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

PhD thesis

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1. LIST OF ABBREVIATIONS

BMI	Body Mass Index
BOP	Bleeding on Probing
CMC	carboxyl-methyl-cellulose
CODS	Clinical Oral Dryness Score
COPD	Chronic Obstructive Pulmonary Disease
CPD	cigarettes per day
DA	Denture Adhesive
ENDS	Electronic Nicotine Delivery Systems
FTND	Fagerström Test for Nicotine Dependence
GCF	Gingival Crevicular Fluid
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HSI	Heaviness of Smoking Index
HTP	Heated Tobacco Products
IgA	Immunoglobulin A
LIS	light smoker
LS	Labial saliva
MHS	moderate or heavy smoker
NCC	number of cigarettes consumed per day
NS	non-smoker
PVM-MA	poly-vinyl-methyl-ether maleic anhydride
PS	Palatal saliva
pSS	primary Sjögren's Syndrome
ST	Smokeless Tobacco
SWS	Stimulated Whole Saliva
TTFC	time to the first cigarette upon waking
UWS	Unstimulated Whole Saliva
WHO	World Health Organization
XI	Xerostomia Inventory

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2. INTRODUCTION – LITERATURE REVIEW

2.1. Oral fluids

The fluids in the oral cavity play important role in maintaining general and oral health, and are gaining increasing diagnostic importance as a source of biochemical data used for detecting and monitoring of oral and systemic diseases and/or conditions, being a rapid and non-invasive alternative to serum testing (1). Oral fluids consist primarily of a mixture of saliva, which is the product of the various salivary glands, and gingival crevicular fluid (GCF), which is an oral mucosal transudate of the periodontal tissues. Besides, in a smaller amount, several other constituents like expectorated nasal and bronchial secretions, serum and blood derivatives and cells, desquamated epithelial cells, bacteria, viruses, fungi and extrinsic substances also contribute to the composition of the oral fluids (2).

2.2. Saliva - salivary glands and flow rates

Saliva is a complex biological fluid, with specially dedicated functions in the oral cavity. It contributes to the preservation, regulation and maintenance of the integrity of oral soft and hard tissues and has several functions including speaking, taste perception and initial digestive tasks involving the oral processing, bolus formation and swallowing of the food (3, 4). The role of a healthy flow rate of saliva in general oral health and well-being is inevitable. However, in almost all areas of clinical dentistry, the presence of saliva around the dental hard and soft tissues can interfere with the majority of operative dental procedures, e.g. adhesive techniques, impression taking, cementation of restorations, endodontic interventions and oral surgery procedures (5, 6). Therefore, the importance of saliva is often neglected among practitioners and patients; nevertheless, its absence is obvious and results in prominent symptoms. This controversy is well illustrated with an ancient axiom, which says, "*you never miss the water till the well runs dry*". (7) Dental schools should pay more attention to the education of the routine procedures of collecting unstimulated whole saliva (UWS) from the patients, to evaluate salivary gland function.

The diagnostic significance of saliva nowadays as an economically and non-invasively collectable body fluid, is also supported by recently developed, advanced molecular analytic methods and techniques. As a result, a new field of research, salivaomics has been evolved in the last 10-20 years, allowing the qualitative and quantitative characterisation of salivary components, including DNA, messenger RNA and micro-RNA (transcriptome), proteins (proteome), metabolites (metabolome) and microorganisms (microbiome). These molecules can be used as disease-specific biomarkers for the early salivary diagnosis of several diseases, for instance, oral cancers, Sjögren's syndrome, or even infections and systemic cancers or genetic, autoimmune, cardiovascular, metabolic and some psychiatric diseases. Besides, collection and analysis of saliva provides the possibility of non-invasive monitoring the serum levels of various medications and drugs. (5, 8, 9)

2.2.1. Composition and secretion of saliva

Saliva consists of mainly water (99.5%), inorganic molecules and electrolytes (0.2%), for instance sodium, potassium, bicarbonate, thiocyanate, calcium, chloride, phosphate ions; and organic molecules, e.g. proteins, glycoproteins, lipids and glucose (0.3%) (3, 4). The normal pH range for whole saliva is 5.5 – 7.9, maintained and influenced by its buffering systems based on the bicarbonate, phosphate and protein constituents (1).

Saliva is secreted by three pairs of major (parotid, submandibular, sublingual), and several (600-1000) minor salivary glands in different locations in the oral cavity (labial, buccal, lingual and palatal) (4) *(Figure 1).*

The composition of whole saliva is influenced by the flow rate and composition of each glandular-derived saliva secreted by the different types of salivary glands. Parotid saliva, as the main contributor to the stimulated secretion, has mainly serous properties and watery consistence. Minor salivary glands, on the other hand, secrete mainly mucous, highly viscous saliva, which provides lubrication and mechanical protection for the oral mucosal surfaces. (10, 11)

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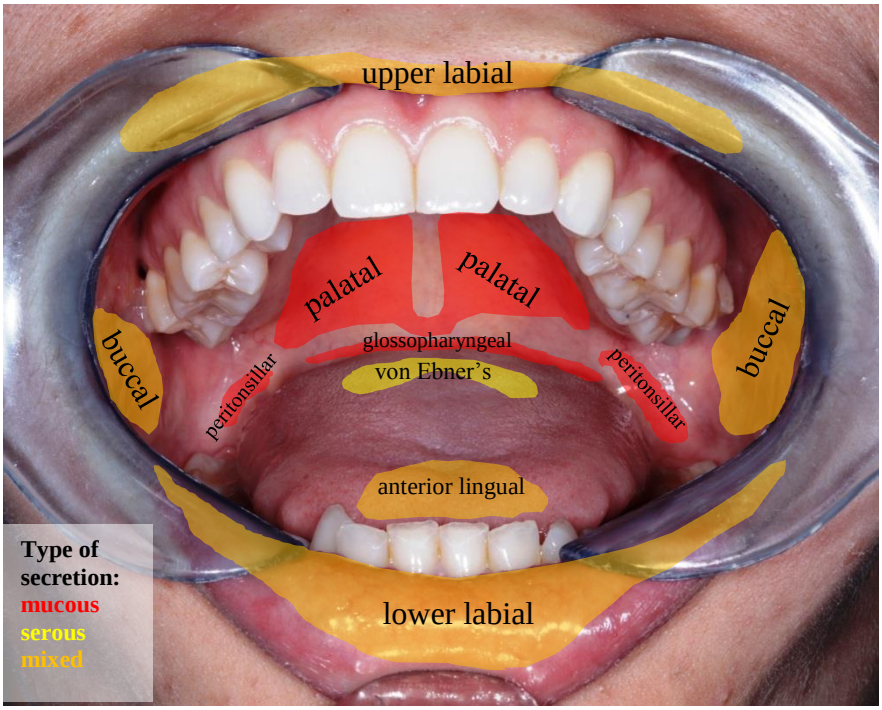

Figure 1. *Location and secretion type of minor salivary glands in the oral cavity, based on the figure of Kessler et al. (12)*

Secretion of saliva has a two-step mechanism: the acinar cells produce isotonic primary saliva, while during its flow through the ductal system, an active reabsorption of sodium and chloride salts takes place and contributes to a hypotonic final saliva. This procedure is regulated by the autonomic nervous system via salivary reflex pathways, activated by gustatory (taste) and/or mechanical (masticatory) stimuli, while olfactory, nociceptive, psychic and thermoreceptive impulses also affect salivary output. The volume and composition depends on the type of stimulation (6, 13). Parasympathetic activity, binding acetylcholine on M3 and M1 muscarinic receptors of the acini, leads to a watery saliva with higher flow rate and a decrease in the viscosity and the organic and inorganic components of the whole saliva. On the other hand, sympathetic stimuli acting on α1-adrenergic receptors result in a decreased flow rate and viscosity together with an increase in the secretion of salivary proteins, with some exceptions like secretory IgA. ß-arenergic stimulation, however, leads to higher protein and mucin content and increased viscosity of the saliva (2, 13).

2.2.2. Saliva flow rates

Generally, major salivary glands produce about 90% (parotid: 25%, submandibular glands: 65%, sublingual glands: 7-8%), while minor glands secrete less than 10% of the whole saliva at rest (4).

UWS is a mixture of secreted saliva from several salivary glands under resting conditions. Additionally, it contains small amounts of GCF, cellular elements like leukocytes, epithelial cells, bacteria, viruses, blood, and food remnants (14). Glandular-derived saliva is mainly collected individually to investigate the metabolic status of the corresponding salivary gland, while whole saliva represents the general status of oral wetness, and is therefore an indicative measure of general oral health (7). The normal range of UWS flow rate is 0.3-0.4 ml/min (10). There is hardly any association between the flow rates of UWS and that of the minor salivary glands (15). Studies show that the flow rate of the buccal minor salivary glands is the highest, followed by the labial (LS) and finally the palatal (PS) saliva flow rate. There are strong inter- and intra-individual variations regarding the whole and minor salivary gland flow rates, which is in a correlation with the variability of the density and number of minor salivary glands in a specific mucosal area (16).

Continuous, unstimulated production and flow of saliva and the normal swallowing mechanism results in a dynamically changing residual saliva in the mouth, which forms a mobile fluid film on the oral mucosal surfaces. The saliva film is in strong correlation with mucosal wetness, and has various thicknesses on different intraoral surfaces. According to the measurements of Collins and Dawes, this thickness varies between 10 and 70 μm, with the thinnest areas to be found on the hard palate and the inner part of the lips. Any alteration of whole saliva flow rate will therefore have an effect on the thickness and quality of the residual saliva film, especially on these sites, which may influence the subjective feeling of mucosal wetness, contributing to the perception of dry mouth. (7, 10, 17-21)

2.2.2.1. Factors influencing salivary flow

Taste or mechanical *stimulus*, e.g. chewing, releases a parotid secretion that contributes to 60% of the whole saliva flow rate. The secretion rates of the submandibular, sublingual glands are less responsive to stimuli, while that of the minor salivary glands

remains relatively unchanged in stimulated conditions. (11) The normal flow rate of stimulated whole saliva is between 1.6-2 ml/min, and is measured by applying mechanical (chewing of paraffin wax) or gustatory (citric acid) stimuli prior to saliva collection (21).

There is a measurable *gender*-difference in the flow rates of whole saliva. According to the results of a population-based study in Hungary by Márton et al, the flow rate of males are higher than that of females in the same age groups (21). This is in accordance with most of the studies (7).

In relation to *ageing*, salivary glands are affected by degenerative changes including alterations in the glandular stroma and acinar cell degeneration by up to 30% (22), however, studies investigating the secretion rates have conflicting results in the literature. Flow rates of UWS showed negative correlation with age in both genders in the Hungarian population examined by Márton et al (21). According to a recent meta-analysis, aging is associated with a gland-specific decrease in the saliva flow rate, where sublingual and submandibular gland secretions are the mostly affected (23). Some studies report a decrease in minor salivary gland flow rates with increasing age, however, most papers agree that minor gland functions remain unchanged (16).

Other factors like body weight (BMI score), periodontal status, oral hygiene awareness, general hydration of the body, nutritional and emotional state, body position, the intake of drugs, and the nature and properties of the stimuli also influence saliva flow rate in various ways (10, 16, 24). Based on the investigations, and taking a normal lifestyle and stimulating circumstances into account, the total daily saliva secretion varies between 560 and 670 ml (22).

2.2.3. Salivary dysfunctions

Salivary dysfunctions can be present in three, solitary or combined forms: xerostomia, hyposalivation, and alterations in the composition of saliva (25). UWS flow rate equal or less than 0.1 ml/min is considered as hyposalivation. Under stimulated conditions, this cut-off point is 0.5-0.7 ml/min (22, 26).

2.2.3.1. Relationship between xerostomia, hyposalivation, minor salivary gland flow rates and salivary film thickness

While the term “hyposalivation” refers to an objective, measureable decrease in the saliva production caused by salivary gland hypofunction, xerostomia stands for the subjective feeling of dry mouth, and it is regarded as a frequent symptom of salivary gland hypofunction. Márton et al revealed a strong correlation between lower levels of UWS and the grade of xerostomia in the Hungarian population (21). Moreover, Dawes found that healthy patients report dry mouth when their resting salivary flow is reduced by 50% (27). In a study investigating healthy adolescents and young adults, the dryness of the lips, as a common sign of oral dryness, was correlated to decreased salivary flow rates (28). However, patients experiencing xerostomia may have normal salivary flow rate, and hyposalivation may also occur without any signs or symptoms of xerostomia (3, 10). Therefore, the feeling of dry mouth is not necessarily connected to salivary gland hypofunction (7, 26).

According to the experiments of several authors, xerostomia is associated with a decrease in the thickness of the residual saliva film, and a reduction in the mucosal wetting on the oral surfaces, even in patients with normal whole saliva flow rate (10, 18, 26). It is especially true on the hard palate, which is the area covered by the thinnest saliva film in the oral cavity. Wolff and Kleinberg measured, that the thickness of palatal saliva film is less than 4-5 μm for patients with hyposalivation, while that is between 14 and 18 μm for subjects with normal unstimulated flow rate. It is suggested that film thickness less than 10 μm on the hard palate is associated with the feeling of oral dryness (20, 26). Niedermeier et al. investigated minor salivary gland secretions in patients with dry mouth and suggested a cut-off value of PS flow rate below 3 μl/cm2/min for the symptoms of xerostomia (29). On the other hand, Márton et al did not find significant difference between the palatal secretions of xerostomic patients suffering from Sjögren’s syndrome compared to healthy controls, therefore the function of the palatal glands may be preserved in patients with dry mouth (30). This is in accordance with the findings of Lee et al (31). Eliasson et al found that reduced LS flow rates are also correlated with the symptoms of xerostomia, regardless of the whole saliva secretion rates (16, 32). Moreover, LS flow rates present a stronger correlation with the changes in the flow rate of UWS, therefore LS secretion rate seems to be a

more reliable predictor of hyposalivation than whole saliva flow rate (33). Consequently, minor salivary gland secretions appear to play an important role in the subjective perception of dry mouth. Measuring saliva film thickness and minor salivary gland secretions especially on these aforementioned sites may be a valuable indicator of dry mouth symptoms.

2.2.3.2. Prevalence of xerostomia

There is a wide variability regarding the frequency of xerostomia in the literature. Márton et al reported a xerostomia prevalence of 34% in their population-based study in Hungary, which is in correspondence with the results of similar studies in other countries (21). According to a recent meta-analysis, which summarized the outcomes of representative epidemiological studies, the overall general prevalence of dry mouth is 22%, however, estimates range from 1% to 62% in the studies, with increasing prevalence among females and in older age groups. It is due to the fact that dry mouth is a subjective symptom, and the methodology used to investigate the presence or absence of this phenomenon is still not uniform in the scientific literature (34). Moreover, in most of the case, the feeling of oral dryness is not an isolated symptom. It may be associated with several xerostomia-related complaints in the oral cavity, including a decrease in the salivary clearance, sticky saliva, mucosal inflammations and ulcerations, burning mouth sensation, increased caries activity, halitosis, dysphagia, dysgeusia, difficulties during speaking and eating, etc. (7, 35). Some of these symptoms are referred to as sicca symptoms, which is most frequently related to autoimmune diseases associated with xerostomia and/or hyposalivation *(Table 1)*.

