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

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Abstract

Objectives

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 Xerostomia Inventory (XI), unstimulated/stimulated salivary flow rates and salivary cytokine profile in pSS.

Methods

Fifty-two pSS patients and 52 sex-/age-matched control participants without systemic autoimmune diseases were comprised in a prospective study. At inclusion, all participants were assessed through a standardized 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, Decayed, Missing and Filled Teeth (DMFT) index was higher in pSS patients than in 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 reduction of at least 6 points (clinical improvement) in XI, but mean XI remained unchanged (p=0.285). PDC resulted in increase in mean unstimulated (p<0.001) and stimulated (p=0.001) salivary flow rates in pSS, without 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
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/polymyalgia, 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 ( Giấy 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 Trial registration: Clinicaltrials.gov (Identifier: NCT03711214).

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Competing interests: none declared.
Outpatient Clinic of the Rheumatology Division, Hospital das Clínicas 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 standardized 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).

**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 laboratory 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 erupted 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 leuoplakia, 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 questionnaires 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-1β, IL-6, BAFF and resistin, were determined, as well as metalloproteinase (MMP-9) (35). Salivary concentrations of TNF-α, IL-1β, 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 COR-PORATION, 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-1β (<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 (rs) 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
Table I. Comparative analysis of pSS patients and control individuals regarding demographic characteristics and comorbidities.

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

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.

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. Hypergamma globulinemia 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 carries [1 (0-4) vs. 0 (0-1), p=0.011], as well as the percentage of restorations due to carries 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 (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 (p=0.05) (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 no 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=0.577, p<0.001) and D90 (r=0.480, p<0.001). There were also positive moderate correlations between XI and ocular/oral dryness scale of ESSPRI at D0 (r=0.497, p<0.001) and D90 (r=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=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=0.249, p=0.074) and D90 (r=0.012, p=0.934). Similarly, no correlations were observed between ESSPRI and stimulated salivary flow rate at D0 (r=0.196, p=0.163) and D90 (r=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=0.013, p=0.927); nor between ESSPRI improvement (decrease of at least 1 point) and stimulated salivary flow at D90 (r=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-1β, IL-6, BAFF and resistin) and MMP-9, ESSDAI, as well as the use of hydroxychloroquine, prednisone, immunosuppressants and biological agents were similar on D0 and D90 (p>0.05) (Table IV).
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Table IV. Comparative analysis of pSS patients who completed clinical assessments at baseline (D0) and at 3 months after PDC treatment (D90).

<table>
<thead>
<tr>
<th>Variable</th>
<th>pSS – D0 n=52</th>
<th>pSS – D90 n=52</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salivary flow rate (mL/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unstimulated*</td>
<td>0.1 (0.04-0.2)</td>
<td>0.3 (0.2-0.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stimulated*</td>
<td>0.5 (0.3-1.1)</td>
<td>0.7 (0.4-1.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>Xerostomia Inventory</td>
<td>39.7 ± 9.5</td>
<td>38.5 ± 8.6</td>
<td>0.285</td>
</tr>
<tr>
<td>Clinical improvement†</td>
<td>-</td>
<td>14 (26.9)</td>
<td></td>
</tr>
<tr>
<td>ESSPRI</td>
<td>5.8 (4.2-7.2)</td>
<td>6.2 (4.8-7.8)</td>
<td>0.072</td>
</tr>
<tr>
<td>Ocular and oral dryness</td>
<td>7.0 (5.0-8.0)</td>
<td>7.5 (5.0-8.0)</td>
<td>0.975</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5.0 (4.5-7.5)</td>
<td>6.5 (4.5-8.0)</td>
<td>0.092</td>
</tr>
<tr>
<td>Pain</td>
<td>6.0 (2.0-8.0)</td>
<td>6.0 (2.5-8.0)</td>
<td>0.806</td>
</tr>
<tr>
<td>Clinical improvement**</td>
<td>-</td>
<td>6 (11.5)</td>
<td></td>
</tr>
<tr>
<td>ESSDAI</td>
<td>3.0 (1.0-7.0)</td>
<td>2.0 (6.0-6.5)</td>
<td>0.111</td>
</tr>
<tr>
<td>Clinical improvement***</td>
<td>-</td>
<td>6 (11.5)</td>
<td></td>
</tr>
<tr>
<td>Salivary levels</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNF-α (pg/mL)</td>
<td>11.5 (6.1-27.3)</td>
<td>11.8 (5.2-24.7)</td>
<td>0.362</td>
</tr>
<tr>
<td>IL-1β (pg/mL)</td>
<td>51.0 (15.1-131.9)</td>
<td>43.0 (16.9-123.9)</td>
<td>0.649</td>
</tr>
<tr>
<td>IL-6 (pg/mL)</td>
<td>41.2 (21.8-82.9)</td>
<td>34.5 (14.6-80.3)</td>
<td>0.469</td>
</tr>
<tr>
<td>Resistin (pg/mL)</td>
<td>51,421.0 (24,750.0-67,385.8)</td>
<td>35,727.5 (17,668.5-70,290.0)</td>
<td>0.052</td>
</tr>
<tr>
<td>MMP-9 (pg/mL)</td>
<td>4.8 (2.6-7.4)</td>
<td>4.5 (2.7-7.7)</td>
<td>0.964</td>
</tr>
<tr>
<td>BAFF (pg/mL)</td>
<td>23.0 (9.5-53.0)</td>
<td>28.0 (7.5-79.0)</td>
<td>0.297</td>
</tr>
</tbody>
</table>

