ORAL FLUID MEASUREMENTS IN RELATION TO DIFFERENT CONDITIONS: DENTURE ADHESIVES AND SMOKING

PhD thesis book

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1. INTRODUCTION

Fluids in the oral cavity, especially saliva and gingival crevicular fluid (GCF), play an inevitable role in maintaining general and oral health, and have an emerging diagnostic significance in dentistry. Saliva is a complex biological fluid, secreted by major and minor salivary glands, with special functions including preservation, regulation and maintenance of the oral soft and hard tissues and furthermore, initial digestion in the gastrointestinal tract.

Normal flow rate of unstimulated whole saliva (UWS) is 0.3-0.4 ml/min, while flow rate less than 0.1 ml/min is considered as hyposalivation. Xerostomia refers to the subjective feeling of oral dryness, with various clinical causes and consequences, and can be a symptom of salivary gland hypofunction of diverse origin. It may be linked to other intra- or extraoral sicca symptoms as well. Though, the diagnosis of xerostomia is based on subjective evaluations with validated questionnaires, according to many studies, the decrease of minor salivary gland secretions and reduction in saliva film thickness on oral mucosal surfaces may be associated with this symptom.

Whole saliva is collected mainly by the spitting method, while absorbent filter papers are predominantly used to collect micro-moisture from minor salivary gland secretions. The Periotron method is applied in the clinical research for the measurement of GCF, minor salivary gland secretions and saliva film thickness based on the electric conductance of the absorbed saliva.

Several factors have been proven to influence salivation and the presence of oral dryness symptoms, affecting the integrity of the intraoral environment. Aging, gender, general hydration of the body, body weight, hormonal changes, intake of medicaments, smoking and alcohol consumption, and various chemical agents can be some of these.

Saliva has a critical role in the retention of removable dentures. Patient comfort, retention and stability, and masticatory performance of complete dentures can be improved using denture adhesives (DAs) that act by increasing the viscosity of the saliva. Studies have shown that they have beneficial effects even for denture-wearer patients suffering from xerostomia. Though DAs are in continuous contact with the oral mucosa for hours, less is known about these materials' possible effect on salivation, including minor gland secretions, xerostomia and associated sicca symptoms.

The habit of using of nicotine-containing products, including various types of tobacco derivatives, has devastating general and oral health effects. Smoking, being the most widespread form of combusted tobacco use, affects the integrity of the oral tissues in various ways. It increases the risk for oral cancer, premalignant lesions, periodontal diseases, dental caries and premature tooth loss, and furthermore, causes impaired wound healing, and lower success rate of implant treatments. Long-term tobacco use is also regarded as a risk factor for reduced salivary flow and xerostomia according to the majority of studies.

These oral health effects are not only related to the harmful chemicals released from the tobacco smoke, but are also consequences of structural, morphological and functional changes, decreased receptor sensitivity and micro-vascular alterations in the various tissues attributed to chronic nicotine consumption.

On the other hand, studies investigating the effects of the duration, intensity and type of tobacco use on salivary parameters, especially minor salivary gland secretions, xerostomia and associated sicca symptoms are still scarce and controversial.

2. AIMS

2.1. Investigating the possible effects of denture adhesive use on salivation and the prevalence and severity of xerostomia and associated sicca symptoms

Our objective with our first study was to determine whether a three-week use of a DA affects the incidence of dry mouth, the subjective orofacial and consecutive extraoral sicca symptoms and/or changes in the severity of the pre-existing subjective dryness symptoms in elderly patients wearing maxillary complete dentures. A further aim was to investigate the possible influence of a three-week use of DA on the UWS flow rate and on the flow rate of the palatal (PS) and labial (LS) minor salivary glands.

2.2. Investigating the possible effects of tobacco smoking on salivation and the prevalence of xerostomia and sicca symptoms in a Hungarian population

In our second study, our aims were to assess the prevalence of both subjective and objective dryness symptoms by smoking status in different age groups, to measure whole and minor saliva flow rates, and to evaluate the possible associations between salivary parameters, oral symptoms and the intensity of smoking.

