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XEROSTOMIA - DIAGNOSIS AND TREATMENT

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Summary

The aim of this report is to summarize the current state of the evidence from the scientific literature regarding xerostomia. Xerostomia is a subjective complaint-symptom of dry mouth. It may be or may be not associated with objectively measured hyposalivation (reduction of saliva secretion). The variety of local and systemic conditions, treatments and medications alter salivary secretion and composition. The degree of salivary glands dysfunction as well as the accompanying oral morbidity as a complication of dry mouth, make xerostomia therapy complex and often refractory.

Treatment of xerostomia essentially is carried out in regard to the cause and is divided in four main categories: palliative or symptomaic, local and systemic stimulation and prevention of complications. Which category will be applied, depends primarily on whether salivary glands can still produce saliva or not. In patients with residual salivary gland function, the use of salivary stimulans appears to be more beneficial than salivary substitutes. When saliva is absent, treatment remains palliative and must include salivary substitutes. During anticancer radio-and chemotherapy xerostomia is the earliest and the most prominent consequence which significantly affects the quality of life and lead to severe and long-term complications. Because management of xerostomia is rarely effective, prevention is paramount.

Preventive measures should include acting on causes of xerostomia, maintaining salivary function and prevention of complications that arise in already developed xerostomia. Therapy of xerostomia depends on whether salivary glands function is preserved or not and includes local treatment and systemic medications as well as non-medication salivary stimulation such as low level laser, acupuncture and electrostimulation.

***Key words*:** dry mouth; xerostomia; hyposalivation; sialometry; xerostomia/oral complications; xerostomia/etiology; xerostomia/prevention; xerostomia/therapy; artificial saliva; supersaturated calcium phosphate remineralizing rinse.

SALIVA IN HEALTH AND DISEASE

Saliva is essential for maintaining good oral and general health but people usually become aware of its presence and importance when they lost it. Deficiency or absence of saliva cause significant morbidity and lead to the reduction of a person's quality of life (1-3).

Saliva is a complex fluid, mostly composed of water (99%) and in minor part of variety of non-organic and organic substances such as enzymes, hormones, antibodies, antimicrobial constituents and growth factors. Most of the constituents are produced within the glands; others are transported from the blood [1].

Salivary components provide the unique prophylactic, therapeutic and diagnostic properties of saliva. It is well established that the composition of saliva reflects the oral and general health status [2-14]. Many of the compounds found in blood could be also detected in saliva, thus saliva is functionally equivalent to serum in reflecting the physiological state of the body, including emotional, hormonal, nutritional, and metabolic variations [4]. A large number of medically valuable analytes in saliva are being gradually discovered and some of them represent biomarkers for different diseases such as periodontal disease [4], oral cancer [5], breast cancer [6,7], autoimmune diseases [8], viral and bacterial diseases [9], HIV [10], cardiovascular diseases [11] and diabetes mellitus [12].

Due to the combination of emerging biotechnologies, such as molecular diagnostics and nanotechnology, saliva is becoming promising and increasingly valuable source of diagnostic information, e.g. biomarkers for early detection of the disease, and basis for the development of a dynamic and emerging field of salivary diagnostics [4,13,14].

In the mouth, saliva serves many purposes. It initiates and participates in digestion, enchances masticatory function, facilitates swallowing and speech, improves taste, lubricates oral mucosa and enables free movement of oral tissues and maintains mucosal integrity. Saliva facilitates irrigation and cleansing of the teeth and oral mucosa and with buffering capacity saliva protects teeth from demineralization and provides antimicrobial and immunological protection against oral infections in the mouth. Saliva is also critical for retention of and comfort in wearing dentures since the adhesion, cohesion and surface tension are interrelated and they all depend on the presence of saliva [1,2,15].

ASSESSMENT OF SALIVARY FLOW RATE

Saliva is a product of three pairs of major salivary glands, parotid, submandibular and sublingual, as well as of hundreds of minor salivary glands distributed thro-

ughout the oral cavity. Their respective estimated flow rates are as follows: parotid (65%~0.26 mL/min), submandibular (20%-30% ~0.08 mL/min), sublingual (6%~0.03 mL/min) and minor salivary glands (5%~0.03 mL/min) [16].

