

# Factors associated to salivary flow alterations in dry mouth female patients\*

## Fatores associados a alterações no fluxo salivar em pacientes com xerostomia

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### ABSTRACT

**BACKGROUND AND OBJECTIVES:** Saliva plays an important role in oral health; it is involved in lubrication of the oral mucosa, protection against infections, transport of nutrients and digestive enzymes, remineralization of teeth, as well as aiding in chewing, swallowing and speech. Reductions in the amount of saliva are known to increase the risk of oral diseases. This study investigated the factors associated to salivary flow alterations and its relationship with age, burning mouth syndrome, psychiatric and sleep disorders, systemic diseases and chronic drug use.

**METHODS:** A total of 30 patients complaining of dry mouth without unbalanced systemic diseases were included. Questionnaires regarding socio-demographic data, xerostomia, burning mouth, depression and anxiety symptoms, and sleep disturbances were applied. Measures of salivary flow rates were obtained using spit method. Correlation of hyposalivation and quantitative data was determined using a multivariate regression model.

**RESULTS:** The age range was 31-83 years, hyposalivation was correlated positively with sleep disorder ( $\beta=0.079$ , 95% CI, 0.033 to 0.124) and negatively with burning mouth ( $\beta=-0.043$ , 95% CI, -0.083 to -0.002).

**CONCLUSION:** These results provide evidences regarding the association between reduced salivary flow and burning mouth, sleep disorders and chronic use of psychotropic medicines, and

we highlighted the important role of antidepressants on modulation of burning mouth sensation.

**Keywords:** Burning mouth, Dry mouth, Hyposalivation, Sleep disorders, Xerostomia.

### RESUMO

**JUSTIFICATIVA E OBJETIVOS:** A saliva tem um papel importante na saúde bucal; está envolvida na lubrificação da mucosa oral, na proteção contra infecções, no transporte de nutrientes e enzimas digestivas, na remineralização dentária e também auxilia na mastigação, deglutição e fala. Sabe-se que reduções na quantidade de saliva aumentam o risco de doenças bucais. Este estudo investigou os fatores associados a alterações no fluxo salivar e seu relacionamento com idade, síndrome de ardência bucal, distúrbios psiquiátricos e do sono, doenças sistêmicas e uso crônico de medicamentos.

**MÉTODOS:** Foi incluído um total de 30 pacientes com queixa de xerostomia sem doenças sistêmicas desequilibradas. Foram aplicados questionários sobre dados sociodemográficos, xerostomia, ardência bucal, sintomas de depressão e ansiedade e distúrbios do sono. As medidas de fluxo salivar foram obtidas pelo método *spit*. A correlação entre hipo-salivação e dados quantitativos foi determinada por um modelo univariado de regressão.

**RESULTADOS:** A idade variou de 31;83 anos, hipo-salivação foi correlacionada positivamente com distúrbios do sono ( $\beta=0,079$ , 95% CI, 0,033 a 0,124) e negativamente com ardência bucal ( $\beta=-0,043$ , 95% CI, -0,083 a -0,002).

**CONCLUSÃO:** Esses resultados trazem evidências sobre a associação entre fluxo salivar reduzido e ardência bucal, distúrbios do sono e uso crônico de psicotrópicos, e destacamos o importante papel dos antidepressivos na modulação da sensação de ardência bucal.

**Descritores:** Ardência bucal, Boca seca, Distúrbios do sono, Hipo-salivação, Xerostomia.

### INTRODUCTION

Saliva plays an important role in oral health. It is involved in protection against bacteria and fungi, transport of nutrients and digestive enzymes, lubrication of the oral cavity, remineralization of teeth, as well as aiding in chewing, swallowing and speech<sup>1</sup>.

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Some patients may complain of halitosis and chronic burning sensation in oral mucosa<sup>2</sup>. The low salivary flow<sup>3</sup> and burning mouth syndrome (BMS) are associated with psychological factors, such as anxiety, stress and depression<sup>4</sup>.

BMS is a condition that expresses a burning sensation in oral mucosa that shows normal condition at clinical examination<sup>5</sup>. It can be accompanied by xerostomia and taste alterations<sup>6</sup>. The etiology of BMS is considered multifactorial and includes local, systemic and psychogenic factors<sup>7</sup>. Besides, some studies have demonstrated changes in levels of salivary cytokines associated with BMS<sup>8</sup>.

Scientific literature indicates that anxiety is associated with BMS and in conditions involving pain, stress, anxiety and many metabolic and endocrine changes occur. Among these, a rise in cortisol levels is one of the most important physiological effects<sup>9</sup>.

