Chemosensory Dysfunction and Oral Disorders Affect Oral Health-Related Quality Of Life in Patients with Primary Sjögren's Syndrome

CURRENT STATUS: UNDER REVISION

Mirjana Šijan Gobeljić
Institute of Rheumatology

Vera Milić
Institute of Rheumatology

Nada Pejnovic
Institute of Rheumatology

Corresponding Author
nada.pejnovic@gmail.com
ORCiD: https://orcid.org/0000-0002-2279-9197

Nemanja Damjanov
Institute of Rheumatology

DOI: 10.21203/rs.2.21168/v1

SUBJECT AREAS
Head & Neck Surgery Dentistry

KEYWORDS
Sjögren's syndrome, saliva secretion, oral disorders, chemosensory dysfunction, quality of life
Abstract

**Background:** The aim of this study was to evaluate chemosensory function and oral disorders in patients with primary Sjögren's syndrome (pSS) and to compare these findings with those of age- and gender-matched healthy controls.

**Methods:** Olfactory and gustatory function, dysgeusia, burning sensations in the tongue (BST), halitosis, and oral health-related quality of life (OHRQoL) using the short-form Oral Health Impact Profile (OHIP-14) were evaluated in 58 patients with primary Sjögren’s syndrome (pSS) and 55 age- and gender-matched healthy controls.

**Results:** Patients with pSS had significantly lower self-reported visual analogue scale (VAS) smell score (8.6±2.2 vs. 9.6±0.7, p=0.016) and VAS taste score (9.5±0.7 vs. 8.5±2.1, p=0.014) than healthy controls. A greater proportion of patients with pSS had anosmia (3.8% vs. 0.0%) or hyposmia (36.5% vs. 13.2%) and ageusia for basic tastes: sweetness (34.0% vs. 7.5%), sourness (10.6 % vs. 0.0), saltiness (10.0% vs. 5.7%) or bitterness (19.1% vs. 1.9%). A higher proportion of pSS patients complained of dysgeusia (52.6% vs. 9.4%, p<0.0001) and BST (45.6% vs. 0.0%, p<0.0001) while similar number of pSS patients and controls reported halitosis (31.6% vs. 28.3%, p=0.434). The mean OHIP-14 score was significantly higher in patients with pSS (6.8±7.0 vs. 2.3±8.5, p<0.001) indicating patients’ poorer OHRQoL compared to controls.

**Conclusions:** The majority of patients with pSS had impaired chemosensory function and indicators of oral health in comparison to the age- and gender-matched healthy controls. Further studies of oral hygiene habits and dietary intake of these patients are needed to ensure better management of oral health problems in patients with pSS.

**Background**

Sjögren's syndrome (SS) is a chronic, systemic, autoimmune disease that mainly affects the exocrine glands, especially the salivary and lacrimal glands, leading to the dryness of the mouth and the eyes, along with fatigue, joint and muscle pain with the prevalence between 0.05% and 1% in European population. Sjögren’s syndrome can be further subclassified as primary disease (primary Sjögren syndrome, pSS) or as a secondary disease (secondary Sjögren syndrome, sSS) when it is associated
with another disease of connective tissue [1].

The pathogenesis of SS is complex. Genetic background and environmental factors including infections, stress and hormonal factors contribute to the pathogenesis of Sjögren’s syndrome with the important role of the immune cells of innate and adaptive immunity such as, dendritic cells (DCs), T and B cells. The hallmarks of SS are lymphocytic infiltration of the exocrine glands and the presence of circulating autoantibodies (anti-Ro/SS-A and anti-La/SS-B) [2]. Moreover, patients with pSS have autoantibodies directed against muscarinic acetylcholine type 3 receptors (M3R) which functionally inhibit salivary secretion [3]. Genetic susceptibility to pSS is evidenced by the presence of single nucleotide polymorphisms (SNPs) in human leukocyte antigen (HLA) alleles (HLA-DRA, HLA-DQB1, HLA-DQA1), STAT4, IRF5, IL-12A and TNIP1, genes involved in the function of innate and adaptive immune cells [4]. Moreover, several candidate genes that regulate matrix metalloproteinase 9 (MMP9) expression, the enzyme that degrades the salivary gland structures, have been identified in patients with pSS [5].

American-European consensus group (AECG) classification criteria are used for establishing the diagnosis of Sjögren syndrome [6]. These criteria include subjective presence of ocular dryness; subjective presence of oral dryness; objective measures of ocular dryness by Schirmer’s test or corneal staining; focus score > 2 in a salivary gland biopsy; salivary scintigraphy showing reduced salivary flow (1.5 mL in 15 minutes) and/or diffuse sialectasias and positive autoantibodies against SS-A and/or SS-B. Primary SS is diagnosed when 4 out of 6 items are present; either salivary gland pathology or the presence of autoantibodies against SS-A/SS-B is mandatory. If the patients have been diagnosed with rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) or scleroderma prior to developing their sicca symptoms the diagnosis of secondary SS is made.

There is no cure for SS. The treatment of patients with SS is mainly symptomatic and the use of substitution therapy with artificial tears and saliva is recommended. Management of oral manifestations includes intense oral hygiene, prevention of oral infections and their treatment, use of artificial saliva, and local and systematic stimulation of salivary secretion [7]. Biological drugs could block several immune pathways or cytokines involved in the pathogenesis of SS, such as BAFF-APRIL
pathway, T cell co-stimulation, IL-17 and IL-6 [8].