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Table 1. *Causes of xerostomia and its associated intra- and extraoral sicca symptoms. (22, 36, 37)*

X E R O S T O M I A	
CAUSES	
Temporary	**Permanent**
▪ **Acute salivary gland infections** ▪ **Mouth breathing** ▪ **Psychogenic causes (emotional stress, anxiety)** ▪ **Depression** ▪ **Dehydration** ▪ **Hormonal changes (pregnancy, menopausa)**	▪ **Systemic diseases** • Autoimmune or inflammatory diseases o Sjögren's syndrome o Rheumatoid arthritis o Systemic lupus erythematosus o Primer biliary cyrrhosis • Viral infections (HIV, HCV) • Neurological diseases (Parkinson's disease; chronic depression) • Endocrine diseases – diabetes type I and II • Graft versus Host disease • Lymphoma ▪ **Radiotherapy of the head and neck region** ▪ **Lifestyle factors** (alcohol, tobacco, eating spicy foods) ▪ **Medications**
ASSOCIATED SYMPTOMS	
Intraoral	**Extraoral**
▪ **Increased caries activity** ▪ **Oral candidiasis** ▪ **Burning mouth, glossodynia** ▪ **Mucosal inflammations** ▪ **Dryness of the lips** ▪ **Dryness & soreness of the mucosa** ▪ **Dryness & soreness of the throat** ▪ **Dysgeusia, dysphagia, impaired chewing** ▪ **Impaired speaking; dysphonia** ▪ **Thick & sticky saliva** ▪ **Halitosis**	▪ **Nasal dryness; dysosmia** ▪ **Xerophtalmia; burning eyes; foreign body sensation; photosensibility** ▪ **Vaginal dryness, recurrent gynecological infections, dyspareunia** ▪ **Xeroderma** ▪ **Fatigue** ▪ **Weakness**

2.2.3.3. Evaluation of xerostomia

Numerous self-report-based appliances are described in the literature to investigate the status of oral dryness, and to examine its correlation to objective measures. These include questionnaires, scales and semi-quantitative investigations for the assessment of severity and frequency of dry mouth. Xerostomia Inventory (XI), a summated rating scale of 11 items designed and employed by Thomson et al., has been validated to many languages. Recently, Osailan et al designed the Clinical Oral Dryness Score (CODS), which is a semi-quantitative assessment tool for the evaluation of the clinical signs of

dry mouth, while Sreebny and Valdini used the question “does your mouth usually feel dry” to assess the presence or absence of xerostomia (26, 34, 38, 39).

The objective evaluation of xerostomia could be enhanced with the aid of a recently introduced oral moisture-checking device, which assesses water content of the oral mucosal epithelium, by measuring electrostatic capacity in 2 seconds on the basis of impedance. Pilot studies revealed, that the lingual mucosa is the most appropriate location for these measurements. According to Fukushima et al, reduced lingual moisture levels are in strong inverse correlation with the intensity of oral dryness. (40). Despite several attempts and approaches, the evaluation and grading of xerostomia is still not standardized in the scientific literature (39).

2.2.3.4. Conditions associated with salivary dysfunctions

There are a number of reasons for having insufficient amount of saliva in the mouth. A variety of diseases or conditions may be associated with xerostomia, which can present in a *temporary* (reversible) form. This is most frequently caused by acute infections of the salivary glands, mouth breathing, emotional stress, depression, anxiety, or dehydration (4, 10). On the other hand, *permanent* oral dryness and associated symptoms may present as oral manifestations of generalized exocrinopathy or systemic diseases, like diabetes, autoimmune diseases (e.g. Sjögren’s syndrome), neurological disorders (Parkinson’s disease), graft versus host disease, radiotherapy of the head and neck region, and the intake of drugs with xerogenic side effects (34) *(Table 1).* Medications might cause salivary dysfunctions through their anticholinergic, sympathomimetic, or cytotoxic pathways, affecting the physiological function of the salivary glands via direct or indirect way (25). According to a recent study, xerostomia with different causes may present in a regional pattern: medication-induced dry mouth is mostly perceived in the anterior tongue, while patients with Sjögren’s syndrome more frequently report dryness of the posterior palate (41). Summarizing the distinct results of investigations in the scientific literature, the prevalence of intraoral sicca symptoms are associated most often with increasing age and drug-use, and positively correlates with the number of drugs taken (22). It is a significant oral health concern especially for the continuously growing elderly population and for patients with polypharmacy.

2.3. Saliva measurement methods

Sialometry is one of the most important clinical diagnostic procedures in the assessment of salivary gland hypofunction and/or xerostomia (25). The measurement must be performed under standardised conditions. Saliva should be collected uniformly in the morning hours, e.g. between 8 and 10 AM to minimize the bias due to the circadian rhythm of salivation (42). Patients should refrain from smoking, eating or drinking (except water), performing any oral hygiene procedures (e.g. teeth brushing) for at least two hours, and avoid the intake of drugs at least eight hours before saliva collection. During the procedures, the patient should sit relaxed in an upright position with the head bent slightly down; avoid swallowing, speaking and doing any head or body movements. According to the most recent literature recommendations, the time required for the collection of whole saliva is 5 minutes. (9, 22, 24, 43)

The majority of the contemporary salivary research, the routinely used saliva collection procedures involves the measurement of unstimulated (UWS) or stimulated whole saliva (SWS), to acquire objective saliva secretion values, and the measurement of minor salivary gland flow rates, as a main determinant of general mucosal wetness and oral fluid film thickness.

2.3.1. Measurement of whole saliva flow rate

Many techniques are described and used for whole saliva collection, including draining, aspiration, or absorption methods, and the modified Schirmer's test. The most widespread method is the expectoration or spitting method, where saliva is collected into pre-weighed collecting vessels or calibrated containers. The patient lets the saliva accumulate in the mouth, then expectorates actively 1-2 times per minute into the container. The volume of the collected saliva is read and evaluated after the collection time elapsed. As an alternative, the saliva collected can also be weighed using a precision scale. As the density of whole saliva is very close to the density of water (1 g/cm^3), the calculations are simplified (9, 22, 44). Spitting and draining methods are the most reliable and reproducible ways of collecting saliva (24). *(Figure 2)*

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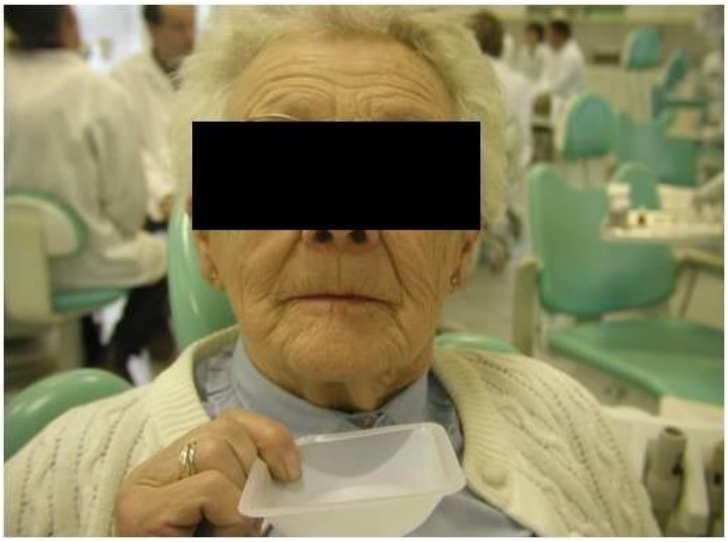

Figure 2. *Spitting method. Collecting sailva into pre-weighed vessels for 5 minutes*

2.3.2. Measurement of minor salivary gland flow rates

Unlike the whole saliva, the collection of minor gland saliva is more complicated and deserves special equipment and/or techniques, due to the small volumes and high viscosity of the secreted fluid, and because of the widespread location of minor gland orifices in the oral mucosal sites. Hamada described the distribution of the palatal minor salivary glands by observing voids in upper jaw impressions caused by palatal saliva droplets (45). Based on these findings and the method described by Márton et al, the collection of PS is carried out on the hard palate, in the region of the upper first molars, 15 mm palatally from the gingival margin (46) *(Figure 3a)*. According to the investigations of Gaubenshtok et al, the number and density of labial minor glands and their secretory activity is higher on the lower labial mucosa near the midline, therefore it is the preferred site for LS collection (47) *(Figure 3b).*

Various qualitative techniques, including photographic analysis of saliva droplets, blotting methods and the use of chromatography papers on the mucosa have been described and used (48). To estimate the saliva volumes, semi-quantitative absorption methods using capillary tubes, sponges, synthetic discs, and filter paper strips and discs are also employed (16).

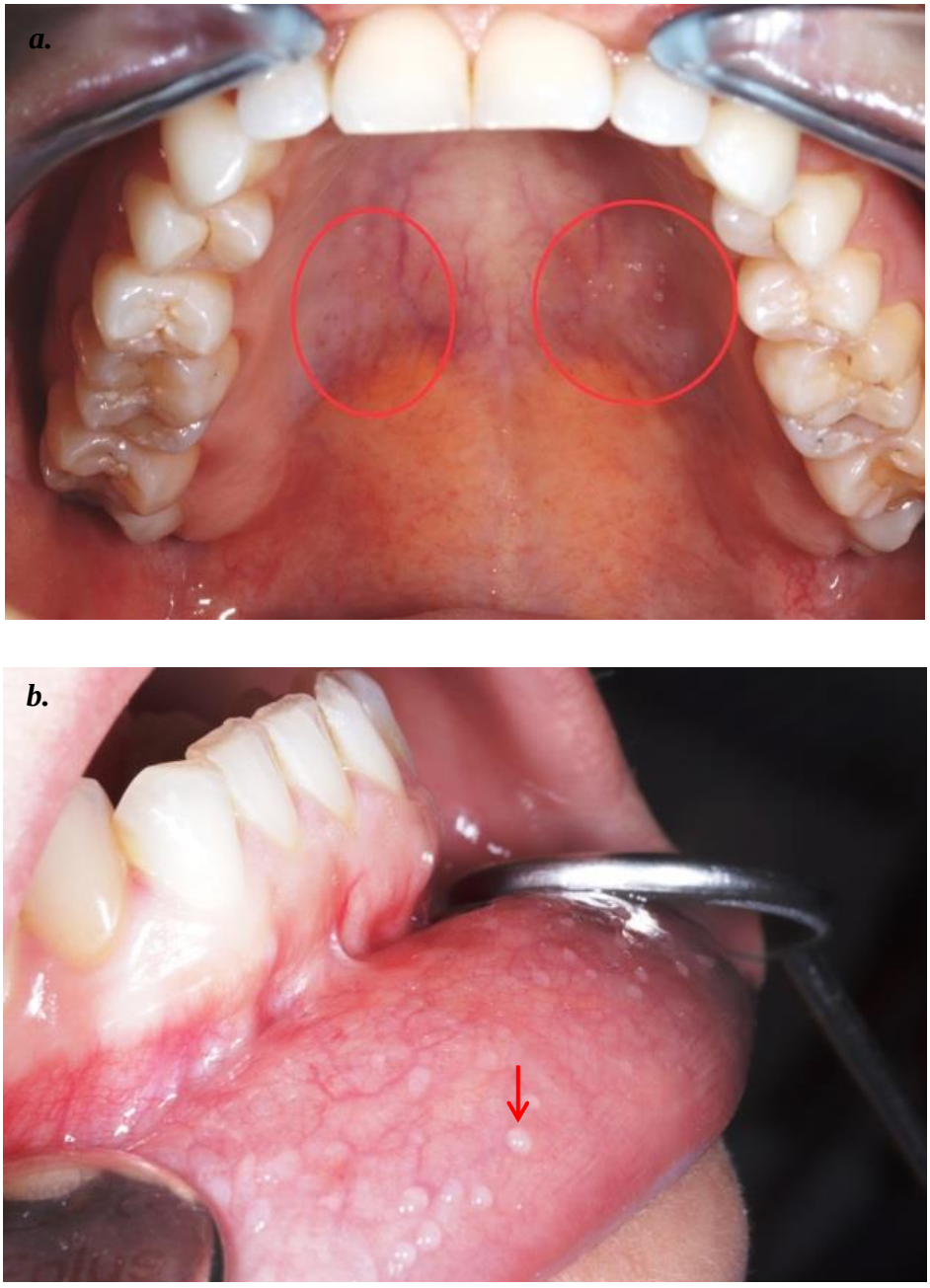

Figure 3. *Beads of saliva marking the orifices of minor salivary glands on the hard palate* ***(a)*** *and on the inner surface of the lower lip* ***(b)***.

Hamada et al used filter papers for the first time to measure minor salivary gland flow rates (45). In the contemporary research, circular (disc) shaped filter papers or strips are the most frequently used absorbent mediums for these assessments on specific mucosal sites. The measurements are carried out during a relative short period of time (mainly 30 seconds), in order to neutralize the effect of evaporation, which is not negligible when collecting low volumes of fluid for longer durations (49, 50). *(Figure 4)* However, the unique method of Boros et al., where the filter paper discs (Rundfilter™, Macherey-

Nagel Co., Germany) were attached to the labial mucosa using pairs of elastic rings prepared from latex foam padding, aimed to overcome this problem (51). Satoh-Kuriwada et al. employed the iodine-starch filter paper method with real-time digital processing for the assessment of LS flow rates on larger areas, while Falcao et al. used the modified Schirmer's test filter paper strips to record PS and LS secretions (33, 48).

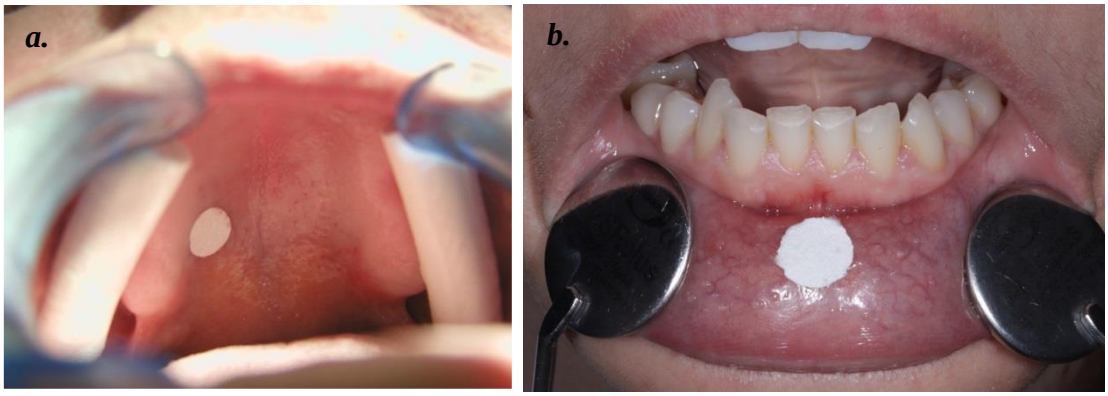

Figure 4. *Measuring minor salivary gland flow rates using filter paper discs (Sialopaper™, Oraflow Inc, Amityville, USA) on the palate* ***(a)*** *and on the inner surface of the lower lip* ***(b)***

For the evaluation of the volume of the absorbed saliva, weighing (gravimetrical) method is one of the possibilities, where analytical precision balances are employed to measure the weight of the absorbent papers before and after collection (49). The other, well-documented method to assess the collected oral micro-moisture, including minor salivary gland secretion volumes and saliva film thickness, is the use of the Periotron® (Pro-Flow™, Inc., Amityville, NY, USA). *(Figure 5a.)* The device is designed to record the electrical impedance of oral fluids absorbed into filter paper strips or discs placed between the two electrodes. Periotron is capable to measure 0-3 µl of absorbed moisture (7, 16, 22). Many researchers evaluated minor salivary gland secretions and furthermore, saliva film thickness on the oral mucosa using the Periotron method, including Shern et al (52), Sivarajasingam and Drummond (53), Niedermeier et al (29), Wolff and Kleinberg (54), Won et al (55), Lee et al (31), Schmideg et al (56), Eliasson et al (32, 57), Smidt et al (58), and Sonesson et al (59) *(Table 2).*

Schmideg et al compared the results of the gravimetric and electromagnetic (Periotron) method applied in the assessment of the minor salivary gland flow rates, and could not report any significant difference (56). Moreover, Gotoh et al. developed a low-cost electronic sialometry device, alternative to Periotron, which is based on the electric

resistance of the absorbed saliva using direct circuit, and registered comparable results to Periotron studies regarding labial secretions (50).