Salivary flow rates provide essential information about salivary gland function. Saliva can be measured from each major gland or from a mixed sample of the oral fluids, termed whole saliva. To assess salivary gland secretion and oral dryness a variety of methods have been used, from self–reported questionnaires (e.g. Xerostomia Inventory) [17-19], visual analogue-scales (VAS), simple functional measures such as observing if a dental mirror adheres to the buccal mucosa or if a patient can chew and swallow dried biscuits without water to contrast sialography, sialoscintigraphy, sialoultrasonography, biopsy and sialometry of the minor salivary glands [20]. Eliasson et al. [21] performed measuring the volume of residual saliva on mucosal surfaces using filter paper and micro-moisture meter and calculating thickness and Takahashi et al. [22] used mucosal wetness (MW) devices. It has been shown that mucosal wetness measured by micro-moisture meter Periotron ® is a reliable measure of oral dryness and had a positive correlation with unstimulated whole saliva [23].

However, sialometry is the most objective method to assess salivary function and to determine the quantity of both resting and stimulated whole saliva. During sialometry, saliva can be collected by several methods including draining, spitting, suction, and absorbent (swab) method and measured. Whichever technique is chosen for saliva collection, it is critical to use a well-defined, standardized, and clearly documented procedure [20,24].

Normal daily secretion of saliva is approximately á 1L to 1,5 L per day (i.e. 0,5 mL/min -1 mL/min) although flow rate varies depending on diurnal variation, hydration, food intake and many other factors. Large variability in salivary flow rates within and between individuals has been reported, which has impaired the establishment of standard values. In a study of Ghezzi et al. [25] among 36 healthy males and females (18 young, ages 20-38; 18 older, ages 60-77) salivary flow rates varied 27-44% during a 6 hour period, suggesting that a 45% range in salivary flow rates could be considered normal salivary variation, and values below 45% of normal levels could be used to define salivary hypofunction. Salivary flow rate of unstimulated saliva less than 0.1 mL/min (measured for 5 to 15 minutes) and less than 0.5 mL/min for the stimulated salivary flow respectively, is indicative for salivary hyposecretion or hypofunction [26].

HYPOSALIVATION AND XEROSTOMIA

Salivary gland hypofunction or hyposalivation is the condition of having reduced saliva production due to various causes. It usually leads to the subjective complaint of oral dryness which is termed xerostomia. The term xerostomia comes from the Greek word *xeros* (dry) and *stoma* (mouth), which means dry mouth. Dry mouth is one of the most common and most unpleasant symptoms for which patients often seek help from a dentist or physician [18].

Dry mouth is a subjective feeling, not a distinct disease. Xerostomia is not a synonym for hyposalivation since it may also occur with the changes in the quality of saliva, while the amount of saliva stay unchanged. This is the reason that people sometimes complain of dry mouth but have proper salivation [3]. Therefore, a patient complaining of dry mouth cannot automatically be assumed to have salivary dysfunction, while oral dryness may have many causes [20]. Any individual may experience xerostomia with or without hyposalivation, experience hyposalivation with or without xerostomia or may have an average salivary flow and normal sensation [17].

Oral dryness is one of the most common and most unpleasant oral symptom which adversely affects all oral functions and compromise oral health in any affected person. It leads to numerous oral sequelae including mucosal dryness, difficulty in chewing, swallowing and speaking, burning and pain of oral mucosa, propensity to damage of oral mucosa and infection, increased fungal infection, demineralization of teeth and increase in caries, dysgeusia, halitosis and difficulty in wearing dentures. Therefore, for the maintaining good oral and general health, saliva should be secreted in an adequate quantity and quality [27].

PREVALENCE OF XEROSTOMIA

Reports of the prevalence of xerostomia in general population are not conclusive and vary, ranging from 0.9% to 64.8%, mainly due to the small numbeof studies in population-based samples [28].

However, the prevalence reaches almost 100% in patients with Sjögren's syndrome and those who are receiving radiation therapy for head and neck cancer [29].

It has been shown that the prevalence increases with age and that xerostomia is more prevalent in postmenopausal women compared to men [16,30]. It is estimated that about 30% of the population older than 65 suffer from xerostomia [29]. Although previous opinion that salivary function declines with aging process, it is now accepted that salivary flow as well as salivary constituens are both age-stable in the

absence of major medical problems and medications. Therefore, increasing age does not by itself cause hyposalivation [31].