Dental erosions, dental caries, mucosal infection, ulcers and oral candidiasis are often present in patients with SS and are related to the decreased salivary flow and the qualitative changes in saliva. Due to the dryness of the oral cavity (xerostomia) the chewing, swallowing, speech and sleeping may be affected resulting in impaired quality of life in patients with pSS [9]. The impairments in olfactory and gustatory functions have been described in patients with pSS [10, 11]. Chemosensory disorders include gustatory and olfactory dysfunctions, which affect the senses of taste and/or smell and could lead to their reduced ability, distortion or absence [12, 13]. Many patients with chemosensory disorders experience burning sensations or numbness in the mouth, especially in or on the tongue. These sensations may originate in the gustatory nerve fibers [14]. Burning mouth syndrome (BMS) is defined as the burning sensation in the tongue (BST), or burning in other mucosal membranes, lasting for at least 4–6 months [15]. Patients with SS and burning mouth syndrome (BMS) often have similar oral complaints; however, these diseases have significantly different etiology, pathogeneses, diagnostic criteria, and treatment [16]. Halitosis (or oral mal-odor, defined as an unpleasant breath odor of oral or extra-oral origin) is another common oral complaint that can be associated with low salivary secretion or chemosensory disorders [17]. The presence of dysgeusia, BST and halitosis are associated with changes in oral health-related quality of life (OHRQoL) with no clear association with saliva secretion rates in patients with pSS [11]. Due to the fact that some reported data show no correlation between low salivary flow and taste performance it is still unclear whether hyposalivation causes smell and taste impairments along with burning sensation in the mouth [18]. Possible underlying cause of the olfactory and gustatory dysfunctions in patients with pSS could be related to immunopathological mechanisms operating in pSS. Systemic chronic inflammation in primary Sjögren’s syndrome is associated with overexpression of interferon-inducible genes [19] and proinflammatory pathways mediated by Toll-like receptors while interferons in taste tissue may interfere with normal taste transduction and turnover of taste bud cells [20].

Both, the patients and the physicians that take care of the patients with primary Sjogren’s syndrome (pSS), most frequently pay attention to the dry mouth and the dry eyes, along with the fatigue, joint
and muscle pain as important signs and symptoms of the disease. However, some of the most important consequences of the nose and mouth dryness, the chemosensory dysfunction, as well as some of the important aspects of the oral disorders, dysgeusia, burning sensations in the tongue (BST), halitosis, and poorer oral health-related quality of life (OHRQoL) are often neglected. Moreover, some of the physicians and patients do not even realize that above mentioned chemosensory dysfunction and oral disorders are directly related to the pSS. The data regarding chemosensory dysfunction and other oral disorders, such as dysgeusia, burning sensations in the tongue and mouth in patients with pSS are limited. Therefore, it is of high importance to assess the impaired olfactory and gustatory functions, and occurrence of oral disorders in patients with pSS.

Patients with Sjögren's syndrome commonly experience oral symptoms and they are often firstly examined by a dentist. Having in mind that prevention and early treatment are crucial for the maintenance of oral health in patients with pSS, dental professionals should recognize the signs and symptoms of xerostomia and immediately connect them to SS. Early and appropriate treatment of patients with pSS is important to prevent the development of chemosensory dysfunction and oral disorders. Oral hygiene and regular dentist care are of importance. In cases of dysgeusia and burning mouth disorder, tricyclic antidepressants and clonazepam can be helpful, but can also potentiate mouth dryness in patients with pSS [21]. In case of severe dysgeusia topical anaesthetics like lidocaine gel is indicated [22]. Artificial saliva may be helpful in patients with xerostomia [23]. Additionally, strategies that capitalize on non-olfactory components of food flavour (altering food texture, primary taste qualities, temperature, and colour) should be implemented to help maintain food enjoyment. Foods and beverages that are salty, sweet, or that stimulate the trigeminal nerve (e.g., black or red pepper, carbonation) may provide another dimension to the eating experience. Enhancing the olfactory component of food flavour can also improve food intake in patients with olfactory dysfunction. These compensatory strategies may help improve dietary choices and maintain both food enjoyment and nutritional health.

The aim of this study was to evaluate olfactory and gustatory function, dysgeusia, burning sensation in the tongue (BST), halitosis, and OHRQoL in patients with primary Sjögren's syndrome and to
compare these findings with those of age- and gender-matched healthy controls.

Methods

**Study participants**

The study was performed at the Outpatient Clinic of the Institute of Rheumatology, University of Belgrade, Serbia. Fifty eight patients with primary SS, all fulfilling the American–European Consensus (AEC) classification criteria [6], and fifty five healthy controls of similar age and gender were enrolled in this comparative cross-sectional study. Some of the healthy volunteers were recruited from the healthy staff of the Institute of Rheumatology. Together with other recruited healthy subjects they completed a health questionnaire. All study participants had given their informed consent according to the Declaration of Helsinki, and the study was approved by the Local Ethics Committee at the Institute of Rheumatology.

The patients with pSS were aged from 25 to 77 years and were randomly and continuously recruited into the study from the Outpatient clinic of the Institute of Rheumatology. The exclusion criteria for the patients were inflammatory rheumatic diseases or systemic connective tissue diseases, active infections, malignant diseases, metabolic diseases or any other condition that may affect oral health, quality of life or patient capability to participate in the study by the investigator’s opinion. The exclusion criteria for the healthy controls were subjective mouth and eye dryness, presence of chronic rheumatic, metabolic or malignant diseases.

**Clinical assessment**

Patients’ disease characteristics (activity of pSS, extraglandular manifestations), medical history, chronic diseases, use of medications, and lifestyle habits (such as smoking) were recorded. Objective xerophthalmia was assessed by Schirmer’s I test and Rose Bengal score determination. Oral involvement was evaluated by salivary scintigraphy of the major salivary glands. Salivary gland scintigraphy was performed with radioactive technetium-99m (Tc99m) pertechnetate. The difference between the maximum and minimum excretion after being stimulated by vitamin C divided by the maximum counts was defined as the excretion rate. It was classed as normal if excretion level was $\geq$50% or dysfunctional if excretion level was <50% [24, 25].
Labial salivary gland (LSG) biopsies were performed in patients with pSS. The changes observed in 4mm$^2$ of salivary gland tissue were scored from 0 to 4, according to the semiquantitative scoring method of Chisholm and Mason [26]. Grade 0 was given based on absence of inflammatory infiltrate; grade 1 on the presence of slight infiltrate; grade 2 on the presence of moderate infiltrate of focus score < 1 (focus score is defined as number of aggregates of $\geq$ 50 lymphocytes per 4 mm2 of tissue). Grades 3 and 4 were given if focus scores were $\geq$ 1. Grades 3 and 4 were defined as pathological findings.