A possible drawback of the contemporarily used filter paper-based methods is the probability of stimulation to the minor salivary glands, caused by the contact of the absorbent paper to mucosal surfaces (50). Moreover, the risk of contamination of the collected minor gland saliva from the saliva from the major glands cannot be neglected, especially at the buccal glands (16). However, this latter problem may be reduced with the use of appropriate isolation. Refinements of the optimal measurement techniques and time may therefore require additional research.

2.4. Employment of Periotron in the measurement of oral micro-moisture

To overcome the methodological difficulties posed by the collection and measurement of very low volumes of oral fluids, an electromagnetic device, the Periotron was developed. After modifications, Periotron gained widespread acceptance in the field of contemporary salivary research for the assessment of saliva film thickness and minor salivary gland secretions. The use of the device was also advocated for general practitioners to evaluate the oral wetness status of the patients, especially for those complaining of dry mouth symptoms (7).

The mechanism of the machine is based on the measurement of the change in the electric capacitance level of the filter papers soaked with small volumes of oral fluids, placed between the two anodized flat electrodes, then loaded with high frequency alternating circuit (50). The numeric values displayed on the device are proportional to the dielectric conductivity of the absorbed fluid. The fluid volumes are calculated using a standard calibration curve *(Figure 5c)*, obtained with different known micro-quantities of clear saliva, saline, distilled water or serum, dropped on the filter paper strip or disc using a 10-µl Hamilton syringe (58). Significant differences were experienced between calibrations performed on different machines, therefore individual instrument calibration is necessary (60). Circular shaped discs (Sialopaper™) with a diameter of 0.8 cm were advocated for salivary research *(Figure 5b).*

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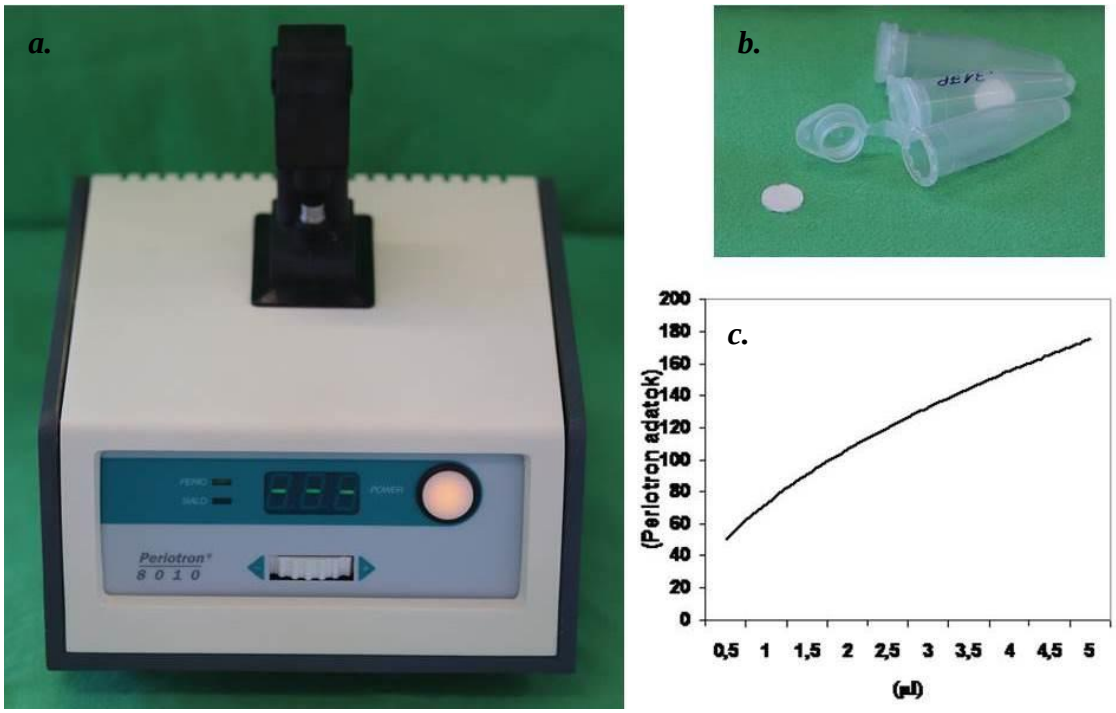

Figure 5. (a) *The Periotron device (Pro-Flow™, Inc., Amityville, NY, USA)* ***(b)*** *Filter paper discs (Sialopaper™).* ***(c)*** *Standard calibration curve used to convert Periotron readings (y axis) into fluid volumes (x axis)*

The use of the device is described in the literature as simple and rapid, producing repeatable and reproducible values with low variation (52, 55). However, inter- and intra-individual variations regarding the buccal, labial and palatal mucosal sites (43% for the palatal, 17% for the buccal and 18% for the labial saliva flow) have been observed by Eliasson et al (57) *(Table 2).* Moreover, small fluid volumes lower than 0.2 µl are subject to measurement errors, due to evaporation and problems with strip or disc placement between the electrodes (61).

Table 2. *Comparison of reported labial (LS) and palatal (PS) minor salivary gland flow rates in the literature, measured by the Periotron method. M: male; F: female.*

Author	Year	n	LS		PS	
			Time (s)	Flow rate (µl/cm²/min)	Time (s)	Flow rate (µl/cm²/min)
Shern et al ***(52)***	1990	14	30	0.96±0.55	30	0.74±0.35
Sivarajasingam et al ***(53)***	1995	99	30	2.38±1.05 (M) 2.00±0.95 (F)	30	0.59±0.25 (M) 0.53±0.25 (F)
Won et al ***(55)***	2001	30	30	2.8±1.0	30	2.2±0.9
Lee et al ***(31)***	2002	20	30	1.9±1.2	30	3.2±2.9
Schmideg et al ***(56)***	2007	17	30	1.9±3	30	2±2.45
Eliasson et al ***(32)***	2009	142	15	3.0±1.4	30	0.8±0.3
Smidt et al ***(58)***	2010	583	120	0.42		
Sonesson et al ***(59)***	2011	30	15	2.5±1.4		

2.5. Saliva and the stability of the maxillary complete denture

The global prevalence of edentulism ranges from 0.1% to 32.3%, with strong variations between countries and regions, and is constantly declining in the industrialized countries (62). In edentulous patients, the traditional removable complete dentures still present a successful treatment option for improving masticatory function and oral health. However, not only tooth loss and edentulism, but also complete dentures, especially those with poor retention and stability may carry negative impacts on oral health-related quality of life (63, 64). Success or failure rate is dependent on various number of factors such as the practitioner's technical skills, oral conditions and patient's compliance (65).

2.5.1. Physical aspects of complete denture retention

The masticatory ability of patients wearing complete dentures are associated with patient- and denture-related factors (66). Retention of the denture is an important aspect of the latter, and is related to the resistance against the force necessary to remove the denture from its basal seat (67). Various models are described in the literature to characterize the physical properties of denture retention. The *solid-joint or cohesion model* is based on the existence of direct cohesive contact between the mucosa and the denture, requires geometrically dependent contacting surfaces of epithelial cells and the

acrylic surface of the baseplate. However, it may result in the development of irreversible lesions. Others emphasized the role of the *negative (subatmospheric) pressure* under the baseplate of the denture, although it can only be maintained by constantly acting forces. According to the generally proposed *liquid-joint model*, the retention is influenced by the physical properties of the continuous fluid film layer between the baseplate and the oral mucosa, namely the adhesion, cohesion, surface tension, capillary pressure, viscosity, fluid film thickness, and atmospheric pressure (68, 69). This physical mechanism is traditionally modelled with the separation of a pair of parallel flat surfaces with a fixed volume of fluid film between them (70).

Darvell et al and Stanitz et al primarily emphasize the role of surface tension and capillary pressure of the liquid film between two closely fitting surfaces, resulting in a negative pressure in the liquid-filled space, therefore a retentive force is experienced. Moreover, the rate of separation of the two surfaces depends inversely on the viscosity of the liquid (71, 72). Uniformly good adaptation of the denture base is an important aspect in terms of retention. Accurate and close fit of the denture results in a narrower gap underneath, filled with a thinner fluid film, which contributes to the retentive force through the enhanced effects of its surface tension (68). According to the physical analysis of Monsenego et al, retention occurs when hysteresis of the denture-saliva contact angle exists. The presence of a continuous fluid film between the denture and the mucosa, and the geometry of the border surfaces at the meniscus contact angle are therefore necessary factors in achieving retention (69). The fabrication of the correct border seal around the denture base has consequently advantageous effects.

2.5.2. Role of saliva in the retention of dentures

Saliva plays an inevitable role in the physical mechanisms of stabilizing of the denture on the oral mucosal surface. According to the experiments of Murray et al, the optimal separation gap between the denture base and the oral mucosa is 15 μm, which is filled with saliva film of the same thickness (70). Minor salivary gland secretions, especially PS contribute to the presence of this mucous layer of saliva film in the denture-mucosa interface. Its viscosity and surface tension contributes to the physical components of denture retention, and the establishment of a good peripherial seal (46). Niedermeier and Krämer found correlation between the UWS, and especially the PS flow rates and

the retention of the maxillary denture. According to their investigations, stimulation of salivary flow resulted in a higher mucin concentration, which increased the retention of the prostheses (29, 73).

Mucous minor salivary gland secretions contribute to the mucosal tolerance against mechanical, chemical and biological harmful effects, including allergic reactions and sore spots or ulcers due to mechanical irritation of the denture (73). Consequently, patients with xerostomia often experience discomfort of the denture bearing tissues and mucosal soreness as a result of inadequate saliva film thickness or viscosity (74, 75). Moreover, the feeling of dry mouth has a significant negative effect on the quality of life of denture-wearing patients, including general satisfaction with removable dentures (76). However, according to the investigations of Márton et al., patients suffering from xerostomia and/or Sjögren's syndrome had similar PS flow rate as healthy controls, and no difference was observed in denture retention and stability. Their results underline the role of adequate palatal saliva and its viscosity in denture retention (46). To date, only limited evidence is available for establishing guidelines for patients with xerostomia and/or hyposalivation related to the use of complete dentures (77). The use of denture adhesives (DA) and saliva substituents or artificial saliva, and the wetting of dentures before placement seems to be beneficial (78).

In conclusion, saliva flow rates of the major and minor salivary glands, especially the palatal glands have an important role in achieving denture stability and proper oral "wettability" of the mucosa.

2.5.3. Effects of wearing denture onto saliva flow rates

It was assumed, that the continuous wearing of the maxillary complete dentures act as a mechanical stimulus for the underlying palatal mucosa. Eliasson et al found significantly higher palatal secretion in denture wearers compared to the control group (16). However, Niedermeier et al regarded the continuous wearing of mucosal supported dentures as a risk factor for decreased PS flow and xerostomia, based on their observations of inflammatory changes and atrophic reactions on the palatal mucosa in denture wearers (29, 79). More recently, Nikolopoulou and Al-Dwairi et al also recorded a high prevalence of xerostomia among removable denture wearers (74, 80). Schmideg et al and Peltola et al found that neither the whole saliva, nor the minor

salivary gland flow rates were influenced by continuous, long-term denture wearing (56, 81).

The mechanical stimuli may cause a short-term increase in the saliva flow rates at the initial placement of new complete dentures, partially due to the stimulation of the palatal mucous glands. Yurdukoru et al, and more recently, Muddugangadhar et al and Sonthalia et al experienced significantly higher unstimulated and stimulated saliva flow rates immediately after insertion of the new dentures (82-84). On the other hand, Márton et al could not find any significant alteration in whole and palatal secretions one week after the placement of newly fabricated maxillary complete dentures (46).

It must be stated that the possible changes of salivary parameters related to denture wearing is still a topic of controversy in the scientific literature, and requires further investigations.

2.5.4. Denture adhesives

The use of DAs dates back to the end of the 18th century (85). They are widespread used commercially available therapeutic aids for improving the retention, stability and masticatory performance of well-fitting removable dentures. DAs effectively enhance satisfaction, general well-being and oral health-related quality of life of denture-wearing patients. Moreover, they offer further advantages by providing a cushioning effect against mechanical friction and tissue irritation, minimizing impaired blood supply of the oral mucosa, reducing the frequency of adjustments, and maintaining a peripheral seal around the denture thus impeding the accumulation of food particles underneath it (86-90). Actually, 34% of complete denture wearers use them on a daily basis in the USA (86).

DAs are available in various forms and consistencies, for example *soluble products* like powder, gel, cream, strips, or *insoluble products* like cushion pads or wafers (85). Apart from added antimicrobial, flavouring and wetting agents and plasticizers, modern DAs consist of a blend of natural and synthetic polymers, e.g. hydroxyl- and carboxyl-methyl-cellulose (CMC), poly-vinyl-methyl-ether maleic anhydride (PVM-MA). *(Figure 6)* These polymer salts swell to many times of their original volume and become viscous when hydrated with oral moisture, filling the spaces between denture base and the underlying mucosa. Adhesion is provided by the electrovalent bond during

the hydration process, between free carboxyl groups of the adhesive polymers and the contacting surface of the oral mucosa (85, 86, 91, 92).