As shown in the study of Murray Thomson W et al. xerostomia may be also a problem for a sizeable minority of young patients in early thirties, particularly those taking antidepressants who had 22 times higher risk for xerostomia [32].

Since there is no evidence that xerostomia is likely to result from the aging process alone it can be concluded that the condition is a side-effect of various diseases and the drugs used to treat these diseases [29,33].

CAUSES OF XEROSTOMIA

Xerostomia has a variety of possible causes [20]. In general, causes may be grouped into two categories [34]:

a) primary or direct causes comprise conditions that directly affect salivary glands and cause decreased salivary production [35]. These conditions include: Sjögren's Syndrome; salivary gland diseases; endocrine conditions, such as type 1 and type 2 diabetes mellitus as well as gestational diabetes; thyroid disease; adrenal conditions; renal or hepatic diseases; infections with hepatitis C virus and HIV.

Sjögren's Syndrome (SS) is the most common autoimmune disease characterized by inflammation of the exocrine glands and may occur independently (as primary Sjögren's syndrome or Sycca syndrome limited to the eyes and mouth, SS-1) or in association with other autoimmune diseases such as rheumatoid arthritis, systemic sclerosis or systemic lupus erythematosus (secondary Sjögren's syndrome that affets connective tissue, SS-2). The prevalence of Sjögren's syndrome is 1% to 4% in older adults and is more common in postmenopausal women [36].

The study of Pijpe et al. [37] showed that duration of Sjögren's syndrome is in positive correlation with severity of xerostomia; patients with Sjögren's syndrome with longer disease duration are characterised by severely reduced secretions of, firstly the parotid, and then submandibular and sublingual gland. Authors conclude that these observations are relevant for identifying patients who would most likely benefit from intervention treatment.

When an autoimmune disease is suspected, a minimally invasive technique of minor salivary gland biopsy of the lower lip should be made with the determination of serum antibodies [38].

In Sjögren's syndrome the progressive lymphocytic infiltration gradually destroys the secretory acini of the major and minor salivary glands which results in hyposalivation and finally in xerostomia. Another explanation for the loss of glandular function may be related to an inhibition of nerve stimuli of the glands [39].

The hypofunction of egzocrine glands causes dryness of mucosal surfaces, most noticeable of the mouth and eyes [36].

b) Secondary or indirect causes of xerostomia are conditions of which hyposalivation or oral dryness are side effects.

Xerostomia and salivary gland hypofunction are major complications of radiation- therapy (RT) or chemotherapy. Head and neck radiation RT is employed as a primary, concomitant or adjuvant treatment modality for primary and recurrent tumors of the head and neck region. Irradiation and cytostatic drugs lead to sialoadenitis which in turn may lead to irreversible damage of acinar cells of major and minor salivary glands and result in hyposalivation and permanent xerostomia [1]. Long-term morbidity in patients receiving combined radiation and chemotherapy is significant because of salivary gland hypofunction, radiation-induced xerostomia, mucositis and severe dysphagia [20].

Although radiotherapy was earlier considered the most common cause of salivary gland hypofunction and xerostomia, in recent years medications have emerged as the most common cause, particularly in elderly people. It has been shown that among the most commonly prescribed drugs 80% of them cause xerostomia with more than 500 medications causing an adverse effect of dry mouth [2,16,20,40].

Xerostomic drugs can be found in 42 drug categories and 56 subcategories [33]. (*Table 1*). The most common medications causing hyposalivation are those with anticholinergic activity, sympatomimetics and benzodiazepines [2]. These are also the most commonly prescribed medications in geriatric population. The risk for xerostomia will increase the synergistic effects of xerogenic medications, multiple medications (polypharmacy), higher dose of medication and the time of starting the medication. This is the main reason that the prevalence of medication-induced xerostomia is highest in the elderly.