**Laboratory assessment**

Routine laboratory and immunoserological tests were carried out on all patients; antinuclear antibodies (ANA; positive if titre $>$ 1:80) were measured by indirect immunofluorescence on the HEp-2 cell line substrate (Organtec Diagnostica, Germany). The serum levels of rheumatoid factor (IgM-RF) were determined by laser nephelometry whereas anti-extractable nuclear antigen antibodies anti-Ro/SS-A and anti-La/SS-B were detected by enzyme-linked immunosorbent assay (ELISA; Organtec Diagnostica) [24, 25].

**Assessment of chemosensory and oral disorders**

The participants were instructed not to eat, drink, or smoke for 1 h before their appointment at the Institute of Rheumatology. A detailed medical history was recorded and participants were examined by specialists in rheumatology and dentistry.

The olfactory and gustatory assessments were carried out as described below. Before olfactory testing, subjects were asked to score their own general subjective smell perception on a visual analogue scale (VAS) from 0 to 10, where self-reported smell score 0 = no smell perception and 10 = very good smell perception. In cognitive evaluation of olfactory function an identification test with 12 odor pens (Sniffin’Sticks-Screening; BurghartMesstechnik, Wedel, Germany) was used. The pens were positioned under the subject’s nose, approximately 2 cm from either nostril, for a maximum of 4sec. The subjects were instructed to choose from the three possible answers (anosmic/hyposmic – 0 points, or normosmic-1 point) for each of a 12 odors on a multiple-choices scoring card [27]. The answers chosen by every individual were recorded on a protocol sheet, and the data were scored for
each of them. A normative classification was used to define anosmic (score: 0–5), hyposmic (score: 6–9), and normosmic (score: 10–12) subjects.

Before gustatory testing, subjects were asked to score their subjective taste perception on a VAS of 0–10, where self-reported taste score 0 = no taste perception and score 10 = very good taste perception. A gustatory assessment was performed after the subjects were given a detailed explanation of the testing procedure. Gustatory function was evaluated using taste strips with four basic taste qualities sweet, sour, salty and bitter [28]. Taste strips (length 8 cm, tip area 2 cm²; Burghart Messtechnik, Wedel, Germany) were gently rubbed onto the anterior tip of the extended tongue. The taste qualities were presented in a random manner. A chart with names of the four taste qualities was placed in front of the subjects during testing in order to ask the subjects to identify the taste of the strip. The subjects were allowed to rinse their mouths with water during the gustatory testing. The semi-quantitative evaluation for each of four taste qualities was performed as follows: 0 = loss of ability to taste, 1 = reduced ability to taste and 2 = normal ability to taste. This protocol resulted in a total of maximum score 8, for each subject.

The subjects of this study completed a questionnaire for the assessment of dysgeusia, burning sensation in the tongue (BST), and halitosis. In addition they described their experience of these conditions using open-ended questions. They completed oral health-related quality of life (OHRQoL) questionnaire using the 14-item short form of the Oral Health Impact Profile (OHIP-14) [29-31]. Serbian source version of OHIP-14 was produced after the questionnaire had undergone back translation, linguistic and cultural validation. The total OHIP-14 sum score ranges from 0 to 56, giving an overall indication of the patient’s OHRQoL. A high OHIP-14 score indicates a poor OHRQoL.

Disease activity and the presence of extraglandular manifestations were estimated using the EULAR index of disease activity (ESSDAI, range 0-123) [32, 33]. The subjective evaluation of the dryness intensity, joint pain and fatigue were assessed using EULAR SS Patient Reported Index (ESPRI, range 0-10) [31].

**Statistical analyses**

Statistical analysis was done using the Statistical Package for the Social Sciences (SPSS) version 16.0.
Independent samples $t$-test was used for comparing normally distributed continuous variables in both patient and control groups. A chi-square test was used to compare dichotomous variables. Odds ratios (ORs) with 95% confidence intervals (CIs) for smell or taste alterations in patients with pSS and healthy controls were determined. $P$ values $< 0.05$ were considered statistically significant.

Results

**Demographical and clinical characteristics of patients with primary Sjögren’s syndrome and healthy controls**

The characteristics of patients with pSS and healthy controls are shown in Table 1. The patients with pSS and the healthy controls had a comparable mean age. The majority of subjects in either group were females. The two groups did not differ significantly in smoking habits. None of the healthy controls had subjective experience of ocular, oral, nasal and vaginal dryness nor dysphagia, salivary gland swelling or Reynaud phenomenon. The mean disease duration in patients with pSS was 7.6 years, ranging from 1 to 22 years. The majority of patients with pSS (43%) had moderate disease activity as estimated by ESSDAI EULAR index of disease activity. More than half of patients (60%) reported that they had not been satisfied with their current health status as assessed by EULAR SS Patient Reported Index ESSPRI. The vast majority of patients (more than 88%) had positive salivary gland scintigraphy, salivary gland biopsy and abnormal tear breaking-up time (BUT), Schirmer’s test and Rose Bengal score. The majority of patients (71%) were positive for antinuclear antibodies, SS-A autoantibodies (81%) and RF (69%). The mean value for erythrocyte sedimentation rate (ESR) was 25.7 mm/hour and it ranged from 2 to 88mm/hour. Leucopenia was found in more than half of the patients (62%). Twenty-two patients with pSS (38%) were on corticosteroid therapy, whereas the majority among them (75%) took 10-50mg of corticosteroids per day. The majority of patients (81%) used artificial tears while only 4% of patients used artificial saliva. Approximately half of the patients (49%) received symptomatic therapy, 46% of patients received Chloroquine or Hydroxychloroquine, 3% Azathioprine and 2% Methotrexate.

**Olfactory function**

The pSS group had a significantly lower mean self-reported smell score on VAS than healthy controls.
(8.6±2.2 vs. 9.6±0.7, p=0.016). Similarly, olfactory testing showed that the patients with pSS were significantly more anosmic and hyposmic and fewer of them were normosmic in comparison with healthy controls, as shown in Fig 1.