3. METHODS

3.1. Measurement of salivary parameters and assessment of xerostomia and sicca symptoms on maxillary complete denture wearers using denture adhesives

The three-week interventional follow-up study included 28 randomly selected elderly patients (11 male, 17 female) with a mean age of 72 ± 11 years, who had been complete denture wearers for over 5 years without using DAs. All selected patients attended for fabricating new maxillary complete dentures to the Department of Prosthodontics, Faculty of Dentistry, Semmelweis University, Budapest, Hungary. The participants were investigated at the appointment of their clinical sessions of the denture fabrication, right before the therapeutic interventions, in the morning hours between 8 and 11 AM. All patients were provided with a written informed consent prior to the examinations.

After detailed medical and dental history taking, a **questionnaire** with 16 questions (constructed especially for our studies investigating oral dryness and related sicca symptoms) was given to the participants at every session prior to the clinical examinations, in order to determine the subjective presence or absence and severity of their possible orofacial and consecutive extraoral sicca symptoms, including xerostomia. The answers were established with a four-grade (visual analogue) scale of *no symptom (0), mild (1), moderate (2)* and *severe (3)* to assess the severity of the certain symptoms. *(Table 1)*

Table 1. *Questionnaire used to evaluate the presence and intensity of xerostomia and the related subjective orofacial and extraoral sicca symptoms.*

1. Does your <u>mouth</u> often feel dry? I—o—o—I—o—o—I—o—o—I None Mild Moderate Severe	**2. Do you have difficulty with <u>swallowing</u>?** I—o—o—I—o—o—I—o—o—I None Mild Moderate Severe
3. Does your <u>tongue</u> often tingle or have a burning sensation? I—o—o—I—o—o—I—o—o—I None Mild Moderate Severe	**4. Is your <u>speech</u> significantly affected, if you talk for a long period?** I—o—o—I—o—o—I—o—o—I None Mild Moderate Severe
5. Do you have <u>tasting</u> problems? I—o—o—I—o—o—I—o—o—I None Mild Moderate Severe	**6. Do you feel to have not enough <u>saliva</u> in your mouth?** I—o—o—I—o—o—I—o—o—I None Mild Moderate Severe
7. Does your <u>saliva</u> often feel thick? I—o—o—I—o—o—I—o—o—I None Mild Moderate Severe	**8. Do your <u>teeth</u> easily decay?** I—o—o—I—o—o—I—o—o—I None Mild Moderate Severe
9. Does your <u>nose</u> dry out sometimes? I—o—o—I—o—o—I—o—o—I None Mild Moderate Severe	**10. Are your <u>eyes</u> often feel dry?** I—o—o—I—o—o—I—o—o—I None Mild Moderate Severe
11. Do your <u>eyes</u> often itch, burn or tingle or you have the feeling of having something inside? I—o—o—I—o—o—I—o—o—I None Mild Moderate Severe	**12. Are you sensitive to <u>light</u>?** I—o—o—I—o—o—I—o—o—I None Mild Moderate Severe
13. Does your <u>skin</u> often feel dry? I—o—o—I—o—o—I—o—o—I None Mild Moderate Severe	**14. Do you suffer from <u>vaginal</u> dryness?** I—o—o—I—o—o—I—o—o—I None Mild Moderate Severe
15. Does your <u>vagina</u> sometimes itch, burn or suffer from recurrent vaginal fungal infection? I—o—o—I—o—o—I—o—o—I None Mild Moderate Severe	**16. Do you often feel <u>tired</u>?** I—o—o—I—o—o—I—o—o—I None Mild Moderate Severe

UWS was determined using the spitting method, described by Sreebny et al, after filling the questionnaire. Saliva was collected into pre-weighed vessels for 5 minutes, while the patients were seated in an upright position. They were asked not to eat or drink 2 hours prior to their visits, and to avoid swallowing and to make as few movements as possible during the procedure. The vessels were weighed before and after each collection using an electronic scale (Acculab VI-200, Sartorius, Goettingen, Germany). Considering the density of the saliva which is regarded as 1 g/cm3, the values displayed on the scale in grams were expressed in ml and the secretion rate was given in ml/min.