However, the evidences of the association between psychological factors and salivary flow remain contradictory. Data of literature suggests that the secretion of saliva from human parotid glands depends on emotional state<sup>10</sup>. One study claims that stress is only related to the reduced flow unstimulated<sup>11</sup> while other study reports that stress is associated with increased salivary flow<sup>12</sup>.

Another important point poorly discussed in the literature is the direct relationship between hyposalivation and sleep quality. The biological significance of decreased saliva during sleep is unknown. Researchers believe that many of the lubricating and protective mechanisms offered by saliva during the day should remain during sleep. Study in Northern population showed that the prevalence of self-reported dry mouth complaint during sleep (associated with awakening and water intake) was 23% of whole population<sup>13</sup>. Other study demonstrated that persons with narcolepsy have lower whole salivary flow rates<sup>14</sup>.

The increasing age has been correlated with a high prevalence of self-reported dry mouth, however there is no evidence that the salivary function deteriorates with age in healthy individuals<sup>1</sup>. Certain types of medications mainly used for older populations can result in xerostomia. In addition, most patients use more than one type of medication, and this polypharmacy itself has been implied in increased prevalence of dry mouth, thus it is difficult to determine which medication is responsible for this sensation. Several drug groups have been associated with dry mouth prevalence, for example, antidepressants, antimuscarinic and antihistamines<sup>15</sup>. Hospitalized patients who experienced dry mouth took more cardiovascular, psychiatric and allergy drugs than those who did not complain of dry mouth<sup>16</sup>.

Considering the relevance of this issue in patients' quality of life, the aim of the present study was to evaluate the factors associated to salivary flow alterations and its relationship with age, burning mouth syndrome, psychiatric and sleep disorders, systemic diseases and chronic drug use in female patients.

## METHODS

A total of 30 female participants complaining of dry mouth were enrolled in this cross-sectional study. They were recruited in the Stomatology Clinic of Hospital de Clínicas de Porto Alegre and the Oral Pathology Clinic of the School of Dentistry of Univer-

sidade Federal do Rio Grande do Sul from 2009 to 2011.

Experienced Dentists performed a complete clinical examination. Patients that presented some oral lesion, candida infection or patients submitted to radiations therapy were excluded from the study. The subjects answered a sociodemographic data questionnaire that recorded data like tobacco and alcohol use, and age. In addition, the medication taken by each patient and the systemic illnesses that they suffered, were recorded. Furthermore, the patients were required to undergo a blood test to determine concentrations of glucose, vitamin B12, ferritin, and folic acid and to perform a blood count aiming at ruling out possible metabolic alterations or nutritional deficiencies associated with oral manifestations including oral dryness and burning pain.

Flow rates of unstimulated and stimulated whole saliva were determined using the draining or spit method<sup>17</sup>. Collection was scheduled in the morning, two hours after breakfast, and patients expectorated in graduated container. The first collection was unstimulated flow and 30min after the stimulated flow was collected, the stimulation was made by salivary mechanical stimulation using an instrument to perform balanced masticatory exercises (mechanical sialogogue— piece of paraffin)<sup>18</sup>. Hyposalivation is usually defined by a flow rate of unstimulated whole saliva (UWS) less than 0.1mL min<sup>-1</sup>, or of stimulated whole saliva (SWS) less than 0.7mL min<sup>-1</sup><sup>19</sup>.

Subjective dry mouth sensation was evaluated through the Xerostomia Inventory (XI), a multidimensional continuous scale that was developed to address this symptom<sup>20</sup>. It contains a total of 11 items designed to assess the broad experience of dry mouth. Using a continuous scale is advantageous because it avoids dichotomizing patients as either xerostomic or non-xerostomic by determining the severity of the condition. The XI also allows changes in severity of the condition to be monitored over time. Each of the 11 items has four possible responses ranging from 'never' to 'always'.

## Questionnaire regarding burning mouth

In all patients, we examined pain intensity and burning mouth sensation using a visual analog scale (VAS: 0, no pain; VAS: 10, extreme pain)<sup>21</sup>.