**Gustatory function**

The patients with pSS had a significantly lower mean self-reported taste score on VAS than healthy controls (8.5±2.1 vs.9.5±0.7, p=0.014). Gustatory testing showed that the pSS patient group had significantly lower mean taste scores than the controls (4.1±1.8 vs.6.1±1.9, p<0.0001) (Table 2). Gustatory testing categorized significantly more patients with pSS as ageusic/hypogeusic and significantly fewer with normal sense of taste than in the control group as shown in Table 2.

**Dysgeusia, burning sensation in the tongue, and halitosis**

Complaints of dysgeusia, BST, and halitosis in the patients with pSS and healthy controls are shown in Table 3. Only five out of 53 healthy controls complained of dysgeusia, while more than half of patients with pSS (53%) reported dysgeusia. Thirty patients with pSS who complained of dysgeusia described the taste as metallic, sour, bitter, rotten or unpleasant. The majority of patients reported distorted bitter taste (36.7%), while all controls that reported dysgeusia (9.4%) complained of unpleasant taste. The majority of patients with pSS (77%) and healthy controls (67%) experienced distorted taste as a daily problem.

While none of the controls complained of burning sensation of the tongue (BST), nearly half of patients with pSS reported BST (46%). The majority of patients with pSS (38%) experienced burning sensation in the tongue during the meals and 39% of them reported sour taste sensation as a type of BST.

About 32% of patients and 28% of controls complained of halitosis. Half of the pSS patients experiencing halitosis complained of halitosis as a persisting daily problem, similarly to the majority of healthy controls (80%) who also reported halitosis as a daily problem.

Crosstabulations showed highly significant differences between patients with pSS and controls in self-reported complaints of dysgeusia ($\chi^2=23.6$, p<0.0001), BST ($\chi^2=31.6$, p<0.0001), but not of halitosis ($\chi^2=0.40$, p=0.434) (Fig 2).
Odds ratios for the development of dysgeusia, BST and halitosis were determined in patients with SS and healthy controls and the results are presented in Table 3. In addition, patients with primary Sjögren’s syndrome and positive findings of anosmia (40.4%) was significantly higher than healthy controls (13.2%) (Odds ratio: 5.2, 95% CI: 1.9-14.3, p < 0.001). The obtained results show that pSS is a risk factor for the development of dysgeusia, BST and anosmia.

The pSS group had a significantly higher mean OHIP-14 sum score than the control group (6.8±7.0 vs.2.3±8.5, p<0.001) (Fig 3). Scores in all domains of OHIP-14 (functional limitation, physical limitation, psychological limitation, and social limitation) were higher in pSS patients than in controls. The pSS group had a significantly lower mean VASEQ5D sum score than the control group (6.7±2.0 vs. 8.3±1.0 <0.0001).

Discussion

The data regarding the associations between chemosensory disturbances, BST, halitosis, salivary gland function, and OHRQoL in patients with SS are limited. The present study demonstrates that patients with pSS had impaired olfactory and gustatory functions, dysguesia and burning sensation of the tongue (BST) and poorer OHRQoL were more frequent among them in comparison with the healthy controls without sicca symptoms. No significant differences were found in the frequencies of halitosis between patients with pSS and the controls. Our findings are in agreement with other studies showing disturbed taste and smell functions in patients with SS [10, 11, 35, 36].

In our study, gustatory dysfunction was found to be more frequently reported than olfactory dysfunction, which is consistent with some studies [10, 11, 36], but contradictory to one of them [35]. The possible explanation may be related to the difference in methods of testing smell function. In this study, detection of the cognitive smell function was performed using smell identification test, whereas in the study by Kamel et al. [35] the chemosensory threshold (which reflects peripheral sensory impairment) was assessed. Smell function would be ideally tested by assessing threshold, detection, and identification tests. However, only identification test was performed in this study. Our findings demonstrate that dysgeusia, BST, and halitosis were often reported among patients with pSS which is in line with the reported data [11]. However, in our study no differences were found in the occurrence
of halitosis between pSS and the control group. There are indications that the cause of smell and taste impairments, as well as a burning sensation in the mouth may be caused by hyposalivation [10, 37, 38]. However, some studies show that salivary factors are not responsible for taste performance [38]. A recent study demonstrated lower salivary secretion rates in patients with pSS, but only weak correlation was found between salivary secretion rates and the presence of oral disorders. These findings indicate that low salivary flow is not a causative factor for the oral disorders examined in the reported study [11].

In our study we observed the relatively high percentage of ageusic and hypogeusic patients within the group of patients with pSS. While ageusia is a rare condition, reported to account for less than 1% of patients with chemosensory dysfunction [39–41] the patients with pSS in this study were categorized as ageusic as they experienced the inability to taste basic tastes: sweetness (34%), sourness (11%), saltiness (10%) or bitterness (19%). Interestingly, between 40–50% of healthy controls were found to be hypogeusic regarding the evaluated four basic tastes. However, the number of patients with pSS with ageusia/hypogeusia was significantly higher compared to healthy controls. As for olfactory function, anosmia is the most common complaint of patients with chemosensory disorders [37–39]. However, in the present study 3.8% of the patients with pSS were categorized as anosmic and 36.5% as hyposmic. The percentage of anosmic patients in our study was found to be lower than in the study conducted by Rusthen et al. [11] where 12.9% of patients with pSS were categorized as anosmic. Some studies indicate that about half of the patients with complaints of anosmia and hyposmia report change in food preferences reflected in higher consumption of sugar and seasonings [39–41] and stated that loss or reduced ability to taste affected their eating habits [42]. This could result in either an increase or a decrease in body weight as both an increase and a reduction in food intake was observed in patients with chemosensory disorders [41].

About half of the patients with pSS complained of BST, which was mainly related to food intake, while none of healthy controls experienced BST. Burning sensation in the mouth is frequently present in patients with SS [14]. More than half of the patients complained of dysgeusia with the distorted taste of bitterness occurring on a daily basis, while dysgeusia was reported by a less than 10% of healthy
controls. The problem of chemosensory dysfunction and oral disorders, such as dysgeusia, burning sensations in the tongue and mouth in patients with pSS is underestimated and the data about the frequency and severity of these disorders are limited. In our study we observed higher percentage of ageusic and hypogeusic patients within the group of patients with pSS, compared to other authors [39–41]. Patients with pSS in our study were categorized as ageusic as they experienced the inability to taste basic tastes: sweetness (34%), sourness (11%), saltiness (10%) or bitterness (19%). This difference in comparison with previous studies is suggesting that problem was underestimated, and needs to be more carefully addressed in the future. The findings of our study show that oral disorders occur on a daily basis in a large proportion of patients with pSS and highlight the need for more attention to be given to these oral problems.