Salivary gland hypofunction and chronic xerostomia can also be side effect of a variety of autoimmune disorders (other than Sjögren's syndrome), such as rheumatoid disorders, scleroderma, mixed connective tissue disease and systemic erythematous lupus [41], advanced stages of HIV infection [42], endocrine disorders, such as uncontrolled diabetes and thyroid and adrenal gland diseases [43], graft versus host disease (GVHD) following allogeneic [44], or autologous hematopoietic stem cell transplantation [45], malnutrition and protein deficiency in anorexia and bulimia (20), chronic or neurogenic pain, smoking tobacco and cannabis [46], consumation of drugs of abuse [47], drinking alcohol or caffeine-containing fluids, sleeping with open mouth or mouth breathing at any time, such as during nasal congestion and using inhalers, iatrogenic procedures and regimens, (anesthesia, intubation/ ventilator-assisted breathing, intravenous feeding etc) [1,2,16,34].

Dehydration of the organism can secondarily affect salivation, and changes in the quantity of water in the body can affect the wetness of oral mucosa which may create a feeling of dry mouth [2,20,29,34]. The feeling of dry mouth can occur also due to the change in cognitive abilities of the central nervous system following a cerebral vascular accident (stroke) (48) and sensory disturbances in the mouth. Alterations in autonomic innervation of salivary glands with predominant sympathetic stimulation, during episodes of acute anxiety or stress, cause changes of salivary composition that creates sensation of oral dryness. There are also psychological conditions that lead to feeling of oral dryness such as depression and insomnia as well [2, 29, 33, 34, 48].

Table 1. Drugs associated with dry mouth (2)

Drugs that directly damage salivary glands
Cytotoxic drugs
Drugs with anticholinergic activity
Anticholinergic agents: atropine, atropinics and hyoscine
Antireflux agents: proton-pump inhibitors (e.g., omeprazole)
Central-acting psychoactive agents
Antidepressants, including tricycliccompounds
Phenothiazines
Benzodiazepines
Antihistamines
Bupropion
Opioids
Drugs acting on sympathetic system
Drugs with sympathomimetic activity (e.g., ephedrine)
Antihypertensives: alpha-1 antagonists (e.g., terazosin and prazosin); alpha-2 agonists (e.g., clonidine); may reduce salivary flow beta blockers (e.g., atenolol, propanolol), which also alter salivary protein levels
Drugs that deplete fluid
Diuretics

RADIATION-INDUCED XEROSTOMIA

Xerostomia is one of the most common complications during high-dose radiation therapy (RT) for head and neck cancer (HNC) and has a significant impact on

quality of life, requireing careful planning of long-term dental and oral care. Standard RT for advanced head and neck cancer involves fractionated doses of 10 grays (Gy) weekly (2 Gy daily on 5 consecutive days) over 5 to 7 weeks to a total dose of 50 to 70 Gy. Parotid glands exposed to doses of greater than 60 Gy sustain permanent damage with no recovery in salivary hypofunction with time [20].

Radiotherapy (RT) of the head and neck region causes both acute and long-term complications on salivary gland tissue and function, as well as radiation-induced compositional salivary change [49].

Acute effects of radiation on salivary function occurs during the first week of RT and deterioration continues until flow rates are barely measurable at 6 to 8 weeks. Frequently seen acute accompanying oral side effects include mucositis, dysphagia, erythema and desquamation of oral mucosa. *Late complications* are result of cronic injury on exposed tissue; mucosa, vasculature, salivary glands, connective tissue and bone. The type and severity of these changes are related directly to total dose administered, fraction size and duration of the treatment as well as on volume of irradiated tissue. *Qualitative changes in saliva* include increased viscosity, increased organic component, altered pH, decreased transparency, and yellowbrown discoloration [50].

Radiation-induced xerostomia starts in the first week of RT during which salivary flow decrease for 50%-60% and after 7 weeks of RT diminishes to aproximately 20% [51]. Salivary function continues to decline for up to several monts after RT [50].

The assessment of the severity of xerostomia in patients with head and neck cancers after radiotherapy and its effect on quality of life (QoL) over a period of 6 months, in a study of Kakoei et al. [52] showed that QoL significantly worsened with increased time along with the severity of xerostomia which increased significantly. With each milliliter decrease in saliva secretion, the QoL score decreased 2.25%. With one score increase in xerostomia, from the QoL mean score there was a 1.65% decrease. [52].

Even though, some recovery is possible after 12 to18 months after RT, with increase in salivary flow up to 32% from 1 to5 years after treatment [53], depending on the dose received and volume of the gland tissue irradiated, xerostomia develops into an irreversible, life-long health problem that significantly reduces quality of life for the patients. It was also shown when multiple daily treatments are given in small fractionated doses (<1,8-2 Gy) this does not increae the incidence of xerostomia [20].