Measurements of the minor salivary gland flow rates were carried out using filter paper discs (Sialopaper™, Oraflow Inc., Amityville, USA) with a standard diameter of

8 mm (area: 0.5 cm²) for 30 seconds on three main sites, according to the distribution of the minor salivary glands in the oral cavity.

In order to measure the PS flow rate, the discs were placed bilaterally on the hard palate and 15 mm medially towards the midline from the site of the maxillary second molars on the edentulous ridge. For measuring the LS flow rate, the discs were positioned on the oral surface of the lower lip in the midline, 3 mm from the outer border of the lower labial mucosa. These measurements took place after gentle drying with a piece of gauze and relative isolation (cotton rolls in the buccal sulcus for preventing parotid flow). After removal from the mouth, the discs were placed between the two electrodes of the Periotron® 8000 (Oraflow Inc. Amityville, USA) device. The exact quantity of the absorbed saliva was recorded based on the electromagnetic properties of the absorbed micro-moisture. The readings displayed on the Periotron were transformed into µl/cm²/min values of minor salivary gland flow rates according to the previous calibration of the device with known quantities of distilled water.

At the initial session, patients were instructed to use the examined **gel-type DA** (Blend-a-Dent Extra Stark Neutral, Procter & Gamble Hungary, Budapest) regularly for the next three weeks. According to the exact manufacturer's instructions, three approximately 2-3 cm long stripes should be placed on the previously cleansed and dried mucosal surface of the maxillary denture, then the denture should be inserted into the mouth and held in position with firm pressure for a few seconds. Patients were required to wait a few minutes before eating or drinking. All patients were informed about the manufacturer's instructions and confirmed the correct use of DA during the whole study. Each patient had three further measurements after the initial appointment, each taking part weekly at the same day and time for the next three weeks. Each of the participants were provided with the following products after the first assessment: Blend-a-Dent Extra Stark Neutral (Procter & Gamble Hungary, Budapest) gel-type DA, Blend-a-Dent 2-Phasen Ultra denture cleansing tablets and Oral-B 3D White toothbrush, for the daily cleaning of the dentures.

Statistical analysis: All data were expressed in the form of means ± the standard deviations. The SPSS 15.0 for Windows software program (SPSS Inc. Chicago, MI,

USA) was used and the following tests were employed in the evaluation of the data: $\chi 2$-test for comparing subjective symptoms; ANOVA, and paired Student's t-tests for evaluating the possible weekly changes of saliva flow rates. Results were considered statistically significant if the P-level was < 0.05.

3.2. Measurement of salivary parameters and assessment of xerostomia and sicca symptoms in Hungarian smokers and non-smokers

We conducted repeated cross-sectional studies in 2003 (n=600) and 2014–2018 (n=301) among randomly selected Hungarian adult patients visiting regional outpatient dental clinics of their residence. **Participants** were inhabitants of the urban and rural areas of different regions in Hungary. Mean age of the aggregated sample (58.3% females) was 46 ± 16 years (range from 18 to 92 years). Data were collected via personal interview and clinical examinations, which took place before the scheduled dental treatments in the morning hours between 8 and 11 AM. All participants provided informed written consent to the study.

All participants have been categorized into 18–29, 30–39, 40–59, and 60+ year-old age groups. The **smoking status of the sample** has been investigated and recorded based on the participants' self-report during the personal interviews. Smokers using tobacco products other than conventional factory-made or roll-your-own cigarettes were excluded from the studies. Current smokers were defined as those who have smoked every day in the past 30 days. Regarding smoking intensity (the number of cigarettes smoked per day – CPD), participants were categorized into moderate or heavy smoker (MHS – smoked ≥11 CPD), light smoker (LIS – smoked 1–10 CPD), and non-smoker (NS) groups, based on the available information about the level of cigarette consumption necessary for nicotine regulation.