Chemosensory and oral disorders, burning mouth syndrome in particular, usually reduce the patients’ quality of life, and ‘psychological dysfunction’ is common in patients with this diagnosis [43]. Consistent with this, the present study showed poor OHRQoL as estimated by OHIP-14score. The OHIP-14 questionnaire is designed to examine certain aspects of OHRQoL and the improved questionnaire is needed for better assessments of chemosensory disorders and OHRQoL in patients with pSS [11].

Oral malodor is a problem that has received increasing attention over the last decades. In the present study, a third of the patients with pSS complained of halitosis, whereas similar proportion of healthy controls reported oral malodor. The main oral causes of this disorder are known as well as effective treatment strategies [44]. Interestingly, it has been reported that a third of the patients seeking treatment for halitosis do not actually have oral malodor caused by the production of volatile sulphur compounds, and therefore they cannot be categorized as ‘genuine halitosis’ patients [17]. This could be one of the explanations of a high percentage of healthy controls complaining of halitosis in our study. Possible underlying cause of the high occurrence of olfactory and gustatory dysfunctions in pSS patients could be found in systemic inflammatory mechanisms operating in pSS such as overexpression of interferon-inducible genes [19]. Toll-like receptor pathways and interferon pathways mediate the inflammatory responses in taste tissue in pSS and may interfere with normal
taste transduction and taste-bud cell turnover [20].

A most recent study demonstrated significantly high occurrence of dysgeusia, burning mouth sensation, halitosis and reduced taste in non-SS sicca patients and patients with pSS. Although non-SS sicca patients do not fulfill Sjögren’s syndrome classification criteria, they had similar or even worse oral complaints than the patients with pSS [45]. Generally it would have been desirable to have a second comparison group with patients with dry syndrome that was not secondary to an autoimmune disease (diabetes, menopause, hypothyroidism, radiotherapy, age, etc.) to demonstrate whether the differences are due to the autoimmune process or the damage caused by the dryness of the mouth. Not having this second comparison group is one of the weaknesses of our study. In our plans for future studies we will try to form this second comparison group to have better insight in the possible association of other autoimmune diseases and the chemosensory dysfunction and oral disorders.

Conclusion
The results obtained in this study showed that patients with pSS had impaired olfactory and gustatory function. The occurrence of oral disorders, such as dysgeusia, BST, and halitosis was frequently found in patients with pSS patients who reported poorer OHRQoL compared to age- and gender-matched healthy subjects. Therefore, the regular assessment of the chemosensory functions and oral disorders in patients with pSS should be performed. Future studies of habits related to oral hygiene and dietary intake are needed to ensure improved treatment of oral health problems in patients with pSS.

Declarations

Ethics approval
All study participants had given their informed consent according to the Declaration of Helsinki, and the study was approved by the Local Ethics Committee at the Institute of Rheumatology, University of Belgrade

Consent to participate
Not Applicable
Consent for publication

All authors read and approved the final manuscript.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Funding

This study was funded by the Institute of Rheumatology, University of Belgrade, Serbia

Competing Interests

Authors declare no conflict of interest

Authors’ contributions

MŠG, VM, ND and NP contributed to the study conception and design. Material preparation, data collection and analysis were performed by MŠG, VM and ND. The first draft of the manuscript was written by NP and all authors commented on previous versions of the manuscript.

Acknowledgements

We would like to thank Zorica Ivkovic for language editing.

Abbreviations

primary Sjögren's syndrome (pSS)
burning sensations in the tongue (BST)
oral health-related quality of life (OHRQoL)
Oral Health Impact Profile (OHIP-14)
visual analogue scale (VAS)
Sjögren's syndrome (SS)
secondary Sjögren syndrome, sSS
dendritic cells (DCs)
muscarinic acetylcholine type 3 receptors (M3R)
single nucleotide polymorphisms (SNPs)
matrix metalloproteinase 9 (MMP9)
human leukocyte antigen (HLA)
American-European consensus group (AECG)
rheumatoid arthritis (RA)
burning sensation in the tongue (BST)
American–European Consensus (AEC)
labial salivary gland (LSG)
anti-nuclear antibodies (ANA)
enzyme-linked immunosorbent assay (ELISA)
rheumatoid factor (RF)
EULAR index of disease activity (ESSDAI)
EULAR SS Patient Reported Index (ESPRI)
Statistical Package for the Social Sciences (SPSS)
odds ratios (ORs)
confidence intervals (CIs)
tear breaking-up time (BUT)
erythrocyte sedimentation rate (ESR)

References
1. Fox RI. Sjogren’s syndrome. Lancet 2005;366:321-331.
2. Both T, Dalm VA, van Hagen PM, van Daele PL. Reviewing primary Sjögren’s syndrome: beyond the dryness - From pathophysiology to diagnosis and treatment. Int J Med Sci 2017;4(3):191-200.
3. Reina S, Rodríguez M, Stranieri G, Borda E. Action of anti-M₃muscarinic acetylcholine receptor IgG of primary Sjögren’s syndrome on the enzymatic antioxidant system in rat submandibular gland. J Oral Pathol Med 2015;44(10):876-883.
4. Reksten TR, Lessard CJ, Sivils KL. Genetics in Sjögren Syndrome. Rheum Dis Clin North Am 2016;42(3):435-447.
5. Shah NR, Noll BD, Stevens CB, Brennan MT, Mougeot FB, Mougeot JC. Biosemantics guided gene expression profiling of Sjögren’s syndrome: a comparative analysis with systemic lupus erythematosus and rheumatoid arthritis. Arthritis Res Ther 2017;19(1):192.

6. Vitali C, Bombardieri S, Jonsson R, Moutsopoulos HM, Alexander EL, Carsons SE, Daniels TE, Fox PC, Fox RI, Kassan SS, Pillemer SR, Talal N, Weisman MH. Classification criteria for Sjogren’s syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis 2002; 61:554-558.