It is obvious that the quality of life in patients who underwent radiotherapy in the head and neck region is strongly influenced by xerostomia and all its consequences. Patients usually suffer from dry, vulnerable and painful oral mucosa, have difficulties in all oral functions (chewing, swallowing and particularly speech), per-

ception of taste is altered or even partially lost. The risk for dental caries increases secondary to number of factors: shift to cariogenic flora, reduction of salivary pH, and loss of mineralizing components. The reduction in salivary flow may contribute to the risk of fungal infection and osteonecrosis of the mandible. All these secondary effects of radiation-induced xerostomia contribute to the so-called *xerostomia-syndrome* [54].

COMPLICATIONS OF XEROSTOMIA

Dry mouth has multiple oral health consequences and affects quality of life (*Table 2*) [33]. Patients with xerostomia may be asymptomatic without complaints, or more frequently, complain of dry mouth and develop various complications. Patients usually experience difficulties while speaking, chewing, swallowing (dysphagia) and wearing dentures [1-3,15,20,34].

Oral mucosa is dry and sensitive, prone to injuries, fungal infection and inflammation, painful with burning sensations, taste is altered and halitosis is present. In patients with Sjogren's syndrome in which exocrine glands and the connective tissue is affected patients complain about the dryness of the eyes. The parotid glands become visibly enlarged. These initial changes may precede clinical evidence of mucosal changes or measurable reduction in salivary gland function [36].

In the *patient with dentures* and insufficient saliva, the lack of lubrication can result in traumatic ulcerations of the mucosa, and increased susceptibility to oral fungal infection, candidosis. Various treatment modalities have been suggested in the literature to overcome the problem of xerostomia in complete denture patients. Incorporating reservoirs containing salivary substitutes into dentures is one of these treatment modalities. Dabas et al. [55] described new split denture technique which resulted in a reservoir denture that provided good lubrication of the oral tissues, can be easily cleaned by the wearer and can be produced from routine denture materials. In addressing such issues Murthy et al. [56] describes a new method by using flexible complete denture construction in radiation induced xerostomic patient with minimal tissue damage during and after denture construction procedures.

Lack of saliva increases the risk of developing *caries* (particularly at the cervical and root areas of the teeth), enamel erosions and periodontal diseases [1,2,33]. Study of Yeh et al. [57] provided the evidence that hyperglycemia in combination with reduced saliva in a model of type1 DM leads to decreased enamel mineralization/matrix proteins and predisposes to excessive wearing and decay. Importantly, hyperglycemia adversely affects enamel matrix proteins and pulp repair. Early detection and treatment of hyperglycemia and hyposalivation may provide a useful

strategy for preventing the dental complications of diabetes and promoting oral health in this population.

Oral fungal infection (candidosis) and enlargement of salivary glands from sialadenitis are seen commonly in patients with moderate-to-severe salivary gland hypofunction [2,20]. The risk of infection is increased in people who wear dentures, smokers and diabetics; in patients with Sjögren's syndrome and connective tissue diseases treated with corticosteroids or other immunosuppressants. These drugs also contribute to candidiasis because they reduce the natural resistance of the mucosa. Lack of saliva creates difficulties in wearing dentures while promoting the development of denture stomatitis [1,2].

Table 2. Consequences and complications of xerostomia

Dry mouth
Thirst
Difficulties in oral function
Dysphagia
Taste disturbances
Altered speech
Difficulties wearing dentures
Mucosal changes
Injuries of oral mucosa
Oropharyngeal burning
Mucus accumulation
Food retention in the mouth
Plaque accumulation
Hyposalivation-associated caries
Changes in oral microbial flora
Oropharyngeal infections
Fungal infections
Nocturnal oral discomfort

TREATMENT OF XEROSTOMIA

Treatment of xerostomia depends on the cause and the degree of damage of the salivary glands, thus it comprises etiologic, stimulative, symptomatic or palliative approach. Current therapies include saliva substitutes and saliva stimulans (sialagogues). In cases when there is still some residual salivary function it was shown that saliva stimulans (local or systemic stimulation of secretory gland) produce greater relief than saliva substitutes. When salivary glands are irreversible dama-

ged and without capability to produce saliva, as is in the cases of head and neck radiotherapy or advanced systemic disease (e.g. Diabetes mellitus, Sjögren sy) palliative treatment remains the option.