The same **questionnaire** with 16 questions investigating sicca symptoms, as described in our first study, has been employed before the clinical examinations. The response options of the four-grade (visual analogue) scale of *no symptom (0), mild (1), moderate (2)* and *severe (3)* were collapsed into dichotomous variable – *yes/no* – for the assessment of sicca symptoms prevalence in relation to smoking status.

After completing the questionnaire, dental clinical examinations were conducted of which the measurement of **UWS** flow rate and **minor salivary gland secretions** (PS, LS flow rates) were included in this study. The detailed methodology of saliva flow rate measurements are described in our first study. For measuring PS flow rate in dentate participants, the filter paper discs were placed individually on both sides of the hard palate, 15 mm palatally towards the midline from the gingival margin of the maxillary first molars.

Statistical analysis: The descriptive characteristics of the sample, subjective sicca symptoms, UWS and minor salivary gland flow rates are presented in percentages, means, and standard deviations (SD). Independent samples t-test, one-way ANOVA, and $\chi 2$ test were used to test associations. All analyses were performed using IBM SPSS version 24.0 software, and significance level was accepted at $p<0.05$.

4. RESULTS

4.1. Investigating the possible effects of denture adhesive use on salivation and the prevalence and severity of xerostomia and associated sicca symptoms

4.1.1. Changes in subjective sicca symptoms

The initial prevalence of *xerostomia* in our sample was 39%. According to the results there was no significant change in the presence or intensity of subjective symptoms including oral dryness, dysphagia, glossopyrosis, dysphonia and dysgeusia. On the other hand, a substantial two-fold increase in the subjective feeling of *saliva thickness* from the initial week to week 1 was recorded. This value increased to a significant 3.3-fold level till the end of week 3 ($p=0.037$ by the $\chi 2$-test).

The number of patients reporting the subjective feeling of "insufficient saliva amount" increased week by week; however, these changes were not statistically significant. Among the extraoral symptoms, an insignificant increase in the complaint of nasal dryness by the end of the third week was detected, while the feeling of fatigue,

xeroderma, photosensitivity, gynaecological and eye dryness symptoms remained unchanged.

4.1.2. Changes in saliva flow rates

The prevalence of *hyposalivation* was 18% at the initial session. According to the measurements, no significant change has been found in *UWS flow rates* during the 3-week period (initial: 0.37 ml/min; week 3: 0.39 ml/min) (p = 0.824). The *LS flow rate* did not decrease significantly (initial: 3.99 µl/cm2/min; week 3: 2.58 µl/cm2/min) (p = 0.145). The *PS flow rate* was recorded 4.21 µl/cm2/min in the initial week, while it continuously decreased to 2.21 µl/cm2/min until week 3, which demonstrates a significant change (p = 0.024). *(Figure 1)*