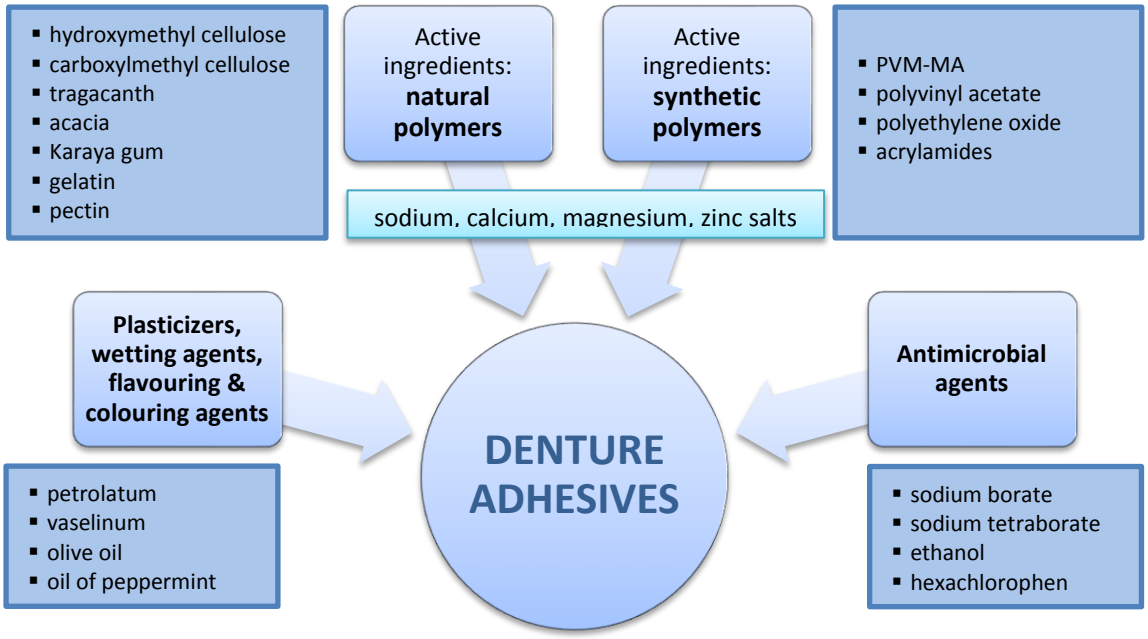

Figure 6. *Main ingredients of gel-type denture adhesives. PVM-MA: poly-vinyl-methyl-ether maleic anhydride. (85, 86)*

2.5.4.1. Performance and biocompatibility of denture adhesives

The effectiveness of DA materials has been extensively researched in the last decades. Subjective evaluations revealed significant improvements in the oral health-related quality of life of patients using DAs (93-96). Various methods are used to objectively assess the enhancements in retention and stability of complete dentures, achieved by the use of DAs. The effect of DAs on denture movement and dislodgement during chewing has been measured traditionally by “cineradiographic” (Tarbet et al, Karlsson et al) and “kinesiographic” methods (Chew et al), or by using magnetometer tracking devices (Rendell et al) (97-100). Several, but not all studies measured significant increase in the incisal bite force until denture dislodgement employing dynamometers and gnathometers (101-104), or calibrated force transducers in recent studies (105-107). Cream, paste or gel-type DAs have been proved to be the most effective and therefore

used most frequently, and they are included in the majority of research studies (86, 108).

For further improvements in denture retention, calcium salts and zinc have been added to several formulations. In some studies, on the other hand, the overuse of zinc containing denture creams have been found to induce hypocupraemia and in some documented cases, the development of serious neurologic symptoms were the consequence (109, 110). Therefore, manufacturers recommend using the adhesives not more than once daily.

Several studies investigated the in-vitro cytotoxicity of DAs in cell cultures by inhibiting fibroblast growth and disruption of F-actin cytoskeleton. DAs also raised the concern of releasing formaldehyde, which is cytotoxic and potentially allergenic (111, 112). Organic polymer constituents, e.g. karaya gum is reported to decrease intraoral pH, and cause allergic reactions with severe side effects in some patients (113). Warning the patients against prolonged overuse of adhesives due to these documented risks is therefore recommended. The prescription of recently introduced novel denture adhesive formulations composed of hypoallergenic natural ingredients could be safer alternatives. Hilmi et al investigated a biodegradable, eco-friendly denture adhesive containing chemically and physically modified natural starches as a replacement of PVM-MA synthetic polymers. The results are promising in terms of effectivity and cytotoxicity according to their first experiments (114). Overall, it is fair to say that comprehensive evaluation of the biocompatibility of DAs have been lacking both in vitro and in vivo.

The colonisation of Candida albicans beneath the denture base and the prevalence of denture stomatitis presents a significant oral health concern for complete denture wearers using DAs and was investigated in a number of studies (115, 116). Antifungal agents are therefore added to the composition of the adhesives to counteract these risks. Jamshidy et al suggested the incorporation of zinc-oxide nanoparticles in DAs to enhance their antifungal effects (117). The improvements of nanotechnology in the field of biomaterials may alleviate microbial colonisation issues more effectively in the near future. However, according to a recent study by Azevedo et al, incorporation of natural olive oil into the DA more effectively inhibits Candida colonisation, furthermore, increased duration of adhesive effect was experienced (118).

The achieved improvements on masticatory performance and quality of life measures were more significant for patients with poor residual ridge conditions or impaired neuromuscular control, therefore administration and use of DAs are specially indicated in these cases (96, 119). On the other hand, the use of these materials neither should compensate for problems due to ill-fitting or overused dentures, nor should resolve any fundamental dissatisfaction with them (86, 95).

2.5.4.2. Use of denture adhesives in patients with xerostomia

According to some studies, the use of DAs effectively alleviate denture-wearing difficulties frequently experienced by patients suffering from xerostomia (77). The use of gel-type DAs resulted in significant improvements regarding patient satisfaction and retention forces of maxillary complete dentures in patients with dry mouth in the studies of Bogucki et al (78, 120). Other studies showed that the use of saliva substituents or oral moisturizing agents might have similar favourable effects in terms of increasing retention, stability and general performance of dentures in dry mouth patients (74, 121, 122). According to a recent Japanese web-based survey, the usage of DAs was more frequent in smoker than in non-smoker denture wearers. Authors state that dry mouth symptoms were more prevalent in smokers, which may have caused denture instability without using adhesives [106].

It is still unknown, whether the continuous use of adhesives influence the salivary parameters, xerostomia and associated sicca symptoms. In a recently published multicenter study, Nishi et al could not find any significant change in the oral moisture levels after the administration of DAs (123). However, more evidence is needed to investigate their mechanism of action in patients with xerostomia or hyposalivation, and to confirm their biologic effects in terms of cytotoxicity and overall safety of use in the long-term (86).

2.6. Oral effects of smoking

Cigarette smoking is the most widespread form of tobacco use worldwide, in Europe and in Hungary as well, by affecting almost 20% of the world’s population and 80% of all tobacco users globally, presenting significant and well-documented health risks (124,

125). Tobacco products are entirely or partially made of the leaf tobacco as raw material, and they can be distinguished between heated or combustible (smoked), and non-combustible smokeless tobacco (ST) products (126). Smoked tobacco products include traditional cigarettes (bidis, hand-rolled or factory-made cigarettes), various types of cigars, water pipes or hookahs, pipes and heated tobacco products (HTPs) introduced in the recent years. ST products, involving chewing tobacco and dry or moist snuff or snus are based on the absorption of nicotine and other chemicals across mucous membranes (127-129). Electronic cigarettes or e-cigarettes or electronic nicotine delivery systems (ENDS) do not belong to the category of tobacco products, because their mechanism of action is based on the inhalation of a propylene-glycol and nicotine-containing e-liquid, aerosolized by the device (130). Their use is continuously gaining popularity within the last decade *(Table 3).*

Table 3. *Classification of nicotine-containing products.(127, 131, 132)*

CATEGORY	Combustible tobacco products	Heated tobacco products (HTP)	Smokeless tobacco products (ST)	NON-TOBACCO PRODUCTS: Electronic nicotine delivery systems (ENDS)
MECHANISM	Dried tobacco leaves burned, and smoke inhaled	Tobacco is heated but not burned to generate inhaled aerosol	Consuming tobacco leaves orally or nasally without heating or burning	Nicotine-containing e-liquid aerosolized by an electric device
EXAMPLES	▪ Cigarettes: • Roll-your-own cigarettes • Factory-made cigarettes • Kretek *(Indonesia)* • Bidi *(South-Asia)* ▪ Cigars, cigarillos ▪ Hookah/Waterpipe ▪ Pipe	▪ **Type 1:** disposable cigarette-like ▪ **Type 2:** electric heating blade ▪ **Type 3:** electric micro-oven ▪ **Type 4:** hybrid, ENDS-like	▪ Chewing tobacco ▪ Moist snuff – orally consumed ▪ Dry snuff/snus – nasally consumed ▪ Dissolvable tobacco products	▪ **1.Generation**: Disposable e-cigarette ▪ **2. Generation**: E-cigarette with cartridge ▪ **3. Generation**: Modifiable tanks ▪ **4. Generation**: Pod Mod devices ▪ **Vaporizers**

2.6.1. Assessment of smoking habits

Cigarette smoking has been characterised and assessed in the scientific literature with various measures investigating tobacco exposure, level of addiction, and disease risks. Cigarette consumption of current smokers can be described by its frequency and intensity, expressed in number of cigarettes consumed per day (NCC) or cigarettes per day (CPD) units, and many subcategories (133). The level of nicotine dependence is a key factor in the characterisation of smoking status. The best-known measure for its assessment is the *Fagerström test for nicotine dependence (FTND)* and its modification, the *Heaviness of Smoking Index (HSI)*. The latter combines two measures: reported CPD and time to the first cigarette (TTFC) upon waking (134).

The intensity and duration of smoking is in strong correlation with oral and general health status and disease risks or severity. It is assessed traditionally by *self-report*, using custom-made or specially designed questionnaires. Objective validation of smoking status or tobacco use or exposure includes measuring salivary, urine or serum *cotinine*, the primary metabolite of nicotine. Its salivary concentration is reported to be in a linear relationship with smoking intensity up to 20 CPD (135). The measurement of *expired carbon monoxide* is another viable method for the assessment of smoking, despite the limitations due to its short half-life and unavailability to check ST use (136). Moreover, higher salivary *thiocyanate* levels can be measured among smokers and its concentration is in correlation with increased duration and frequency of smoking (137).

2.6.2. Epidemiology of smoking

Tobacco use is a global health threat and is simply the most preventable and leading cause of premature death worldwide, killing half of its users (125, 126, 138). It is responsible for 8 million deaths globally every year: 16% of all deaths in adults over 30 years in Europe, and an annual death rate of 700.000 in the EU alone (124, 126). In Hungary, 15% of healthy life years are lost as a consequence of smoking, which is the fourth worst rate worldwide (139).

The World Health Organization (WHO) has released seven reports to date, in order to track the status of tobacco epidemic, and to implement cessation policies and strategies. According to their estimations, the global prevalence of tobacco use was 1.3 billion people in 2018, which is a significant reduction compared to 1.4 billion in the year 2000

(124). The use of tobacco products has been decreased in the United States, hence the use of e-cigarettes has been continuously increasing since 2011 (140). A significant reduction in tobacco use by 26% within the last two decades has been observed in Europe as well. On the other hand, a significant increase by 57% has been reported in Africa and the Middle East. This strengthens the fact that more than 80% of the tobacco users live in low- and middle-income countries (126, 141).

In Hungary, according to the most recent Eurobarometer survey published in 2021, the overall prevalence of smoking is 28%, which is in correspondence with the actual European prevalence estimates (142). A favourable decline in smoking prevalence has been observed in Hungary within the last 15-20 years: the overall prevalence of smoking has dropped from the peak of 34% in 2003, predominantly due to the decrease in the percentage of male smokers (143). On the other hand, the use of novel nicotine delivery products like heated tobacco products and e-cigarettes is continuously increasing. The current prevalence of e-cigarette use in Hungary is 9% for ever-users and 1% for current users, which is below the European average of 14% and 2%, respectively (142).

2.6.3. General and oral consequences of smoking

Tobacco use and regular exposure to second-hand smoke (passive smoking) have devastating health, social, economic and environmental effects, by harming almost every organ of the body. Tobacco smoke contains more than 7000 chemicals, including approximately 250 harmful agents, from which 70 have been proved to cause cancer (144, 145). Exposure to these free radicals from the smoke causes oxidative stress, inflammatory reactions and DNA damage in several pathways (146). Nicotine, one of the main agents is not only responsible for the establishment of addiction, but has acute toxicity and adversely affects the general health of smokers (147).

According to decades of scientific evidence, tobacco use is in causal relationship with lung, liver, and colorectal cancers, and associated with the development of oro-pharyngeal, bladder, cervix, oesophagus and breast cancers. Moreover, smoking is causally linked to severe cardiovascular diseases and events including coronary heart disease and stroke, and adversely affects the respiratory system by being a major cause of chronic obstructive pulmonary disease (COPD) and worsening asthma in adults.

Even low levels (1-4 CPD) of daily smoking have adverse health effects. Furthermore, long-term exposure to second-hand smoke affects cardiovascular and respiratory systems, and increases the incidence of head and neck, lung and breast cancers nearly as effective as active smoking does. (148)

The oral cavity is the first part of the body that contacts the noxious components of tobacco products, therefore smoking has mainly carcinogenic, immunologic, microbial and clinical adverse effects on oral health (129, 149). According to the latest systematic review issued by the WHO in 2017, there is strong evidence that all forms of tobacco use increase the risk for oral premalignant lesions including leukoplakia, oral cancers, periodontal disease and premature tooth loss (150). Moreover, delayed or impaired wound healing and bone remodelling, lower success rate of implant treatments, halitosis, altered taste sensation and tooth discoloration, mucosal alterations like hairy tongue, melanin pigmentations and smoker's palate are also frequent oral manifestations in smokers (138, 149, 151). Smoking is a major risk factor for developing periodontal disease due to localized vascular dysfunction and reduced gingival blood flow in the periodontal tissues, by accounting for more than half of the periodontitis cases in the US (152). Oral hygiene measures in smokers, especially in heavy smokers are significantly worse than non-smokers. Similar outcomes have been observed for e-cigarette users in a recent study by Kaán et al (153). There is a clear association between the use of tobacco products and dental caries, however, causal relationship is not firmly proven (154). Evidence suggests that exposure to second-hand smoke is also associated with increased risk for dental caries in deciduous and permanent teeth (150). *(Table 4)*

According to our current knowledge, exposure to the harmful chemicals generated by the aerosol of e-cigarette devices and the smoke of HTPs may be associated with less health risks compared to smoking, however, evidence is still lacking for well-documented long-term health effects (155). Regular tobacco and e-cigarette users belong to a high-risk group for developing dental and oral diseases, while cessation of use is significantly associated with improved oral health status and reduced risks of tobacco-related systemic and oral diseases in smokers at all ages. (156, 157).

Table 4. *Oral health effects of smoking.*

ORAL HEALTH EFFECTS OF SMOKING
increased risk for oral **premalignant lesions** (incl. leukoplakia)
increased risk for **oral cancer**
increased risk for **periodontal diseases**
increased risk for **dental caries**
increased risk for **premature tooth loss**
delayed or impaired **wound healing** and bone remodelling
lower success rate of **implant treatments**
mucosal alterations (hairy tongue, melanin pigmentations, smoker's palate)
halitosis
dysgeusia
tooth discoloration

2.6.4. Smoking in relation to oral exocrine functions

Saliva is the first biological fluid that is exposed to the various bioactive chemical components found in tobacco smoke or smokeless tobacco products. Therefore, tobacco use may have various adverse effects in the structure, composition and function of saliva and salivary glands (158). Ferragut et al found substantial unfavourable structural alterations in parotid and submandibular salivary glands in rats exposed to passive smoking (159). In another study by Fujinami et al, cigarette smoking was associated with vasodilatation and hyperaemia in the parotid and submandibular glands and a decrease in the total protein amount, amylase and peroxidase activity of the saliva in rats (160). In a study in humans, intensive smokeless tobacco use caused degenerative changes in minor salivary glands at the site of chronic tobacco placement (161).