## Psychological evaluation

On their second visit to the clinic, each patient answered a standardized series of questions concerning depressive symptoms, anxiety and sleep disorders. Psychological disturbances were measured by Beck self-applied questionnaire on depression (The Beck Depression Inventory - BDI). For anxiety symptoms the State and Trait Anxiety Index (STAI) was used, and for sleep disorders the Pittsburgh Sleep Quality Index (PSQI). BDI is a 21 item self-report questionnaire with item scores ranging from 0 to 3 and a total score of 0–63<sup>22,23</sup>. The BDI is known to have appropriate psychometric features including good reliability statistics, and is one of the most commonly used self-report measures for depressive symptoms. The STAI form is an instrument for self-measuring anxiety in adults. It can clearly differentiate between a transient condition of "state anxiety" and a more general and long-standing quality of "trait anxiety." It consists of 2 questionnaires.

naires containing 20 multiple-choice items on which a score of >40 is considered pathologic<sup>24,25</sup>. PSQI is a self-rated questionnaire that assesses sleep quality and disturbances. Nineteen individual items generate 7 component scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication and daytime dysfunction. The sum of scores for these 7 components yields a global score<sup>26</sup>. All of the psychological tests used in this study were validated for the Brazilian population.

Descriptive statistical methods (mean ± standard error) or frequency were used for presenting sociodemographic data, and independent-Samples *t*-test and Chi-square test were used to compare groups, respectively.

Data were compared using logistic regression with the forward stepwise method, with the unstimulated salivary flow (UWS) as the dependent variable, in order to test xerostomia, burning sensation, psychological factors and age. The use of psychotropic medication was treated as dummy variable, and backward stepwise method was used, and the burning sensation dropped out of the model.

Data were analyzed with the Statistical Package for the Social Sciences (SPSS; SPSS Inc., Chicago, IL, USA) for Windows 18.0. *P* values less than 0.05 were considered significant.

The study was approved by the Hospital de Clínicas de Porto Alegre Ethics Committee and all participants gave written informed consent (protocol number: 2008-350).

## RESULTS

In the present study, 30 female subjects presenting dry mouth complaint, with an age range of 18-80 years were recruited. Patients' characteristics are summarized in table 1; no significant differences were found between patients who use and do not use antidepressant. No patients had changes in hematologic tests (data not shown).

Major symptom in addition to dry mouth was burning mouth, which was perceived in 63.3% of patients. Mean intensity, evaluated by VAS, was 4.38±0.73 cm, with the tongue and the lower lip being the most affected areas. Overall 73.3% of patients presented chronic diseases, with cardiovascular and psychiatric diseases being the most prevalent (46.7%). Systemic drugs were taken by 83.3% of patients, the most common being antihypertensive (46.7%), anxiolytics (36.7%) and antidepressants (26.7%). These conditions did not present a significant correlation with hyposalivation (Table 2).

A correlation between the severity of hyposalivation and burning mouth sensation and sleep disorder is presented in table 3. The adjusted analysis using a regression model demonstrated that hyposalivation was correlated positively with sleep disorder, and negatively with burning mouth. Also, it was tested the possible relationship between the variables age, anxiety and depressive symptoms and hyposalivation. However, these variables did not remain in the equation (data not shown).

**Table 1.** Characteristics of the study sample

Characteristics	Antidepressant use		OR	95% CI
	Yes (n=08)	No (n=22)		
Age (years) #	51.75±5.25	58.36±3.47	3.33	0.38-28.96
Smoking§ (Yes/No)	2/6	2/20		
Systemic diseases§ (Yes/No)	7/1	15/7	3.26	0.33-31.91
Cardiovascular	3/5	11/11	0.60	0.11-3.14
Psychiatric	8/0	6/16	0.42	0.23-0.78
Medication§ (Yes/No)	8/0	17/5	0.68	0.52-0.89
Antihypertensive	3/5	11/11	0.60	0.11-3.14
Anxiolytic	3/5	8/14	1.05	0.19-5.60

Values are in means ± standard Error or frequencies (n=30); # Independent-Samples *t*-test to compare means; § Chi-square test to compare frequencies

**Table 2.** Psychological characteristics, sleepiness levels, burning mouth, xerostomia and chronic pain

Scales	Antidepressants use	
	Yes	No
Trait anxiety	50.75±2.15	53.68±1.36
State anxiety	49.62±2.11	51.45±1.33
Depressive symptoms	11.12±2.09	15.90±5.84
Sleep disorder	8.12±1.55	6.77±0.70
Burning mouth	3.29±1.37	4.77±0.87
Xerostomia	27.00±2.35	26.68±1.50
Chronic pain	2.60±1.59	2.25±0.73
Unstimulated whole saliva	0.19±0.01	0.22±0.11
Stimulated whole saliva	0.45±0.09	0.57±0.12

Values are in means ± standard Error. No significant differences between patients who use and do not use antidepressant on chronic pain, burning mouth, xerostomia and sleepiness scales (Student *t*-test *p*>0.05, n=30).