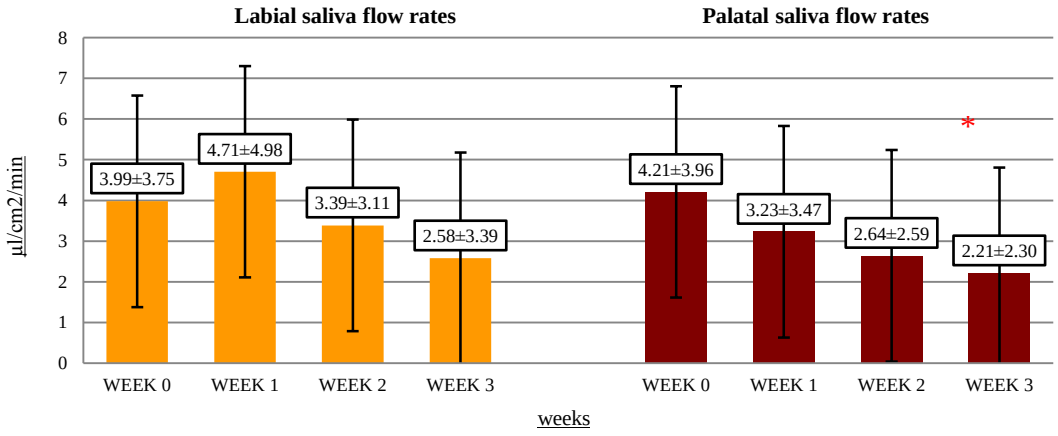

Figure 1. *Change of mean labial and palatal saliva flow rates (µl/ cm2/min) in the complete denture wearer sample (n=28) during the three weeks of denture adhesive use. The continuous decrease of palatal flow rates became significant by the end of week 3. * = p<0.05, according to ANOVA test*

4.2. Investigating the possible effects of tobacco smoking on salivation and the prevalence of xerostomia and sicca symptoms in a Hungarian population

4.2.1. Smoking status of the sample

The overall prevalence of smoking was 35.9% in our sample (43.4% of males and 30.5% of females, p<0.001). 51.3% of female smokers and 60.7% of male smokers belong to the MHS group. The percentage of all smokers, and the ratio of MHS was highest in the 40-59-year-old age group in females (38.0% and 20.9%, respectively),

however, in males, the highest prevalence of smoking was recorded in the 18–29-year-old age group (60.4%), while the highest ratio of MHS in the 30–39-year-old age group (38.3%). *(Figure 2)*

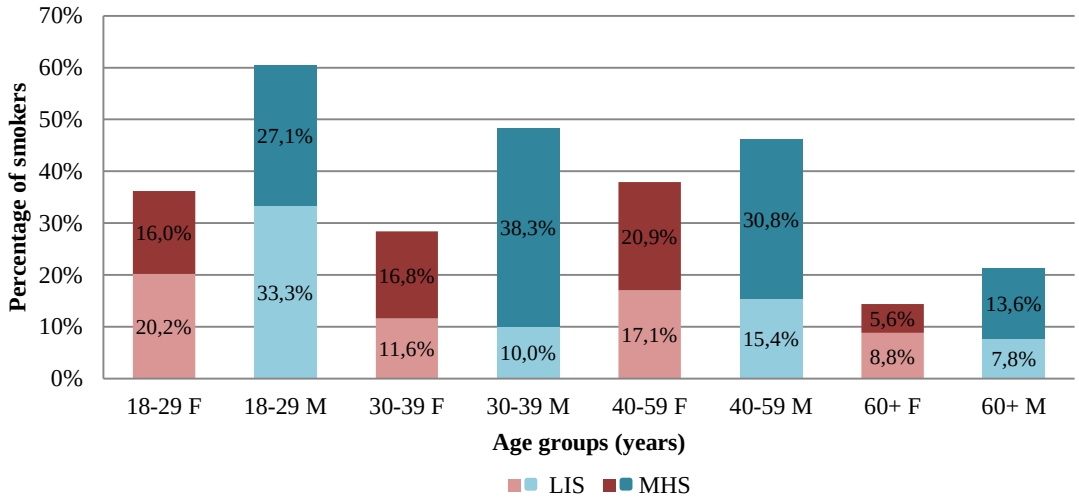

Figure 2. *Prevalence and intensity of smoking by gender and age groups in our sample (n=901). M: male; F: female; LIS: light smoker; MHS: moderate or heavy smoker.*