2.6.4.1. Saliva flow rates

The possible effects of tobacco use on saliva flow rates are controversial in the scientific literature (162, 163). Some authors found positive correlation between smoking and salivary parameters. Smoking is reported to cause an acute, short-term increase in salivary flow, as a result of an initial mechanical, thermal and chemical stimulation of the salivary glands involving the excitatory effects on the glandular nicotinic

acetylcholine receptors (164, 165). In one of their earlier studies, Eliasson et al reported an increase in PS flow rates by 27% in tobacco users, explained by an increase in water permeability and higher glandular output due to the local irritant effect of tobacco smoke on the palatal mucosa (16). Bayraktar et al measured higher stimulated whole saliva flow rates among smokers both in haemodialysis patients and in healthy controls, compared to subjects without habits (166). Moreover, increased stimulated whole saliva flow rate has been registered in smoker males compared to non-smokers in a Swedish population-based study, however, smokers reported more frequently dry mouth (167). According to a few studies, smoking may be regarded as a protective factor against primary Sjögren-syndrome, explained by the suppression of immunological factors including autoreactive B-cells as a consequence of long-term tobacco smoking (168, 169).

On the contrary, Fenoll-Palomares et al did not find any effect of smoking, obesity and alcohol consumption on the whole saliva flow rate and buffer capacity in a sample of healthy volunteers (43). Similarly, habits like smoking and alcohol consumption had no influence on labial and whole salivary flow rates and sicca symptoms in a random group of elderly people (58).

The majority of researchers agree that tobacco use have predominantly negative effects on salivation. Petrušić et al. examined the effects of tobacco smoking on salivary parameters. Most of the smokers had predominantly thick, while non-smokers had thin and serous saliva. There was no difference in the whole saliva flow rate between the two groups, although, an inverse correlation has been shown between age, duration of smoking, drug use and the amount of saliva in smokers (170). According to a number of studies, long-term smoking, and especially ST use is reported to result in a decrease of the salivary pH, enhancing the vulnerability of the oral environment to various diseases and unfavourable conditions (158, 171, 172). Saputri et al showed that the decrease in salivary flow rate and pH is in correlation with the intensity and duration of smoking, and the nicotine concentration of the tobacco product used (173). Long-term tobacco use is associated with lower unstimulated salivary flow rates compared to the values of matched non-smoker controls in a number of other studies. These outcomes may be explained by the known long-term vasoconstrictive effect of nicotine affecting the blood supply of salivary glands, resulting in compromised function and reduced poorer quality

saliva (161, 162, 170, 171, 174-176). Moreover, decreased secretion rates of minor salivary glands at different sites, including PS, was also reported in tobacco users (16).*(Table 5)*

2.6.4.2. Xerostomia

Tobacco use is generally regarded as one of the factors affecting the prevalence of dry mouth symptoms. In the study of Dyasanoor et al, a significant increase in the symptoms of xerostomia and a reduction in UWS secretion was registered in long-term smokers (162). Smoking habit and impaired health were associated with daytime xerostomia in a Swedish 15-year longitudinal study by Johansson et al (177), while Astrom et al registered similar outcomes in Swedish and Norwegian cohorts (178). Moreover, dry mouth symptoms were more prevalent in regular smokers in studies investigating elderly denture wearers (74, 76). On the other hand, in a population-based study by Schein et al, no associations were found between smoking and alcohol consumption and sicca symptoms in the elderly (179). *(Table 5)*

Long-term tobacco use is regarded as a risk factor for reduced salivary flow and xerostomia (161), however, studies investigating the effects of the duration, intensity and type of tobacco use on salivary parameters, especially minor salivary glands are still scarce.

Table 5. *Summary of studies in the literature investigating the associations of smoking habits with salivary parameters, dry mouth and sicca symptoms. (+: positive effect;* ***0****: no effect/no association; -: negative effect; BOP: bleeding on probing; UWS: unstimulated whole saliva; SWS: stimulated whole saliva; LS: labial saliva; PS: palatal saliva; pSS: primary Sjögren's syndrome; ST: smokeless tobacco; CPD: cigarette per day)*

Author	Year	Type of study	Sample characteristics	Main outcomes	
Kakoei et al **(180)**	2021	cross-sectional study	5639 individuals; 2211 xerostomia/3429 controls	xerostomia is highly prevalent in female daily smokers	-
Astrom et al **(178)**	2019	longitudinal cross-national cohort study (5 years)	2947 Norwegian and 4862 Swedish community-dwelling older people (age: 65, 70)	association of xerostomia with smoking	-
Ibraheem et al **(176)**	2018	cross-sectional study	25 smokers/21 passive smokers/24 non-smokers; healthy individuals	decreased UWS, pH and BOP in smokers and passive smokers	-
Alaee et al **(175)**	2017	cross-sectional study	50 smokers/50 non-smokers; healthy individuals	decreased UWS in smokers	-
Saputri et al **(173)**	2017	cross-sectional study	40 male smokers (≥1 CPD); age range: 17-55	decreased UWS and pH associated with smoking intensity and nicotine levels	-
Rehan et al **(172)**	2017	cross-sectional study	70 smokers/70 ST users/70 non-smokers; healthy individuals; age range: 20-50	no association of UWS with smoking and ST use; decreased pH in smokers and ST users	**0**
Olsson et al **(168)**	2017	nested case-control study	63 pSS patients/63 matched controls	current smoking is associated with a lower risk of later being diagnosed with pSS	+
Stone et al **(169)**	2017	cross-sectional study	587 pSS patients/701 non-pSS patients with sicca symptoms	current smoking is negatively and independently associated with pSS	+
Petrusic et al **(170)**	2015	cross-sectional study	30 smokers/30 non-smokers; randomly selected individuals; age ≥18	1. no association of UWS, SWS and smoking 2. decreased UWS and SWS associated with increasing age, smoking duration and drug use in smokers	**0** -
Singh et al **(171)**	2015	cross-sectional study	35 smokers/35 non-smokers; males; age range: 20-50	decreased UWS; decreased pH in smokers	-
Dyasanoor et al **(162)**	2014	cross sectional study	60 smokers/60 non-smokers; healthy individuals	decreased UWS; increased xerostomia prevalence in smokers	-
Kanwar et al **(174)**	2013	cross-sectional study	20 smokers/20 ST users/20 non-smokers; healthy individuals; age ≤ 40	decreased UWS; decreased pH in smokers and ST users	-
Villa et al **(181)**	2011	population-based study	601 individuals; age range: 18-88	no association of xerostomia with smoking	**0**
Rad et al **(161)**	2010	cross-sectional study	100 smokers/100 non-smokers	decreased UWS; increased xerostomia prevalence in smokers	-
Khan et al **(182)**	2010	cross-sectional study	20 smokers/20 non-smokers; healthy males; age range: 25-30	no association of UWS and SWS with smoking	**0**
Smidt et al **(58)**	2010	population-based study	668 individuals; age range: 65-95	no association of sicca symptoms, UWS and LS with smoking	**0**
Johansson et al **(177)**	2009	longitudinal cohort study (15 years)	4714 individuals (age: 50, 55, 60, 65)	association of daytime xerostomia with smoking	-
Fenoll-Palomares et al **(43)**	2004	observational prospective study	159 healthy individuals; age ≥ 18	no association of UWS and pH with smoking	**0**
Bayraktar et al **(166)**	2002	cross-sectional study	50 hemodyalysis patients/50 controls; age range:16-86	increased SWS among smokers in both hemodyalysis and control groups	+
Thomson et al **(183)**	2000	longitudinal cohort study (5 years)	700 community-dwelling older people; age range: 65-100	increased UWS in smokers	+
Schein et al **(179)**	1999	population-based study	2481 individuals; age range: 65-84	no association of sicca symptoms with smoking	**0**
Axelsson et al **(167)**	1998	population-based study	1093 individuals; randomized sample of 35-, 50-, 65- and 75-year-old subjects	1. increased SWS in male smokers 2. increased xerostomia prevalence in smokers	+ -
Eliasson et al **(57)**	1996	cross-sectional study	127 individuals; age range: 22-89	increased PS in tobacco users	+

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3. OBJECTIVES

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

Saliva flow rates of the major and minor salivary glands, namely the palatal salivary glands have important role in denture stability and in the proper oral "wettability" of the mucosa. It is not known whether administration and/or the continuous use of DAs might influence either the UWS, the minor salivary gland flow rates or the previously present intra- and extraoral sicca symptoms of maxillary complete denture wearing persons.

Our objective 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 unstimulated whole saliva flow rate (UWS) and on the flow rate of the palatal (PS) and labial (LS) minor salivary glands.

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

There are scarce data in the literature investigating the correlation of smoking intensity with salivary parameters and oral dryness symptoms. Additionally, only limited evidence is found in the current publications about the possible intra- and extraoral xerogenic effects of tobacco smoking.

Therefore, 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.

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4. MATERIALS AND METHODS

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

4.1.1. Ethical approval

Regional and Institutional Committee of Science and Research Ethics of Semmelweis University (No. 104/2003)

4.1.2. Patient selection

This 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. (184)

4.1.3. Assessment of the subjective orofacial and consecutive extraoral sicca symptoms

After detailed medical and dental history taking, a questionnaire (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 list of the 16 questions asked in the questionnaire is shown in *Table 6.* 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. (184)

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Table 6. *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

4.1.4. Clinical examinations (saliva flow rate measurements)

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). (7)

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. UWS flow rate less than 0.1 ml/min was considered as an objective sign of salivary hypofunction (hyposalivation) (21, 185).

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 cm^2) 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. *(Figure 4)* 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. *(Figure 5a)* 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/cm^2/min values of minor salivary gland flow rates according to the previous calibration of the device with known quantities of distilled water. (46, 184)

4.1.5. Application of the denture adhesives

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 *(Figure 7).* 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. (184)

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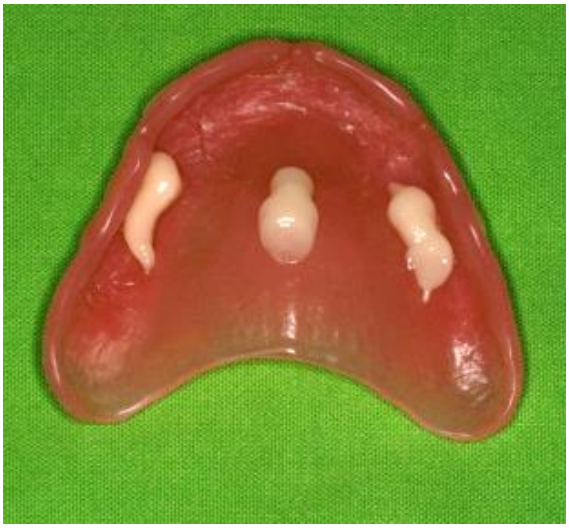

Figure 7. *Application of the denture adhesive according to the manufacturer's instructions.*

4.1.6. 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.

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

4.2.1. Ethical approval

Regional and Institutional Committee of Science and Research Ethics of Semmelweis University (No. 104/2003)

4.2.2. Patient selection

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. Smokers using tobacco products other than conventional factory-made or roll-your-own cigarettes were excluded from the studies. All participants provided informed written consent to the study. (163)

4.2.3. Assessment of the subjective orofacial and consecutive extraoral sicca symptoms

The same questionnaire with 16 questions investigating sicca symptoms, as described in our first study in *Chapter 3.1.*, 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. *(Table 6)*

4.2.4. Assessment of the smoking habits and socio-demographics of the sample

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. 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 (163, 186).

4.2.5. Clinical examinations (saliva flow rate measurements)

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 the study. The detailed methodology of saliva flow rate measurements are described in *Chapter 3.1.* 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.

4.2.6. 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 $p<0.05$.

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5. RESULTS

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

5.1.1. Changes in subjective sicca symptoms

The summarized weekly answers to the questionnaire are presented on *Figures 8 and 9.* 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 χ2-test). *(Figure 8).*

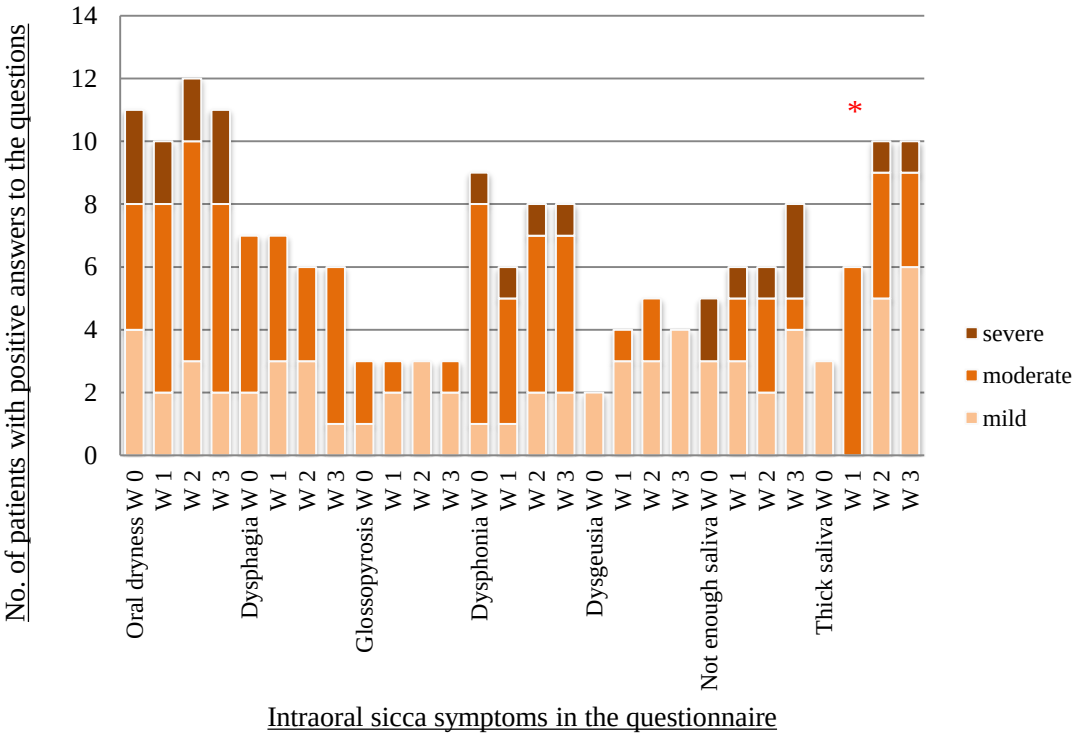

Figure 8. *Change of intraoral subjective sicca symptoms in the complete denture wearer sample (n=28) during the three weeks of denture adhesive use. Number of positive answers to the question "Does your saliva often feel thick" was significantly higher on the 3rd week (n=10) compared to the initial week (n=3). *= p<0.05 according to chi-square test. W: week (184)*

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 *(Figure 9)*. (184)