**Table 3.** Multivariate logistic regression analysis for the association among Unstimulated Whole Saliva (UWS), sleep disorder, burning sensation and antidepressant drug

Dependent variables: Unstimulated Whole Saliva (n=30) <sup>a</sup>				
	T	β	95% CI	p value
Sleep disorder	3.546	0.079	0.033 to 0.124	0.001
Burning sensation	2.170	-0.043	-0.083 to -0.002	0.039
Analysis stratified by non-use of antidepressant (n=22) <sup>b</sup>				
Dependent variables: Unstimulated Whole Saliva				
Sleep disorder	2.823	0.082	0.021 to 0.143	0.011
Burning sensation	-2.718	-0.064	-0.113 to -0.015	0.014
Analysis stratified by use of antidepressant (n=8) <sup>b</sup>				
Dependent variables: Unstimulated Whole Saliva				
Sleep disorder	3.535	0.100	0.031 – 0.169	0.012

<sup>a</sup>Stepwise forward regression model; <sup>b</sup>Stepwise backward regression.

## DISCUSSION

The present study showed an association between hyposalivation, burning mouth, sleep disorders and psychotropic drugs use. In addition, we observed a high prevalence of dry mouth complaint in postmenopausal women and those using a diverse group of medicines, such as antihypertensive and antidepressants.

The complaint of burning mouth sensation was the main symptom reported by patients with dry mouth. The percentage of BMS patients was 73.5% corroborating other authors<sup>2,27</sup>. Patients showed normal oral mucosa and hematologic parameters (serum concentrations of glucose, iron, folate and vitamin B12, data not shown). Our results highlight an interesting point; there is an association between burning sensation and spontaneous salivary flow. However when stratified by antidepressant use this relationship disappears. These findings suggest that there is a modulation of BMS by antidepressant, supporting the hypothesis of neuropathic etiology of BMS. Evidence in the literature relates BMS to a peripheral neuropathy, a study showed a significantly lower density of epithelial and subpapillary nerve fibers in tongue of BMS patients in comparison to control subjects<sup>28</sup>. Besides, studies have shown a relationship between dysregulation of the nigrostriatal dopaminergic system and BMS, the frequency of BMS in patients with Parkinson's disease was five times higher than the general population<sup>28,29</sup>.

Standard treatments for neuropathic pain were effective in treating BMS, a randomized double blind placebo controlled trial showed that gabapentin alone (300mg daily) or in combination with alpha lipoic acid (ALA) (600mg daily) was beneficial in reducing symptoms in 50 and 70% of patients with BMS, respectively<sup>29,30</sup>. This contributes to the hypothesis of neuropathic etiology of BMS.

Our results demonstrated an opposite relationship of unstimulated flow and sleep disorder assessed by PSQI. Our results contradict the majority of studies that report the prevalence of dry mouth upon nocturnal awakening<sup>31,32</sup>. Atropinic side effects like dry mouth are very common in patients using tricyclic antidepressant<sup>33</sup> and these medications were taken by most of our patients. Although these patients improved sleep quality, they showed an increase in dry mouth symptoms. In addition, we

found high prevalence of cardiovascular and psychiatric diseases in patients with dry mouth sensation. Although it has not been found a significant relationship between these variables and low salivary flow.

Xerostomia is commonly linked to polypharmacy, despite of this relationship remaining poorly understood. Study showed that xerogenic medication used alone presented a dry mouth effect, and when associated to another medicine there was improvement of this symptom. This demonstrates that the interaction between specific drugs may involve xerostomic effect<sup>34</sup>.

Our patients did not present a significant association between age and reduced salivary flow. Aging is not considered a systemic disease *per se*, although this process may be associated with slight reductions in UWS flow. In addition, it may induce salivary gland hypofunction when associated to systemic diseases and the use of medications<sup>1</sup>. One important point observed was a large number of women in the fifth decade of life. This period corresponds to the menopause process, when important physiological changes are happening in women's life. Some studies relate the complaint of dry mouth with menopause period<sup>35,36</sup>. Menopausal women with oral dryness have low the estrogen level in comparison with women outside this period<sup>37</sup>.

In summary our results suggest an association between hyposalivation and burning mouth, sleep disorders and psychiatric alterations. We did not find a significant association between socio-demographic features and hyposalivation, although we observed a high prevalence of dry mouth complaint in post-menopausal women and those using a diverse group of medicines. In addition, these patients showed improvement in sleep quality probably due to the use of psychotropic medicines. It is important to highlight that these findings were the result of a cross-sectional study, and it is not possible to determine the absolute risk. Therefore, it is important to carry out longitudinal studies in order to establish a relationship of causality.

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