4.2.2. Subjective sicca symptoms in relation to smoking status

The overall prevalence of dry mouth in our sample was 38%. Among smokers, 35.6% of males and 41.9% of the females reported *xerostomia*, and 7.4% and 9.4% indicated it to be severe, respectively. No significant difference has been observed compared to the results of non-smokers (28.6%, 42.7%, 5.6% and 7.4%, respectively). The prevalence of dry mouth was significantly higher among male smokers in the 30–39-year-old age group (44.8%; p=0.001), and female smokers in the 18–29-year-old age group (52.9%; p=0.013), compared to their non-smoker counterparts (6.7% and 27.1%, respectively). Male smokers in the age of 30-39 also experienced the subjective feeling of *fatigue* significantly more frequently (p=0.001), while 60+ -year-old smokers complained more often about *dysphagia* (p=0.008) than the non-smokers from the same age-groups. Female smokers in the 18–29-year-old group more frequently reported *increased caries activity* compared to non-smokers (p=0.021). Among 60+ -year-old female smokers, the proportion of participants complaining about *dysgeusia* (p=0.040) was significantly higher, however, *xerophtalmia* (p=0.030) and *itching or burning sensation in the eyes* (p=0.032) was significantly lower compared to their non-smoker counterparts. Non-smoker females reported suffering from *vaginal dryness* more frequently than smokers

(p=0.049), regardless of age groups. No differences were observed in the tested groups regarding other subjective sicca symptoms. *(Tables 2 and 3)*

Table 2. *Prevalence of intra- and extraoral sicca symptoms with significant difference between smokers and non-smokers in Hungarian males. Red numbers indicate the significant differences between smokers and non-smokers. S: smokers, NS: non-smokers.*

Subjective symptoms in %	**Age groups (years)**										**p**
	18-29 (n=96)		**30-39 (n=60)**		**40-59 (n=117)**		**60+ (n=103)**		**Total (n=376)**		
	NS (n=38)	**S (n=58)**	**NS (n=31)**	**S (n=29)**	**NS (n=63)**	**S (n=54)**	**NS (n=81)**	**S (n=22)**	**NS (n=213)**	**S (n=163)**	
Xerostomia	28.2	29.3	**6.7**	**44.8**	22.2	31.5	42.0	50.0	28.6	35.6	0.001
Dysphagia	12.8	10.3	10.0	13.8	11.1	18.5	**12.4**	**36.4**	11.7	17.2	0.008
Fatigue	59.0	69.0	**26.7**	**72.4**	50.8	53.7	60.5	50.0	52.6	62.0	0.001

Table 3. *Prevalence of intra- and extraoral sicca symptoms with significant difference between smokers and non-smokers in Hungarian females. Red numbers indicate the significant differences between smokers and non-smokers. S: smokers, NS: non-smokers.*

Subjective symptoms in %	**Age groups (years)**										**p**
	18-29 (n=94)		**30-39 (n=95)**		**40-59 (n=211)**		**60+ (n=125)**		**Total (n=525)**		
	NS (n=59)	**S (n=35)**	**NS (n=68)**	**S (n=27)**	**NS (n=131)**	**S (n=80)**	**NS (n=107)**	**S (n=18)**	**NS (n=365)**	**S (n=160)**	
Xerostomia	**27.1**	**52.9**	39.7	25.9	43.5	43.8	52.3	38.9	42.7	41.9	0.013
Dysgeusia	6.8	5.9	7.4	7.4	14.5	13.8	**10.3**	**27.8**	10.7	12.5	0.040
Increased caries activity	**62.7**	**85.3**	82.4	77.8	74.8	75.0	64.5	77.8	71.2	78.1	0.021
Xerophtalmia	25.4	23.5	29.4	22.2	36.6	33.8	**43.9**	**16.7**	35.6	27.5	0.030
Itching, burning of the eyes	49.2	47.1	36.8	37.0	49.6	41.3	**55.1**	**27.8**	48.8	40.0	0.032
Vaginal dryness	6.8	8.8	11.8	3.7	22.9	15.0	22.4	11.1	**18.1**	**11.3**	0.049

4.2.3. Salivary parameters in relation to smoking status

UWS flow rates of males did not show any difference in relation to smoking intensity: neither in the overall male sample, nor in the view of the age groups. The same was observed in the overall sample of females, however, lower flow rates were measured among MHS females compared to NS and LIS females in the 18–29-year-old group (p=0.019; p=0.015, respectively).