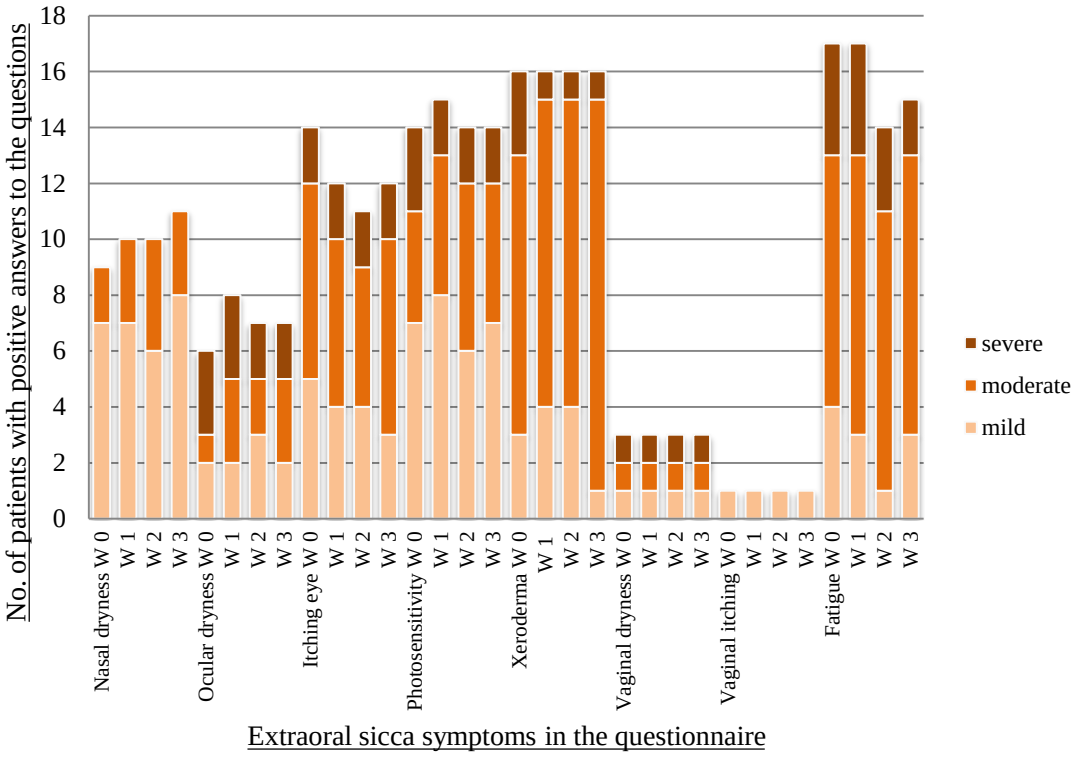

Figure 9. *Change of extraoral subjective sicca symptoms in the complete denture wearer sample (n=28) during the three weeks of denture adhesive use. No significant change was observed in the presence and intensity of the symptoms during the three weeks. W: week (184)*

5.1.2. Changes in saliva flow rates

The prevalence of hyposalivation was 18% at the initial session. The changes of UWS flow rates are shown on *Figure 10.* According to the measurements, no significant change has been found in UWS flow rates during the 3-week period (p = 0.824). The LS flow rate did not decrease significantly (initial: 3.99 µl/cm2/min; week 3: 2.58 µl/cm2/min) *(Figure 10)* (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 *(Figure 11)*, which demonstrates a significant change (p = 0.024). (184)

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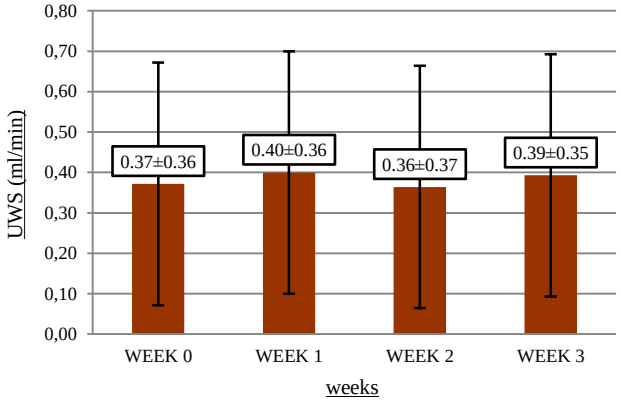

Figure 10. *Change of mean unstimulated whole saliva (UWS) flow rate (ml/min) in the complete denture wearer sample (n=28) during the three weeks of denture adhesive use. No significant change was detected according to the paired Student's t-test (184)*

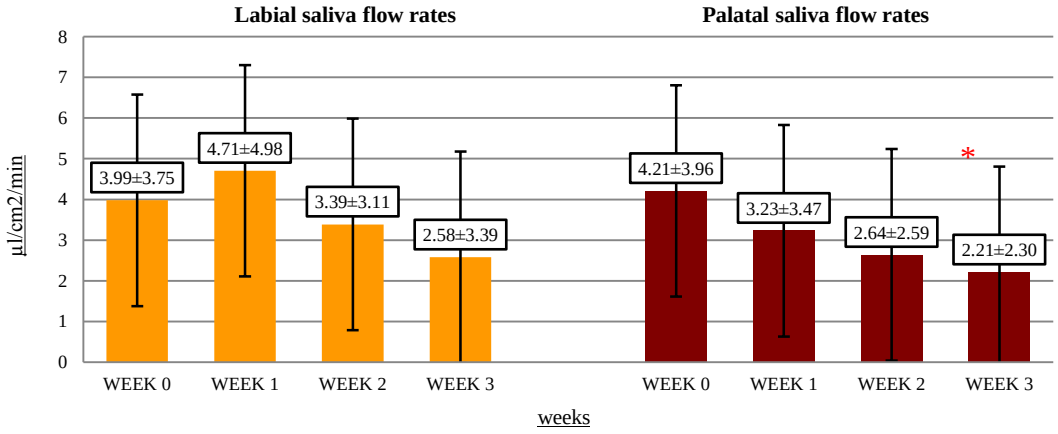

Figure 11. *Change of mean labial and palatal saliva flow rates (µl/ cm2/min) in the complete denture wearer sample (n=28) during the three weeks of denture adhesive use. The continuous decrease of palatal flow rates became significant by the end of week 3. * = p<0.05, according to ANOVA test (184)*

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

5.2.1. 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). The proportion of smokers and intensity of smoking in different age groups by genders is visualized in *Figure 12.* 51.3% of female smokers and 60.7% of male smokers belong to the MHS group. The prevalence and intensity of smoking were highest in the 40–59-year-old age group in females (38.0% and 20.9%,

respectively); however, in males, the highest prevalence was recorded in the 18–29-year-old age group (60.4%), while the highest intensity in the 30–39-year-old age group (38.3%). (163)

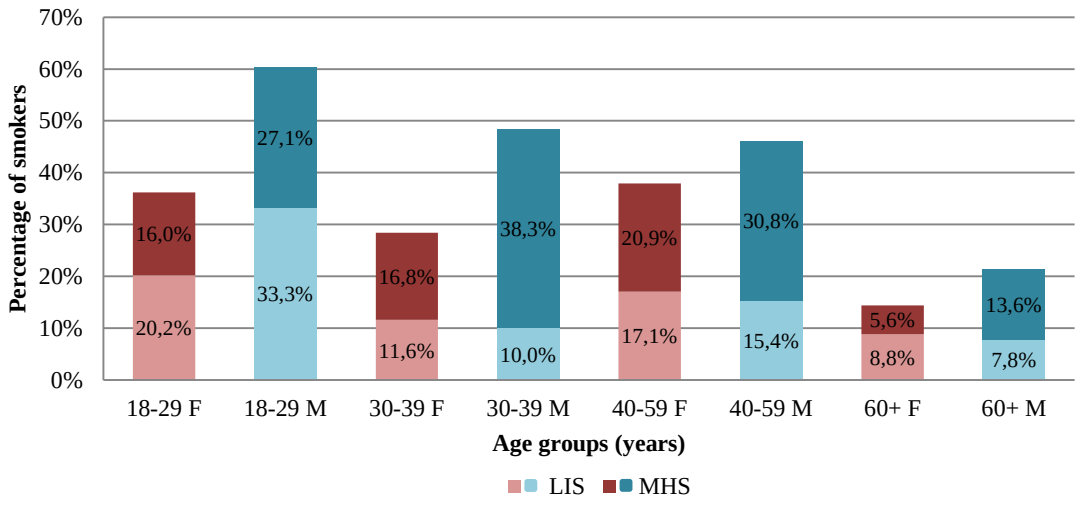

Figure 12. *Prevalence and intensity of smoking by gender and age groups in our sample (n=901). M: male; F: female; LIS: light smoker; MHS: moderate or heavy smoker.(163)*

5.2.2. 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 *(Tables 7 and 8).* 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). *(Figure 13)* 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 7 and 8)* (163)

Table 7. *Prevalence of intra- and extraoral sicca symptoms by smoking status in Hungarian males. Red numbers indicate significant differences between smokers and non-smokers according to chi-square test. S: smokers, NS: non-smokers. *p <0.05; **p<0.001 (163)*

Subjective symptoms in %	Age groups (years)									
	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)
1. Xerostomia	28.2	29.3	6.7	44.8 **	22.2	31.5	42.0	50.0	28.6	35.6
2. Dysphagia	12.8	10.3	10.0	13.8	11.1	18.5	12.4	36.4 *	11.7	17.2
3.Glossodynia, burning mouth	10.3	6.9	13.3	3.5	7.9	13.0	1.2	9.1	6.6	9.2
4. Dysphonia	35.9	46.6	26.7	27.6	25.4	33.3	27.2	18.2	28.2	35.0
5. Dysgeusia	5.1	10.3	3.3	10.3	6.4	13.0	12.4	4.6	8.0	10.4
6. Reduced saliva feeling	5.1	12.1	3.3	17.2	9.5	7.4	22.2	9.1	12.7	11.0
7. Mucous saliva	18.0	29.3	16.7	24.1	22.2	18.5	18.5	9.1	19.3	22.1
8. Increased caries activity	64.1	74.1	66.7	79.3	68.3	77.8	66.7	72.7	66.7	76.7
9. Nasal dryness	15.4	32.8	40.0	41.4	25.4	31.5	29.6	40.9	27.2	35.6
10. Dryness of the eyes	28.2	20.7	13.3	17.2	22.2	16.7	19.8	13.6	21.1	17.8
11. Itching, burning of the eyes	30.8	27.6	23.3	44.8	30.2	37.0	38.3	40.9	32.4	35.0
12. Light sensitivity	43.6	34.5	36.7	51.7	36.5	37.0	44.4	63.6	40.9	41.7
13. Xeroderma	30.8	48.3	43.3	44.8	39.7	42.6	49.4	54.6	42.3	47.2
14. Fatigue	59.0	69.0	26.7	72.4 **	50.8	53.7	60.5	50.0	52.6	62.0

5.2.3. 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 *(Figure 14)*. 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) *(Figure 15).*

Table 8. *Prevalence of intra- and extraoral sicca symptoms by smoking status in Hungarian females. Red numbers indicate significant differences between smokers and non-smokers. S: smokers, NS: non-smokers. *p <0.05; **p<0.001 (163)*

Subjective symptoms in %	Age groups (years)									
	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)
1. Xerostomia	27.1	52.9 *	39.7	25.9	43.5	43.8	52.3	38.9	42.7	41.9
2. Dysphagia	10.2	20.6	13.2	14.8	22.9	25.0	16.8	22.2	17.3	21.3
3.Glossodynia, burning mouth	6.8	8.8	5.9	7.4	11.5	12.5	6.5	11.1	8.2	10.0
4. Dysphonia	50.9	47.1	42.7	25.9	34.4	41.3	38.3	61.1	39.7	41.9
5. Dysgeusia	6.8	5.9	7.4	7.4	14.5	13.8	10.3	27.8 *	10.7	12.5
6. Reduced saliva feeling	10.2	5.9	13.2	14.8	17.6	15.0	15.0	33.3	14.8	15.0
7. Mucous saliva	20.3	32.4	17.7	14.8	10.7	16.3	12.2	16.7	14.0	19.4
8. Increased caries activity	62.7	85.3 *	82.4	77.8	74.8	75.0	64.5	77.8	71.2	78.1
9. Nasal dryness	40.7	32.4	29.4	44.4	42.0	31.3	33.6	44.4	37.0	34.4
10. Dryness of the eyes	25.4	23.5	29.4	22.2	36.6	33.8	43.9	16.7 *	35.6	27.5
11. 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
12. Light sensitivity	54.2	44.1	52.9	40.7	60.3	65.0	50.5	38.9	55.1	53.1
13. Xeroderma	72.9	79.4	70.6	70.4	71.0	68.8	79.4	72.2	73.7	71.3
14. Vaginal dryness	6.8	8.8	11.8	3.7	22.9	15.0	22.4	11.1	18.1	11.3*
15. Vaginal itching, burning, fungal infections	15.3	26.5	25.0	14.8	18.3	11.3	12.2	5.6	17.3	13.8
16. Fatigue	69.5	79.4	70.6	55.6	69.5	76.3	71.0	61.1	70.1	71.9

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 16).* 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 17).*

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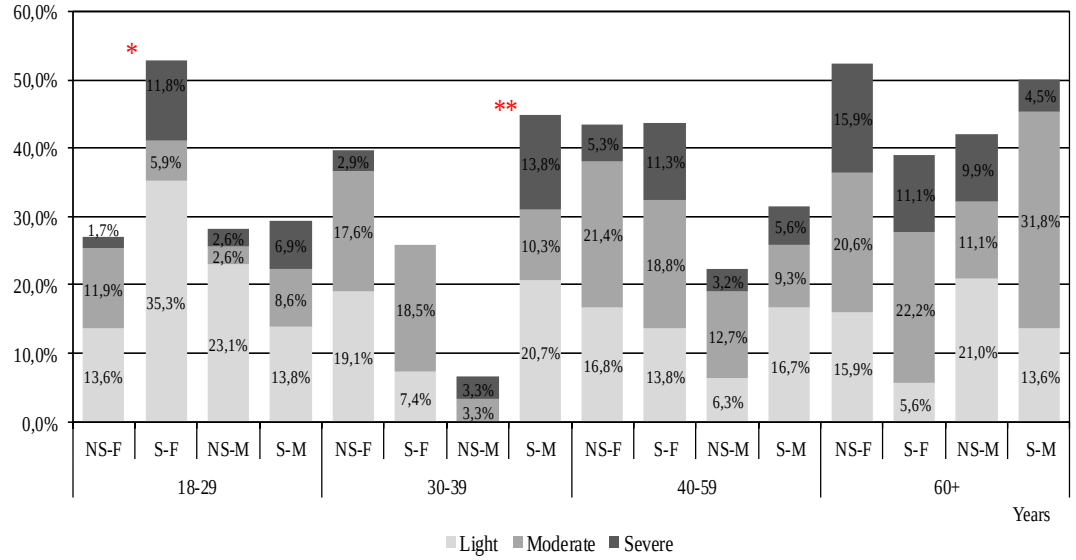

Figure 13. *Comparison of xerostomia prevalence and intensity among female and male smokers and non-smokers in different age groups. NS: Non-smoker; S: Smoker; M: male; F: female. *= p<0.05; **= p<0.005according to χ2 test (163)*