7. Venables PJ. Management of patients presenting with Sjogren’s syndrome. Best Practice & Res Clin Rheumatol 2006;20:791-807.

8. Nocturne G, Cornec D, Seror R, Mariette X. New biological therapies in Sjögren's syndrome. Best Pract Res Clin Rheumatol 2015;29(6):783-793.

9. Enger TB, Palm O, Garen T, Sandvik L, Jensen JL. Oral distress in primary Sjogren’s syndrome: implications for health-related quality of life. Eur J Oral Sci 2011;19:474-480.

10. Henkin RI, Talal N, Larson AL, Mattern CF. Abnormalities of taste and smell in Sjögren’s syndrome. Ann Intern Med 1972;76:375-383.

11. Rusthen S, Young A, Herlofson BB, Aqrawi LA, Rykke M, Hove LH, Palm Ø, Jensen JL, Singh PB. Oral disorders, saliva secretion, and oral health-related quality of life in patients with primary Sjögren's syndrome. Eur J Oral Sci 2017;125(4):265-271.

12. Murphy C, Doty RL, Duncan HJ. Clinical disorders of olfaction. In: DOTY RL, ed. Handbook of olfaction and gustation, 2nd ed. Basel and New York: Marcel Dekker, 2003;461-478.

13. Bromley SM, Doty RL. Clinical disorders affecting taste: evaluation and management.
In: DOTY RL, ed. Handbook of olfaction and gustation, 2nd ed. Basel and New York: Marcel Dekker, 2003;935-958.

14. Grushka M, Ching V, Epstein J. Burning mouth syndrome. Adv Otorhinolaryngol 2006;63:278–287.

15. Scala A, Checchi L, Montevecchi M, Marini I, Giamberardino MA. Update on burning mouth syndrome: overview and patient management. Crit Rev Oral Biol Med 2003;14:275–291.

16. Aljanobi H, Sabharwal A, Krishnakumar B, Kramer JM. Is it Sjögren's syndrome or burning mouth syndrome? Distinct pathoses with similar oral symptoms. Oral Surg Oral Med Oral Pathol Oral Radiol 2017;23(4):482-495.

17. Falcao DP, Vieira CN, Batista DE Amorim RF. Breaking paradigms: a new definition for halitosis in the context of pseudo-halitosis and halitophobia. J Breath Res 2012;6:017105.

18. Poon R, Su N, Ching V, Darling M, Grushka M. Reduction in unstimulated salivary flow rate in burning mouth syndrome. Br Dent J 2014;217(7):E14.

19. Gottenberg JE, Cagnard N, Lucchesi C, Letourneur F, Mistou S, Kazure T, Jacques S, Ba N, Ittag M, Lepajolec C, Labetoulle M, Ardizzone M, Sibilia J, Fournier C, Chiocchia G, Mariette X. Activation of IFN pathways and plasmacytoid dendritic cell recruitment in target organs of primary Sjögren's syndrome. Proc Natl Acad Sci USA 2006;103:2770-2775.

20. Wang H, Zhou M, Brand J, Huang L. Inflammation and taste disorders: mechanisms in taste buds. Ann N Y Acad Sci 2009;170:596-603.

21. Mann NM. Management of smell and taste problems. Cleve Clin J ed. 2002;69:329–36.

22. Welge-Lüssen A. Re-establishment of olfactory and taste functions. GMS Curr Top Otorhinolaryngol Head Neck Surg. 2005;4:Doc06.
23. Bromley SM. Smell and taste disorders: A primary care approach. Am Fam Physician. 2000;61:427–36.

24. MilicVD, Petrovic RR, Boricic IV, Marinkovic-Eric J, Radunovic GL, Jeremic PD, Pejnovic NN, Damjanov NS. Diagnostic value of salivary gland ultrasonographic scoring system in primary Sjogren's syndrome: a comparison with scintigraphy and biopsy. J Rheumatol 2009; 36(7):1495-500.

25. Milic VD, Petrovic PP, Boricic IV, Radunovic GL, Pejnovic NN, Soldatovic I, Damjanov NS. Major salivary gland sonography in Sjogren`s syndrome: diagnostic value of a novel ultrasonography score (0-12) for parenchymal inhomogeneity. Scand J Rheumatol 2010;39:160-166.

26. Chisholm DM, Mason DK. Labial salivary gland biopsy in Sjögren’s syndrome. J Clin Pathol 1968;21:656–60.

27. Hummel T, Kobal G, Gudziol H, Mackay-Sim A. Normative data for the “Sniffin’ Sticks” including tests of odor identification, odor discrimination, and olfactory thresholds: an upgrade based on a group of more than 3,000 subjects. Eur Arch Otorhinolaryngol 2007;264:237–243.

28. Landis BN, Welge-Luessen A, Bramerson A, Bende M, Mueller CA, Nordin S, Hummel T. “Taste Strips”- a rapid, lateralized, gustatory bedside identification test based on impregnated filter papers. J Neurol 2009;256:242–248.

29. Slade GD. Derivation and validation of a short-form oral health impact profile. Community Dent Oral Epidemiol 1997;25:284–290.

30. Locker D. Measuring oral health: a conceptual framework. Community Dent Health 1998;5:3-18.

31. Slade GD, Spencer AJ. Development and evaluation of the Oral Health Impact Profile. Community Dent Health 1994;11:3-11.
32. Seror R, Ravaud P, Bowman SJ, et al. EULAR Sjogren’s syndrome disease activity index: development of a consensus systemic disease activity index for primary Sjogren’s syndrome. Ann Rheum Dis 2010;69:1103-1109.

33. Seror R, Bowman SJ, Brito-Zeron P, Theander E, Bootsma H, Tzioufas A, Gottenberg JE, Ramos-Casals M, Dörner T, Ravaud P, Vitali C, Mariette X, et al. EULAR Sjögren's syndrome disease activity index (ESSDAI): a user guide. RMD Open 2015;1(1):e000022. doi: 10.1136/rmdopen-2014-000022.