Regarding *minor salivary gland flow rates*, 30–39-year-old MHS males had significantly higher PS flow rates compared to non-smokers (p=0.046) *(Figure 3)*. Among females, the overall MHS sample presented significantly lower LS flow rates than non-smokers (p=0.046), whereas lower PS flow rates were measured among LIS females in the age group of 60+ compared to their NS counterparts (p=0.004) *(Figure 4)*.

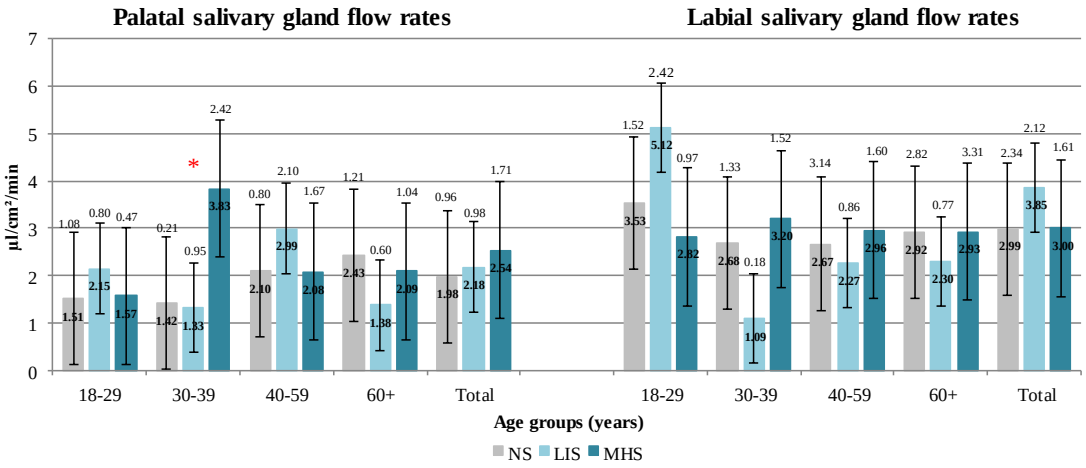

Figure 3. *Minor salivary gland flow rates in males in different age groups according to smoking status. Means and standard deviations are presented. NS: Non-smoker; LIS: Light smoker; MHS: Moderate or heavy smoker. *= p <0.05 according to independent samples t-test*

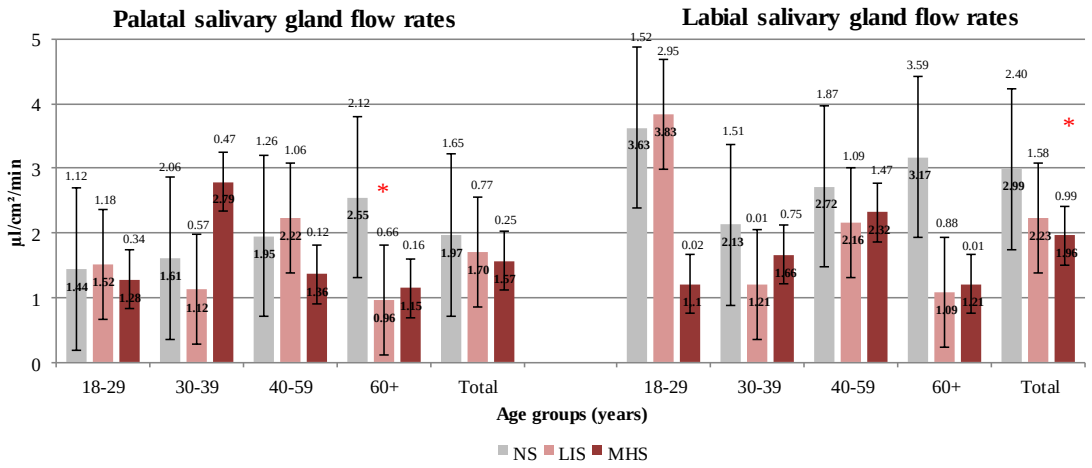

Figure 4. *Minor salivary gland flow rates in females in different age groups according to smoking status. Means and standard deviations are presented. NS: Non-smoker; LIS: Light smoker; MHS: Moderate or heavy smoker. *= p <0.05 according to independent samples t-test*

Hyposalivation was detected in sixty-two out of all 901 participants (6.9%), the majority (82.3%) of them were women, and almost half of them (48.4%) were in the 40-59 year-old group. 9.0% of non-smoker and 11.3% of smoker females, and 4.2% of non-smoker and 1.2% of smoker males had UWS flow rate ≤ 0.1ml/min.