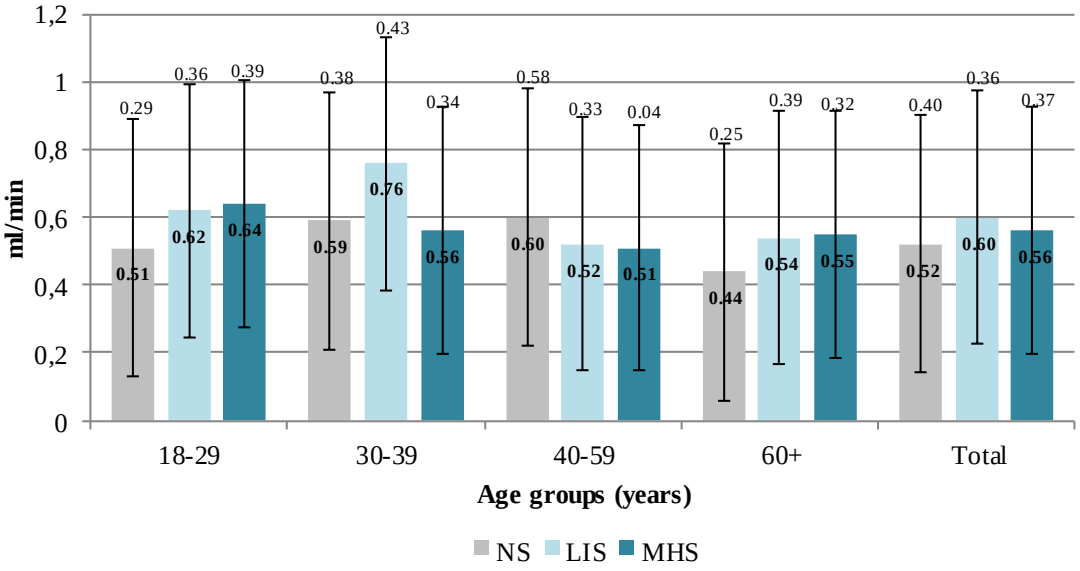

Figure 14. *Unstimulated whole saliva flow rates in males in different age groups according to smoking status. Means and standard deviations are presented. NS: Non-smoker; LIS: Light smoker; MHS: Moderate or heavy smoker. (163)*

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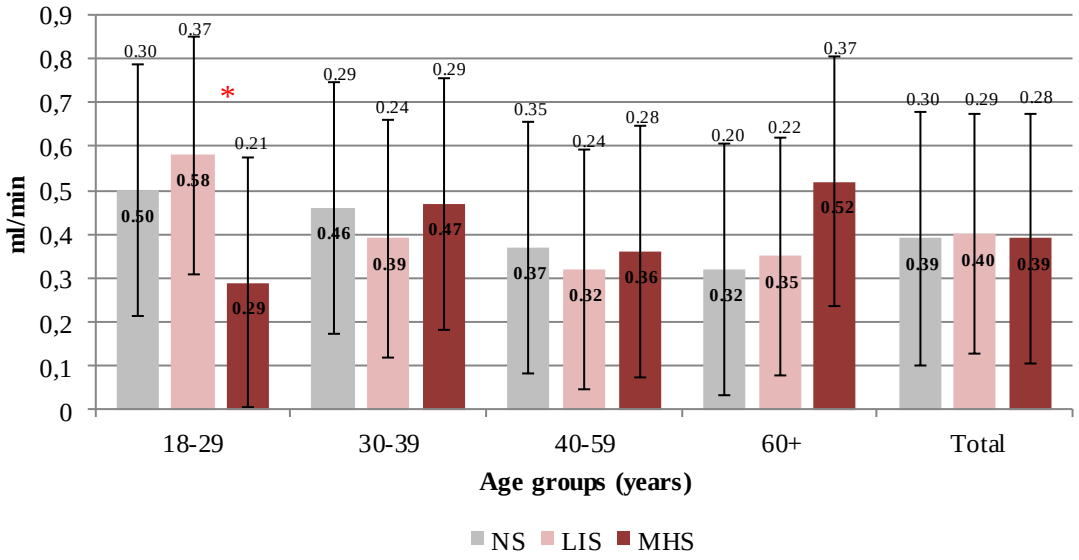

Figure 15. *Unstimulated whole saliva flow rates in females in different age groups according to smoking status. Means and standard deviations are presented. NS: Non-smoker; LIS: Light smoker; MHS: Moderate or heavy smoker. *= p<0.05according to independent samples t-test (163)*

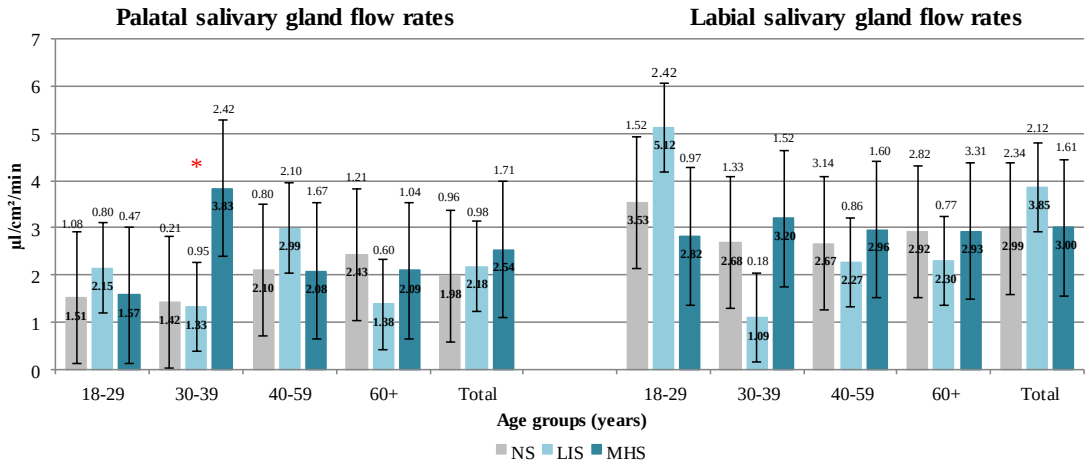

Figure 16. *Minor salivary gland flow rates in males in different age groups according to smoking status. Means and standard deviations are presented. NS: Non-smoker; LIS: Light smoker; MHS: Moderate or heavy smoker. *= p <0.05 according to independent samples t-test (163)*

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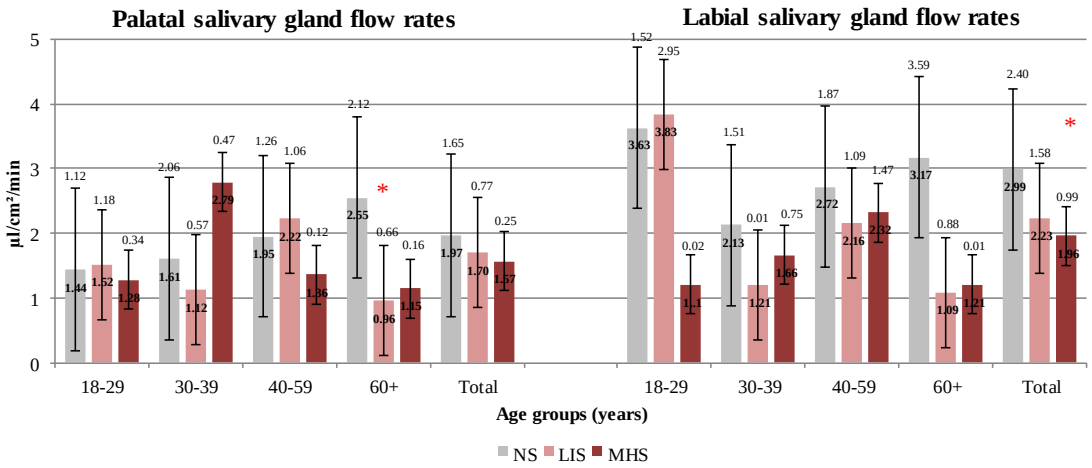

Figure 17. *Minor salivary gland flow rates in females in different age groups according to smoking status. Means and standard deviations are presented. NS: Non-smoker; LIS: Light smoker; MHS: Moderate or heavy smoker. *= p <0.05 according to independent samples t-test (163)*

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 *(Table 9)* (163).

Table 9. *Prevalence of hyposalivation (unstimulated whole saliva flow rate ≤ 0,1 ml/min) by smoking status in different age groups. (163)*

Prevalence of hyposalivation in %	**Age groups**									
	18-29		**30-39**		**40-59**		**60+**		**Total**	
	NS	**S**	**NS**	**S**	**NS**	**S**	**NS**	**S**	**NS**	**S**
Females (n=525)	1.7	2.9	7.4	3.7	13.0	16.3	9.4	16.7	9.0	11.3
Males (n=376)	0.0	1.7	0.0	0.0	7.9	0.0	4.9	4.6	4.2	1.2

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 *(Figure 18).*

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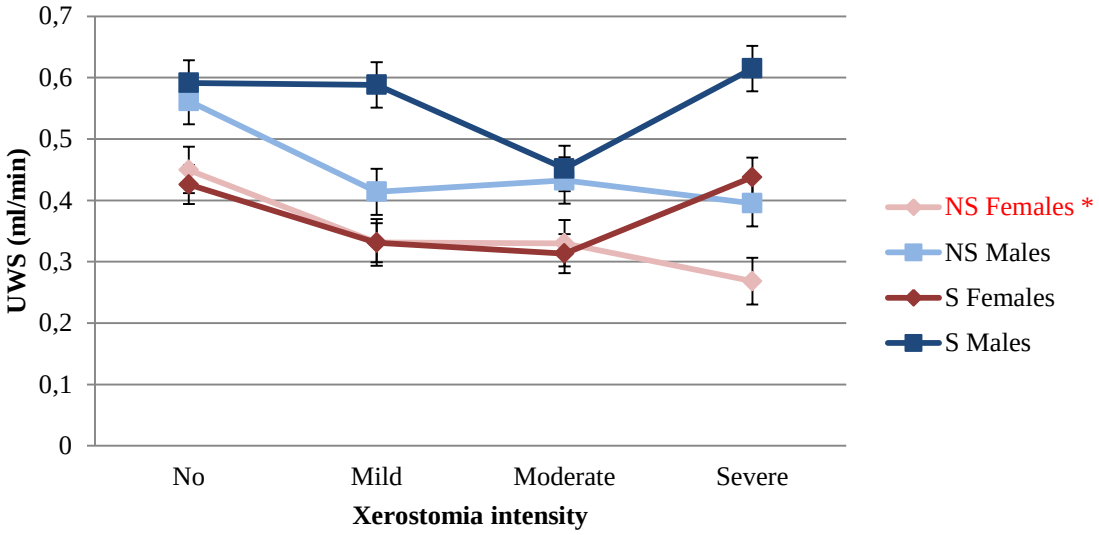

Figure 18. *Association between the intensity of xerostomia and UWS flow rate among non-smokers and smokers in both genders. UWS: unstimulated whole saliva; NS: non-smoker; S: smoker. *= p<0.005, according to ANOVA*

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6. DISCUSSON

Changes in the salivary parameters, including hyposalivation and/or dry mouth symptoms, can affect the functions of the oral cavity in several ways. Aim of this thesis was to investigate the possible alterations in xerostomia, the associated orofacial dryness symptoms, and saliva flow rates, with special interest on minor salivary gland secretions, related to frequently occurring clinical circumstances like smoking and the use of DAs.

There is a lack of universally used or semi-quantitative tool for evaluating dry mouth and associated complaints in the scientific literature due to methodological differences. The apparent versatility of assessment methods used in the publications (including XI by Thomson et al, CODS by Osalian et al, and the questionnaire designed by Fox et al) makes the outcomes difficult to compare (38, 39). Prevalence estimates for xerostomia have therefore high variability, ranging from 0.01 to 45 per cent (34). Our evaluation method for xerostomia using a dry mouth and sicca questionnaire of 16 items with a four-grade visual analogue scale *(Table 6)*, is based on the investigations of Sreebny and Valdini. It has a sensitivity and specificity of 93% and 68% for hyposalivation, respectively, and has been proved to be effective in our previous studies as well [1-3]. The physiological process of aging per se is generally associated with lower UWS flow rates and increased frequency of dry mouth symptoms. This experience is further supported by higher presence of systemic medical conditions and the intake of xerogenic drugs affecting salivary parameters in the elderly (23, 34, 187). Our study group of patients wearing complete dentures belong to the elderly age groups with a mean age of 72 years. Taking this into account, the initial prevalence of dry mouth (39%) and hyposalivation (18%) in our sample is in agreement with the xerostomia study conducted in Hungary by Márton et al (21), and slightly higher than the 33% reported in a recent systematic review investigating elderly people aged 60 or higher (188).

Current evidence of recently published systematic reviews suggests that by administering DAs, an overall better retention and stability of dentures, increased incisal bite forces and chewing ability, higher patient confidence and ease of social integration as a consequence is expected (189, 190). These materials have been proved to be more effective compared to surface treatments such as sandblasting or moisturizers (191).

Bogucki et al and Nishi et al recently found that gel-type DAs significantly improved the performance of complete dentures in patients with xerostomia (78, 123). However, according to our results, the previously present dry mouth symptoms were not influenced by the use of adhesives, neither in its frequency nor in severity, among these complete denture wearer elderly patients. Our study was the first of its kind to assess changes in the rate of xerostomia related to the use of DAs, and its outcome is in concordance with the results of the multicentre randomized controlled trial conducted more recently by Nishi et al. They observed that the administration of DAs did not change the oral moisture levels, which is an objective measure for oral dryness (123).

Though, the complaints of dysphagia and dysphonia slightly decreased during our three-week test period of using the DAs among the participants, this change was not significant. These lower levels might be explained by gaining higher level of retention and stability of maxillary dentures. On the other hand, in some cases, where the adhesive could not improve the performance of the old dentures effectively, the betterment in stability and its effect on speech and swallowing properties was possibly less pronounced.

Patients recorded a higher subjective level of viscosity of saliva (increased saliva thickness) by the end of week 3 and also experienced minor reductions in their saliva amount *(Figure 8).* A substantial two-fold increase was registered in the number of patients with subjective feeling of "increased saliva thickness" by the end of week 1, which further developed to a 3.3-fold increase by the end of our test period, compared to the control week. One possible explanation for this increase is a change in the viscosity and consistency of saliva caused by the use of DA. The eligibility criterion for the enrolled patients in our study was the actual wear of maxillary complete dentures for at least five years. However, the retention, stability and accuracy of fit of their currently worn dentures were assessed only by the clinical examiner, and were not standardized using objective, quantitative or validated subjective measures. Therefore, the presence of varying amounts and thickness, or even pooling of the applied DA layer on the palatal mucosal surfaces during the examination time period could not be excluded. Considering the fact that DAs act by increasing the viscosity of saliva in contact with the oral mucosa and the baseplate (189), this may have led to an excessive increase in saliva viscosity, which could be a possible explanation for our outcome of increased

number of patients with subjective feeling of thick saliva. Besides, our study group consisted of elderly patients whose dexterity and vision was likely below average levels. This may have caused difficulties with the removal of excess adhesive material from the oral mucosal surfaces after use, which in turn could have resulted in this phenomenon.