34. Seror R, Ravaud P, Mariette X, et al. EULAR Sjogren’s Syndrome Patient Reported Index (ESSPRI): development of a consensus patient index for primary Sjogren’s syndrome. Ann Rheum Dis 2011;70:968-972.

35. KamelUF, Maddison P, Whitaker R. Impact of primary Sjögren’s syndrome on smell and taste: effect on quality of life. 2009;48:1512–1514

36. Weiffenbach JM, Schwartz LK, Atkinson JC, Fox PC. Taste performance in Sjogren’s syndrome. Physiol Behav 1995;57:89–96.

37. Poon R, Su N, Ching V, Darling M, Grushka M. Reduction in unstimulated salivary flow rate in burning mouth syndrome. Br Dent J 2014;17:E14.30.

38. Weiffenbach JM, Fox PC, Baum BJ. Taste and salivary function. Proc Natl Acad Sci USA 1986;83:6103–6106.

39. Ferris AM, Schierberl MJ. Nutrition and taste and smell deficits: a risk factor or an adjustment? In: MEISELMAN HL, RIVLIN RS, eds. Clinical measurement of taste and smell. New York: MacMillan, 1986;264–278.

40. Deems DA, Doty RL, Settle G, Moore-Gillon V, Shaman P, Mester AF, Kimmelman CP, Brightman VJ, Snow JB. Smell and taste disorders, a study of 750 patients from the university of Pennsylvania Smell and Taste Centre. Arch Otolaryngol Head Neck Surg 1991;117:519–528.
41. Mattes RD, Cowart BJ. Dietary assessment of patients with chemosensory disorders. J Am Diet Assoc 1994;94:50–56.

42. Rehwaldt M, Wickham R, Purl S, Tariman J, Blendowski C, Shott S, Lappe M. Self-care strategies to cope with taste changes after chemotherapy. Oncol Nurs Forum 2009;36:E47–E56.

43. Gorsky M, Silverman S Jr, Chinn H. Clinical characteristics and management outcome in the burning mouth syndrome. An open study of 130 patients. Oral Surg Oral Med Oral Pathol 1991;72:192–195.

44. Rösing CK, Loesche W. Halitosis: an overview of epidemiology, etiology and clinical management. Braz Oral Res 2011;25:466–471.

45. Singh PB, Young A, Homayouni A, Hove LH, Petrovski BÉ, Herlofson BB, Palm Ø, Rykke M, Jensen JL. Distorted Taste and Impaired Oral Health in Patients with Sicca Complaints. 2019;24;11(2). pii: E264. doi:10.3390/nu11020264.

Tables
Table 1. Characteristics of patients with primary Sjögren’s syndrome and healthy controls
| Characteristics                              | Patients with pSS (n=58) | Healthy controls (n=55) | P     |
|---------------------------------------------|--------------------------|-------------------------|-------|
| Age (yrs)                                   | 54.9±13.7                | 51.4±13.8               | 0.917 |
| Gender                                      |                          |                         |       |
| Female                                      | 55 (94.8)                | 55 (100.0)              | 0.244 |
| Smoking status                              |                          |                         |       |
| Current smoker                              | 13 (22.4)                | 8 (14.5)                |       |
| Former smoker                               | 5 (8.6)                  | 5 (9.1)                 | 0.560 |
| Never smoked                                | 40 (60.9)                | 42 (76.4)               |       |
| Disease duration (yrs)                      | 7.6±5.8                  | N/A                     | <0.0001|
| Ocular dryness                              | 51 (87.9)                | 0 (0.0)                 |       |
| Oral dryness                                | 53 (91.4)                | 0 (0.0)                 | <0.0001|
| Dysphagia                                   | 35 (60.3)                | 0 (0.0)                 | <0.0001|
| Nasal dryness                               | 18 (31.0)                | 0 (0.0)                 | <0.0001|
| Dyspareunia                                 | 21 (36.2)                | 0 (0.0)                 | <0.0001|
| Salivary gland enlargement                  | 28 (48.3)                | 0 (0.0)                 | <0.0001|
| Reynaund phenomenon                         | 24 (42.1)                | 0 (0.0)                 | <0.0001|
| ESSDAI*                                     |                          |                         |       |
| <5 low activity                             | 15 (26.8)                |                         |       |
| 5-13 moderate activity                      | 24 (42.8)                |                         |       |
| >13 high activity                           | 17 (30.4)                |                         |       |
| ESSPRI**                                    |                          |                         |       |
| <5 satisfactory                             | 23 (40.4)                |                         |       |
| >=5 unsatisfactory                          | 34 (59.6)                |                         |       |
| symptom state                               |                          |                         |       |
| Scintigraphy of salivary glands             |                          |                         |       |
| Positive                                    | 41 (89.1)                | N/A                     |       |
| Salivary gland biopsy                       | 28 (87.5)                | N/A                     |       |
| Positive                                    | 45 (90.0)                | N/A                     |       |
| Schirmer’s test                             | 38 (95.0)                | N/A                     |       |
| Abnormal                                    |                          |                         |       |
| Rose Bengal score                           | 43 (93.5)                | N/A                     |       |
| Abnormal                                    |                          |                         |       |
| Tear break-up time (BUT)                    | 41 (70.7)                | N/A                     |       |
| Abnormal                                    |                          |                         |       |
| Antinuclear antibody                        | 47 (81.0)                | N/A                     |       |
| Positive                                    | 27 (46.6)                | N/A                     |       |
| SS-A                                        | 40 (69.0)                | N/A                     |       |
| Positive                                    |                          |                         |       |

Values are given as mean±SD or n (%); Statistical analysis was performed using chi-square tests except for age (t-test); *(n=57); ** (n=56)

Table 2. Gustatory function in patients with pSS and healthy controls
Patients with pSS \((n=58)\) & Healthy controls \((n=55)\) & \(P\) \\
\hline
**Self-reported taste score (VAS)** & 8.5±2.1 & 9.5±0.7 & 0.014 \\
**Taste score** & 4.1±1.8 & 6.1±1.9 & <0.0001 \\