When salivary function is preserved stimulation of salivary glands aimed to increase the salivary output, include:

1. Local stimulation

The combination of chewing and acidic taste, as provided by chewing gums or solid food or fruits, preferentially acidic (apple, pinneapple, carrots etc.) can be very effective in stimulating saliv flow for patients who have remaining salivary function. Patients with dry mouth must be told not to use sweets, sweetener in food and drink and various other sugar products due to the increased risk for dental caries. *Acidic soft drinks* are an increasing source of dental erosion as is *excessive intake of white wine*

The use of laser infrared light of 904nm (low level laser therapy, LLLT) on salivary glands in the treatment of xerostomia proved to be not only stimulative but also regenerative in nature [58].

Use of acupuncture in the treatment of xerostomia have focused earlier mainly on a curative approach when the salivary gland tissues are already damaged and xerostomia is present. Recent study by Braga et al. [59] showed that acupuncture can be used efficiently as preventive approach in the management of patients with head and neck cancer undergoing RT. Although preventive acupuncture approach did not prevent the oral sequelae of RT completely, it significantly minimized the severity of radiation-induced xerostomia.

Electrical stimulation has also been used as a therapy for salivary hypofunction but has been inadequately investigated clinically. A device that delivers a verylow-voltage electrical charge to the tongue and palate has been described although its effect was modest in patients with dry mouth [16].

2. Systemic stimulation

Any agent that has the ability to influence salivary glands to increase production of saliva is termed a *secretagogue*. Among 24 examined agents only four sialagogues have been examined extensively in controlled clinical trials; these are bromhexine, anetholetrithione, pilocarpine hydrochloride (HCl), and cevimeline HCl, but with mixed results [20].

The mechanism of action for salivary stimulation of a mucolytic agent bromhexine and anetholetrithione is not fully understood. No proven benefit to salivary function

has been shown for bromhexine yet it may stimulate lacrimal function in patients with Sjögren's syndrome although this is controversial. It has been suggested that anetholetrithione may up-regulate muscarinic receptors and increased saliva flow in patients with mild salivary gland hypofunction, but was ineffective in patients with marked salivary gland hypofunction.

Pilocarpine HCL is the best studied sialagogue. As a parasympathomimetic agent it causes stimulation of cholinergic receptors on the surface of acinar cells. Pilocarpine increases salivary output, stimulating any remaining gland function. Current indications are for patients following radiotherapy and for those with Sjögren's syndrome. In doses of up to 15 mg/day, it increases secretion of saliva, and for optimal results patients should be treated during 8-12 week. After the administration of pilocarpine, salivary output increases rapidly, usually reaching a maximum within 1 hour. The best-tolerated doses are those of 5.0 to 7.5 mg, given three or four times daily. The duration of action is approximately 2 to 3 hours. [20]. Pilocarpine may be used as maintenance therapy during longer periods and as a salvage therapy for salivary gland function during RT. Stimulation of the salivary glands during radiation therapy has been suggested as a possible means of reducing damage to the glands.

The synergistic effect of anetholetrithione in combination with pilocarpine was shown [20]. The mechanism of action of anetholetrithione may be to increase the number of cell surface receptors on salivary acinar cells and pilocarpine stimulates the receptors thus, in combination, these drugs have synergistic effect [20]. Pilocarpine is contraindicated in patients with pulmonary disease, asthma, cardiovascular disease, gastrointestinal diseases and glaucoma [20].

Cevimeline is another parasympathomimetic agonist that has been recently approved for the treatment of oral dryness in patients with Sjögren's syndrome. Due to similar side effects as to those of pilocarpine it must be prescribed with caution.

3. Symptomatic approach

Palliative treatment remains as only choice in cases when there is no functionally salivary tissue present as is in the disorders of irreversible damage of salivary secretory cells (such as in radiation-induced xerostomia). Most remedies available today for patients with dry mouth are only symptomatic and aimed to avoid or alleviate discomfort and pain as well as to prevent complications of xerostomia.

