data from a large therapeutic trial. *Arthritis Care Res* (Hoboken) 2017; 69: 528-35. https://doi.org/10.1002/acr.22974
52. MCCOY SS, BARTELS CM, SALDANHA IJ *et al*.: National Sjögren's Foundation Survey: burden of oral and systemic involvement on quality of life. *J Rheumatol* 2021; 48: 1029-36. https://doi.org/10.3899/jrheum.200733