Gustatory function

| **Ability to taste sweet** | Patients | Healthy controls | \(P\) |
|---------------------------|----------|-----------------|-------|
| Loss of taste             | 16 (34.0) | 4 (7.5)         | <0.0001 |
| Reduced taste             | 29 (61.7) | 17 (32.1)       |       |
| Normal taste              | 2 (4.3)   | 32 (60.4)       |       |

| **Ability to taste sour** | Patients | Healthy controls | \(P\) |
|---------------------------|----------|-----------------|-------|
| Loss of taste             | 5 (10.6) | 0 (0)           | 0.054 |
| Reduced taste             | 22 (46.8)| 24 (45.3)       |       |
| Normal taste              | 20 (42.6)| 29 (54.7)       |       |

| **Ability to taste salty** | Patients | Healthy controls | \(P\) |
|---------------------------|----------|-----------------|-------|
| Loss of taste             | 5 (10.0) | 3 (5.7)         | 0.018 |
| Reduced taste             | 30 (60.0)| 21 (39.6)       |       |
| Normal taste              | 15 (30.0)| 29 (54.7)       |       |

| **Ability to taste bitter** | Patients | Healthy controls | \(P\) |
|-----------------------------|----------|-----------------|-------|
| Loss of taste               | 9 (19.1) | 1 (1.9)         | 0.001 |
| Reduced taste               | 28 (59.6)| 27 (50.9)       |       |
| Normal taste                | 10 (21.3)| 25 (47.2)       |       |

Values are given as mean±SD or \(n\) (%); Statistical analysis was performed using chi-square test (gustatory function) and Mann-Whitney test (taste score VAS, taste score)

Table 3. Frequency of dysgeusia, burning sensations in the tongue (BST) and halitosis and Odds ratio for the development of dysgeusia, halitosis and BST in patients with primary Sjögren’s syndrome and healthy controls
|                        | Patients with pSS (n=57) | Healthy Controls (n=53) | P      | Odds ratio | 95%CI       | P     |
|------------------------|--------------------------|-------------------------|--------|------------|-------------|-------|
| **Dysgeusia**          |                          |                         |        |            |             |       |
| Yes                    | 30 (52.6)                | 5 (9.4)                 | <0.0001| 10.7       | 3.7-30.7    | <0.001|
| No                     | 27 (47.4)                | 48 (90.6)               |        |            |             |       |
| **Distorted taste**    |                          |                         |        |            |             |       |
| Metallic               | 3 (10.0)                 | 0 (0.0)                 |        |            |             |       |
| Rotten                 | 3 (10.0)                 | 0 (0.0)                 |        |            |             |       |
| Bitter                 | 11 (36.7)                | 0 (0.0)                 |        |            |             |       |
| Sour                   | 5 (16.7)                 | 0 (0.0)                 |        |            |             |       |
| Unpleasant             | 8 (26.7)                 | 5 (100.0)               |        |            |             |       |
| **Frequency of distorted taste** |                |                         |        |            |             |       |
| Constantly             |                          |                         |        |            |             |       |
| Daily                  | 2 (6.7)                  | 1 (3.3)                 |        |            |             |       |
| Sometimes              | 23 (76.7)                | 2 (66.7)                | n.s.   |            |             |       |
| In bad periods         | 1 (3.3)                  | 0 (0.0)                 |        |            |             |       |
|                        | 4 (13.3)                 | 0 (0.0)                 |        |            |             |       |
| **BST**                |                          |                         |        |            |             |       |
| Yes                    | 26 (45.6)                | 0 (0.0)                 | <0.0001| *          |             | <0.001|
| No                     | 31 (54.4)                | 53 (100.0)              |        |            |             |       |
| **Frequency of BST**   |                          |                         |        |            |             |       |
| Constantly             | 5 (19.2)                 | N/A                     | <0.0001|            |             |       |
| Sometimes              | 5 (19.2)                 | N/A                     |        |            |             |       |
| During the meal        | 10 (38.5)                | N/A                     |        |            |             |       |
| Between the meals      | 6 (23.1)                 | N/A                     |        |            |             |       |
| **Type of BST**        |                          |                         |        |            |             |       |
| Harsh                  | 5 (27.8)                 | N/A                     |        |            |             |       |
| Sour                   | 7 (38.9)                 | N/A                     |        |            |             |       |
| Sweet/Sour             | 3 (16.7)                 | N/A                     |        |            |             |       |
| Other                  | 3 (16.7)                 | N/A                     |        |            |             |       |
| **Halitosis**          |                          |                         |        |            |             |       |
| Yes                    | 18 (31.6)                | 15 (28.3)               | 0.434  | 1.2        | 0.5-2.6     | 0.708 |
| No                     | 39 (68.4)                | 38 (71.7)               |        |            |             |       |
| **Frequency of halitosis** |                    |                         |        |            |             |       |
| Constantly             | 5 (27.8)                 | 3 (20.0)                |        |            |             |       |
| Daily                  | 9 (50.0)                 | 12 (80.0)               |        |            |             |       |
| Sometimes              | 2 (11.1)                 | 0 (0.0)                 | 0.328  |            |             |       |
| In bad periods         | 2 (11.1)                 | 0 (0.0)                 |        |            |             |       |

Values are given as n (%); Statistical analysis was performed using chi-square test; n.s. (not significant) *Odds ratio could not be calculated due to the number <10 of observations in one group. Figures
Olfactory function in patients with pSS and healthy controls. Significantly higher frequencies of pSS patients with anosmia and hyposmia in comparison with healthy controls ($\chi^2=9.9; p=0.002$).
Dysgeusia, burning sensations in the tongue (BST), and halitosis in patients with primary Sjögren’s syndrome and in healthy controls. Significantly higher frequencies of pSS patients with self-reported complaints of dysgeusia ($\chi^2=23.6, p<0.0001$), BST ($\chi^2=31.6, p<0.0001$), but not of halitosis ($\chi^2=0.40, p=0.434$) in comparison with healthy controls.
Figure 3

Oral health-related quality of life (OHRQoL) in patients with pSS and healthy controls

Patients with pSS had a significantly higher mean OHIP-14 sum score using the short-form Oral Health Impact Profile (OHIP-14) questionnaire than healthy controls reflecting poorer OHRQoL (p<0.0001; Mann-Whitney U test)