We should also emphasize that the regular use of the examined DA led to a substantial fall of the PS flow rate *(Figure 11).* A possible explanation for this can be that the gel-type adhesive might cause obstructions in the orifices of the palatal minor salivary glands. The active ingredients of DAs (CMC, PVM-MA polymer salts) swell to many times of their original volume during their hydration and contact with the proteins of saliva and oral mucosal surfaces (85). This extensive volume gain can lead to the obstruction of the glandular orifices being in a close proximity to the applied adhesive layer. A slight (but not significant) decrease in the LS flow rate was also detectable which might raise our attention to the decreased mobility and improved stability of the worn dentures due to the regular use of adhesives. The denture mobility per se might be a mechanical stimulus for salivation even for the minor salivary glands, so stabilizing dentures could reduce the flow rate. On the other hand, it is proven that wearing well-fitting and stable dentures increase occlusal forces and saliva flow rates (192, 193). Gel-type adhesives might also cause atrophy of the palatal minor salivary gland tissue, which can even more reduce flow rate. According to the opinion of our study group, considering the marked decrease in the PS flow rate only, the obstruction of the glandular orifices seems to be the most probable cause, though its verification requires further, mainly in vitro, histopathological examinations.

UWS flow rate did not change significantly ($p=0.824$) *(Figure 10),* consequently it seems, that the employment of gel type DAs do not influence the function of the major salivary glands. The adhesive material is certainly not in direct contact with the major glands' tissues. This fact supports our assumption regarding the minor glands, that the material's continuous direct contact with the orifices of the glands might be a possible reason for a partial obstruction or narrowing of the ducts near the orifices. Another possible explanation can be that the major glands' higher flow rate provides a continuous washing-clearing effect that keeps the orifices always free, which in turn is less effective in the case of the minor glands observed in the palatal region.

Therefore, the elevation of the saliva thickness may also result from undersecretion of the minor salivary glands, independent from the fact that no changes were observed in patient-reported xerostomia rate and intensity (184). A possible explanation for this could be that the observed decrease in PS flow rates did not result in a thinner layer of the palatal saliva film, which is a key factor in the feeling of dry mouth (46, 54). By comparing the significant changes of the PS flow rate (p=0.024) with the non-significant changes of the UWS flow rate (p=0.824), it is perceived that the DAs may have expressively influenced the secretion of the palatal minor salivary glands.

Tobacco use as a frequent oral habit has deleterious effects on general and oral health. In our study, the effect of smoking intensity on xerostomia and sicca symptoms and salivary parameters including minor salivary gland secretions were investigated on a sample of 901 participants in a cross-sectional design. The registered prevalence and intensity of current smoking *(Figure 12)* in these patients, who were selected from the dental outpatient services, was higher than in the related national and international reports based on representative samples of Hungarian adults (141-143). The highest prevalence and intensity of smoking was recorded among male smokers in the age groups of 18-29 and 30-39, which corresponds with the results of a national survey published by Cselkó et al in 2018 (143). 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, which was previously supported by other authors as well (129, 156, 194), therefore their attendance to dental health service is more frequent (195).

The statistical tests investigating the effects of smoking intensity on salivary parameters and sicca symptoms in our study were conducted after allocating our study population of 901 participants into pre-specified age-groups and genders. According to logistic regression analyses conducted in a recent Iranian population-based study with more than 5.000 participants by Kakoei et al, the relationship between daily smoking and dry mouth is influenced by age and gender (180). These findings support our study methodology, and are reflected in our results. Some authors found that xerostomia is more prevalent in smokers (161, 162, 177, 196), while others found no correlations between smoking status and dry mouth (58, 179, 181) *(Table 5).* In our sample, the overall prevalence of dry mouth among smokers and non-smokers did not differ

significantly, when the age groups were not considered *(Tables 7 and 8).* However, in female smokers in the 18-29 age group and male smokers in the 30-39 age group, both the ratio and the intensity of xerostomia was higher than in non-smokers, therefore a positive correlation may be suspected between the prevalence of dry mouth and smoking intensity in younger adults (163).

In addition, significantly lower UWS flow rates were measured among MHS in the youngest age group of females, compared to LIS and NS groups *(Figure 15).* Consequently, heavier smoking in young females may significantly affect their salivary output and therefore their subjective feeling of dry mouth. The feeling of increased caries activity was also higher among smokers in the youngest female sample *(Table 8),* which can be linked to the reduced amount of saliva and therefore, decreased activity of salivary buffer systems. These outcomes are in correspondence with the similar findings of Kakoei et al, who stated that daily smoking could put females in a higher risk for xerostomia and decreased salivation (180). In our study, no other substantial differences were registered among NS, LIS and MHS subjects in other age groups in terms of UWS flow rates. These results are supported by several studies that did not found any correlation between smoking status and UWS or SWS flow rates (43, 58, 170, 172, 182). However, many other publications reported decreased saliva flow rates in association with long-term smoking (161, 162, 171, 173-176). The variability of these results in the literature can be derived from differences in the definition and type of smoking, study methodology or sample selection *(Table 5).*

The strong correlation between the subjectively reported intensity of xerostomia and the reduction in the UWS flow rates has been previously reported by Márton et al in a sample of Hungarian adult population (21). In our current study, similar correlation could have been observed only for NS females *(Figure 18).* It is possible that for smokers with xerostomia, factors other than reduced levels of UWS flow rate, for example increased evaporation, may contribute to their subjective feeling of dry mouth.

Smoking also affects the function of the minor salivary glands. Interestingly, not only the prevalence of xerostomia, but also the PS flow rates were higher among 30-39 year-old male smokers *(Figure 16).* This increase can be attributed either to an initial compensatory mechanism of the palatal glands to xerostomia, or to the high level of tobacco smoke directly stimulating the minor salivary glands in the palatal region,

increasing their production. This is in correspondence with the results of Eliasson et al, who suggested the local irritative effect of smoked tobacco on the minor salivary glands, resulting in a higher water permeability and glandular output (16).

On the other hand, the significantly lower LS flow rates measured among the overall sample of MHS females may induce the feeling of oral dryness. According to the investigations of Eliasson et al, reduced LS flow rates are also correlated with the symptoms of xerostomia (16, 32). This is represented significantly in the increased frequency of xerostomia measured among the 18-29 age group. (163)

Xerostomia can be manifested with or without various sicca symptoms intra- and extraorally, and their appearance may be credited to oral and systemic health factors and age. In our sample, the prevalence of fatigue was significantly higher in male smokers in the 30-39 year-old group *(Table 7),* which can be connected to a number of reasons including higher level of heavy smokers in this age group, increased stress levels, and furthermore, dry mouth. Dysphagia, albeit being a common symptom of diverse oropharyngeal or gastroenterological origin, is reported frequently in xerostomia and salivary dysfunctions including Sjögren's syndrome (21, 197). This symptom was significantly more prevalent in the 60+ age group of male smokers, however, neither the prevalence nor the intensity of xerostomia was affected by the smoking status in this geriatric age group. Edentulousness or inflammation of the oropharyngeal mucosa induced by tobacco smoke can be an explanation for this outcome, although more investigations are needed to support these assumptions. Similarly, increased frequency of dysgeusia was found in 60+ female smokers *(Table 8).* Though, significantly lower PS flow rates were measured among light smokers in this age group as well *(Figure 17),* neither higher prevalence of dry mouth, nor decreased UWS flow rates were experienced. Therefore, most probably, taste disturbances could be derived to the changes in form, quantity and vascularization of the taste buds, caused by the long-term tobacco smoke exposure. It is worth noting however, that current literature evidence about the effects of tobacco use on taste alterations is still scarce (198). In contrast to the findings of Sendecka et al (199), ophthalmological symptoms including xerophtalmia, burning and itching of the eyes were found more commonly in non-smoker female geriatric participants (60+ age group) than in smokers. Though, a meta-analysis by Xi Lu et al revealed, that significant relationship between cigarette smoking

and risk of dry eye syndrome is only experienced in terms of general population, but not when age and genders were adjusted (200). These outcomes suggest that several factors other than smoking may cause ocular dryness symptoms in elderly females. (163)

A possible limitation of our study is that the smoking status of our participants has been assessed only via self-report. However, measurement of salivary cotinine may serve as an objective and therefore more reliable marker of smoking status in future studies (135). Moreover, the duration of smoking was not specified in our sample, therefore the possible differences between long- and short-term effects of smoking on salivary parameters remain controversial. The duration of smoking and nicotine levels of cigarettes can be an influencing factor regarding oral health measures and may negatively affect salivary parameters of current smokers. This assumption is supported by the results of some studies. Petrušić et al. showed that the duration of smoking is associated with decreased UWS and SWS flow rates in elderly smokers (170), while Saputri et al found inverse correlation between nicotine levels of tobacco products, the duration and intensity of smoking and saliva flow rates (173). It is worth mentioning however, that there is an apparent lack of studies assessing the effects of smoking duration, type and composition of tobacco products on salivary parameters, dry mouth and related symptoms. Possible oral health and salivary effects of novel tobacco products like HTPs, or ENDS should also be investigated and compared to traditional tobacco products in the near future (163).

Within those two younger age groups of our sample, where the ratio of smoking subjects was directly proportional to the prevalence of xerostomia, the ratio and intensity of smoking was substantially high. Some authors found similar results, which may be explained by reduced blood supply of the salivary glands, due to the known effects of chronic smoking on the microcirculation at tissue-level (173). Nicotine, the main constituent of cigarette smoke has a short-term stimulating effect on saliva secretion, acting as a sialagogue on nicotinic acetylcholine receptors (165, 172, 201). However, long-term increased plasma levels of nicotine may decrease receptor sensitivity. In addition, experimental studies on animals confirm that either chronic tobacco smoke (159, 160), or solely nicotine exposure (202, 203) induces structural, morphological and functional changes in salivary glands. The detrimental effects of other harmful constituents in tobacco smoke at either systemic or glandular level can be

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an additional explanation for decreased UWS flow rate and higher incidence of dry mouth (161). It is suspected that a threshold exists in the intensity of smoking, where these components reach a certain blood level, leading to the appearance of these systemic symptoms, and reducing the function of salivary glands either at the level of the organs, or at systemic level, affecting their blood supply.

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7. 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.

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8. SUMMARY

Dry mouth is one of the most frequent symptoms affecting the oral health and quality of life of patients. Despite its extensive scientific literature, this topic still has areas that are less investigated in details.

The aim of this thesis was to examine the effects of frequently occurring clinical circumstances like smoking habits, or the use of DAs on the prevalence of dry mouth and sicca symptoms, and the flow rates of UWS and minor salivary glands. Xerostomia and associated sicca symptoms were evaluated using a four-grade questionnaire with 16 questions, UWS flow rate was determined by the spitting method, while minor salivary gland flow rates were measured using the Periotron method.

Our investigations revealed, that the use of gel-type DAs neither had effect on UWS flow rates, nor on the prevalence and intensity of xerostomia and most of the sicca symptoms. On the other hand, a significant decrease was registered in the PS flow rates, which may be explained by the obstruction of the orifices of palatal minor salivary glands. Moreover, DAs tend to increase the viscosity of saliva, therefore patients may feel their saliva thicker or stickier.

Smoking can affect saliva flow rates and dry mouth symptoms in different extent, depending on genders and age groups. Based on our investigations, xerostomia was more prevalent in smoker females in the 18-29 age group and smoker males in the 30-39 age group, moreover, UWS flow rates were decreased in MHS females in the age group of 18-29, compared to non-smokers. LS flow rates were also decreased in the overall group of MHS females; however, higher PS flow rates were registered among MHS males in the 30-39 age group.

In the geriatric age groups (60+), smoker males reported dysphagia more frequently, while dysgeusia was more prevalent among smoker females. The prevalence of ophthalmological sicca symptoms was lower in smoker females.

We can conclude that smoking influences the function of salivary glands, directly and indirectly, depending on gender and age groups, especially in younger ages. This effect is manifested in the decrease of function, or rarely in stimulation. We also showed that the change in salivary parameters depends on the intensity of smoking.

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9. ÖSSZEFOGLALÁS

A szájszárazság egyike a leggyakoribb, a szájüregi egészséget és páciensek életminőségét egyaránt befolyásoló tüneteknek. A témának, kiterjedt irodalma ellenére, napjainkban is vannak kevésbé vizsgált területei. Jelen dolgozat célja annak vizsgálata volt, hogy bizonyos, gyakran előforduló klinikai körülmények, úgymint a teljes lemezes fogpótlások stabilizálására alkalmazott műfogsorrögzítők, valamint a dohányzási szokások hogyan befolyásolhatják a szájszárazság és a társult szárazság-tünetek megjelenését, valamint a nyugalmi kevert és kisnyálmirigyek szekrécióját. A szájszárazság és a sicca tünetek felmérését négy fokozatú, 16 kérdéses kérdőív segítségével, a nyugalmi kevert nyálszekréciót köptetéses módszerrel, a kisnyálmirigyek szekrécióját a Periotron-módszerrel határoztuk meg.

Vizsgálataink alapján megállapítottuk, hogy a gél típusú műfogsorrögzítők használata során a nyugalmi kevert szekréció mértéke, továbbá a szájszárazság és a legtöbb sicca tünet megjelenése és súlyossága nem változott, ugyanakkor szignifikánsan csökkent a palatinalis kisnyálmirigyek szekréciója. Ennek hátterében a kisnyálmirigyek szájadékának obstrukciója állhat. A műfogsorrögzítők megnövelhetik továbbá a nyál viszkozitását, amelynek következtében a páciensek nyálukat sűrűbbnek érezhetik.

A dohányzás nemenként és életkori csoportonként különböző mértékben befolyásolhatja a nyálszekréciót és a szájszárazság-tüneteket. Vizsgálataink alapján a rendszeresen dohányzó 18-29 éves nők, valamint 30-39 éves férfiak körében a szájszárazság szignifikánsan gyakoribbnak bizonyult, emellett a közepesen vagy erősen dohányzó 18-29 éves nők körében a nyugalmi nyáltermelés is alacsonyabb, a nemdohányzókkal összehasonlítva. A labialis szekréció a közepesen vagy erősen dohányzó nők összességénél alacsonyabb, a palatinalis szekréció a 30-39 éves, közepesen vagy erősen dohányzó férfiaknál ugyanakkor magasabb volt.

Az idősebb (60+) korcsoportokban, férfiakban a nyelési nehézség, nőkben az ízérzékelési problémák jelentkeztek gyakrabban, míg a szemészeti szárazság-tünetek ritkábbak voltak a dohányzó nőknél.

A dohányzás tehát direkt és indirekt módon, nemtől és korcsoporttól függő mértékben, de különösen a fiatalabb korosztályokban hatással van a nyálmirigyek működésére, mely leginkább funkciócsökkenésben, ritkább esetben stimulációban nyilvánulhat meg. Kimutattuk, hogy a nyálszekréciós értékek változása függ a dohányzás intenzitásától.

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11. BIBLIOGRAPHY OF THE CANDIDATE'S PUBLICATIONS

11.1. Related publications

1. **Demeter T**, Houman AB, Gótai L, Károlyházy K, Kovács A, Márton K. [Effect of a gel-type denture adhesive on unstimulated whole saliva and minor salivary gland flow rates and on subjective orofacial sicca symptoms]. Orv Hetil 2018;159(40):1637-44.

   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

11.2. 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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