Current treatments

Sicca syndrome

Topical

- Artificial saliva: 28 (53.9) vs 25 (48.1) (p=0.371)
- Artificial tears: 47 (90.4) vs 41 (78.9) (p=0.041)

Oral route

- Pilocarpine: 4 (7.7) vs 4 (7.7) (p=1.00)
- N-acetylcysteine: 26 (50) vs 22 (42.3) (p=0.221)
- Linseed oil: 22 (42.3) vs 19 (36.5) (p=0.371)

Systemic manifestations

- Prednisone: 21 (40.4) vs 20 (38.5) (p=1.00)
- Dose (mg/day): 5 (5-10) vs 5 (5-17.5) (p=0.240)
- Hydroxychloroquine: 26 (50) vs 22 (42.3) (p=0.221)

Immunosuppressants

- Methotrexate: 6 (11.5) vs 4 (7.7) (p=0.617)
- Leflunomide: 3 (5.8) vs 4 (7.7) (p=1.00)
- Azathioprine: 8 (15.4) vs 9 (17.3) (p=1.00)
- Mycophenolate mofetil: 9 (17.3) vs 5 (9.6) (p=0.134)
- Cyclophosphamide: 0 (0) vs 1 (1.9) (p=1.00)

Biological agents

- Rituximab: 3 (5.8) vs 3 (5.8) (p=1.00)

Data are presented as n (%), mean ± standard deviation (SD), or median (25th percentile – 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.

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 (including age, sex, race, education level, smoking status, and comorbidity profile) were considered. The model was adjusted for multiple comparisons using the Bonferroni correction. The results indicated that current use of artificial saliva (p=0.600) and the use of Rituximab (p=0.043) were associated with increased stimulated salivary flow rate at D90. Other factors, such as age, sex, race, education level, smoking status, and comorbidity profile, were not significantly associated with stimulated salivary flow rate at D90.

Discussion

This study demonstrated that PDC treatment promoted improvement in 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 comorbidities.

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

<table>
<thead>
<tr>
<th></th>
<th>Controls – D0 n=49</th>
<th>Controls – D90 n=49</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SALIVAR FLOW RATES</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unstimulated</td>
<td>0.6 (0.3-0.8)</td>
<td>0.6 (0.3-1.1)</td>
<td>0.680</td>
</tr>
<tr>
<td>Stimulated</td>
<td>2.2 ± 1.3</td>
<td>2.5 ± 1.4</td>
<td>0.089</td>
</tr>
<tr>
<td><strong>XEROSTOMIA INVENTORY</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical improvement</td>
<td>18.6 ± 6.4</td>
<td>19.9 ± 7.0</td>
<td>0.124</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>6 (12.3)</td>
<td>-</td>
</tr>
<tr>
<td><strong>SALIVARY LEVELS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNF-α (pg/mL)</td>
<td>4.3 (1.9-8.3)</td>
<td>4.7 (2.5-9.5)</td>
<td>0.861</td>
</tr>
<tr>
<td>IL-1β (pg/mL)</td>
<td>38.2 (10.9-74.5)</td>
<td>29.3 (13.6-56.0)</td>
<td>0.296</td>
</tr>
<tr>
<td>IL-6 (pg/mL)</td>
<td>23.0 (6.2-37.4)</td>
<td>14.9 (7.6-32.3)</td>
<td>0.249</td>
</tr>
<tr>
<td>Resistin (pg/mL)</td>
<td>32.965.8 ± 27.504.6</td>
<td>30.872.9 ± 27.116.9</td>
<td>0.480</td>
</tr>
<tr>
<td>MMP-9 (pg/mL)</td>
<td>2.3 (1.2-4.7)</td>
<td>2.5 (1.6-3.7)</td>
<td>0.846</td>
</tr>
</tbody>
</table>

Data are presented as n (%), mean ± standard deviation (SD), or median (25th percentile – 75th percentile).

*pReduction of at least 6 points.

**PICTURE:**

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 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 present study demonstrated 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 carries (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 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 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).

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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 observe 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 (53). 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