Among NS females, a significant correlation has been shown between the subjectively reported intensity of xerostomia and reduced levels of UWS flow rates (p=0.0005), however, this was neither the case among NS males, nor among other smoker groups.

5. CONCLUSIONS

New statements provided by these studies

1. Neither the previously present dry mouth, nor the most of the sicca symptoms were influenced by the use of DAs, in terms of their frequency and severity, among the examined complete denture wearer elderly patients.
2. Regular adhesive use resulted in the decrease of the PS flow rate, because the gel-type adhesive might cause obstructions in the orifices of the palatal minor salivary glands.
3. The use of adhesive had no effect on the UWS flow rate. The washing-clearing effect of the major salivary glands' flow rates keeps their orifices always free, which, in turn is less effective in the case of the palatal minor glands. The DAs may expressively influence the secretion of the palatal minor salivary glands.
4. Patients reported the feeling of increased saliva thickness, which can be attributed to the change in the viscosity and consistency of saliva caused by the use of DA.
5. The overrepresentation of smokers in our sample might be explained by the generally poorer oral hygiene and increased risks for dental and periodontal diseases among smokers, resulting in their higher attendance to dental outpatient departments.
6. Higher intensity of smoking in young females may significantly affect their salivary output by decreasing UWS flow rates, and also increase their subjective feeling of dry mouth.
7. Significantly lower LS flow rates measured among the overall sample of MHS females could be a trigger for the feeling of xerostomia in younger female heavy smokers.
8. The ratio and the intensity of xerostomia and fatigue in male smokers in the 30-39 age group was higher than in non-smokers, which can be explained by the higher number of heavy smokers, and increased stress levels in this male age group.
9. PS flow rates were increased among 30-39 year-old MHS males compared to non-smokers. High level of tobacco smoke in the oral cavity of heavy smokers

may cause direct stimulation or exert local irritative effects on the palatal minor salivary glands, increasing their output.

10. It is suspected that a threshold exists in the intensity of smoking, where components of tobacco smoke reach a certain blood level, reducing the function of salivary glands either at the level of the organs, or at systemic level, affecting their blood supply.
11. The higher prevalence of dysphagia in the 60+ age group of male smokers can be explained by inflammation of the oropharyngeal mucosa induced by tobacco smoke, or by the higher ratio of edentulousness at this age.
12. Increased frequency of taste disturbances were registered in 60+ female smokers, which could be derived to the changes in form, quantity and vascularization of the taste buds, caused by the long-term tobacco smoke exposure.
13. Intraoral symptoms like dysphagia and dysgeusia might be increased in the 60+ geriatric age groups by cigarette smoking via other ways than provoking oral dryness. These symptoms can be associated with inflammatory or provocative effects of tobacco smoke.

6. BIBLIOGRAPHY OF THE CANDIDATE'S PUBLICATIONS

6.1. Related publications

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   IF: 0.564

2. **Demeter T**, Pénzes M, Kovács A, Károlyházy K, Nimigean VR, Nimigean V, Dézsi A, Székely M, Márton K. Smoking Related Major- and Minor Salivary Gland Flow Rates, Xerostomia and Other Sicca Symptoms in Hungary. Revista de Chimie 2020;71(4):373-83.

   IF: 1.755

6.2. Not related publications

1. Dézsi A, Erdei C, **Demeter T**, Kovács A, Márton K. Histopathological Sample Preparation with Unique Biopsy Forceps in The Diagnosis of Sjögren's Syndrome. J Dent Oral Health 8: 1-5. (2021)

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