A number of saliva substitutes have been developed for the palliative care of patients with salivary hypofunction to supplement the saliva and alleviate oral symptoms of dryness. These agents, in liquid, spray, or gel form have moistening and lubricating properties, and their purpose is to provide prolonged wetness of the oral mucosa. Commercial artificial saliva should resemble normal saliva in its

biophysical properties. Preetha and Banerjee [60] compared artificial saliva based on carboxymethylcellulose and the xanthan gum and found that the examined substitutes fall short of required biophysical criteria and modifications are required to improve them.

The advantages of saliva substitutes or artificial saliva are in the coating and moisturizing oral mucosa and teeth, and disadvantages are their short-term activity without preventive effect on oral tissue. Commercialy available alcohol containing oral rinses should be avoided due to their drying effect. As shown in the study of Gil-Montoya et al. [61] the evaluated mouthwash and oral gel as saliva substitutes may improve some subjective and clinical aspects in elderly individuals with dry mouth, although a placebo effect cannot be entirely discarded.

Patients with irreversible xerostomia should be instructed to maintain proper hydration of the oral cavity by taking plenty of fluids throughout the day and keeping the mouth moist, and using artificial saliva preparations. Frequent sips of water throughout of day and during the meals will facilitate chewing and swallowing and may also improve the taste of food. The use of bedside *humidifiers* may lessen discomfort of dryness, especially at night during sleep when any residual salivary secretion is physiologically decreased. Patients should avoid any caffeinated drinks (tea, coffee) and soft drinks and alcohol, as well as smoking and alcohol-containing mouthwases to prevent further desiccation. Special *denture adhesives* for individuals with xerostomia also may provide some retention aid for removable dentures. Periodontal diseases may be prevented by using an *alcohol-free, antibacterial mouth rinse*, such as *chlorhexidine*.

Professional *oral hygiene* procedures and instructions in home care as well as diligent and meticulous oral hygiene are crucial to reduce the bacterial load in the oral cavity and thus the risk for halitosis and oral infection. Oral care is also important for the patient's general health (*Table 3*).

PREVENTION OF XEROSTOMIA

There are several options how to prevent development of xerostomia or decrease its severity:

a) Acting on the cause of xerostomia – possible adjustment of medications and possibly amelioration or elimination of the underlying cause

In the case of drug induced xerostomia - it is important to discuss possible prescription of alternative drugs with less desiccative side effects, decreasing the dose of prescribed drug or the number of xerogenic drugs (particularly in the case of poypharmacy).

Table 3. Treatment of xerostomia by dental professionals and recommendations to patient [34]

All patients with xerostomia	Actions by Dental Care Provider	Recommendations to Patients
	Conduct careful medical history	Proper oral hygiene
	Carefully record ALL medications (type, dosage, frequency, start date)*	Do not brush teeth immediately upon wakening when thin surface layer of enamel is slightly softened due to acidic activity and lack or liquid intake during sleep
	Inquire regarding compliance with medicine regimen prescribed	Sip water frequently
	Conduct thorough oral examinations and keep in mind all possible underlying causes deducted from any source,	Rinse mouth with plain water during eating & drinking Anti-caries mouth rinse without alcohol
	Casual conversation with patient:	Anti-caries xylitol-containing products
	- Medical history	Anti-periodontal-bacterial mouth rinse without alcohol
	- Medication use	Avoid alcoholic and caffeinated beverages
	- Oral signs, symptoms, lesions,	Discontinue tobacco smoking,
	- Dentures	Use a humidifier at night
		Use salivary flow stimulants: sugarless gum, hard candy, or lozenges
		Use palliative saliva substitutes, Such as: liquids, gels, sprays

Decreasing dosage of psychopharmaca could be attained by psychotherapy or adding a light exercise regimen to the patient.

For a patient with uncontrolled type 2 diabetes, regular glycemic control (using modifications of diet, exercise, and possibly oral anti-diabetic medication or insulin), may eliminates the hypo-salivation. Xerostomia being caused by uncontrolled diabetes, can be cured by bringing diabetes under control.

b) Maintaining salivary function - Certain patients with hyposalivation may benefit from administration of medications that stimulate salivary output (sialagogues such as pilocarpine or cevimeline if there is no contraindications for these medications)

In a 30-week longitudinal study of women with Sjögren's Syndrome, daily doses of 400 mg hydroxychloroquine were found to increase unstimulated, but not stimulated, salivary flow rate. Hydroxychloroquine is classified as an anti-malarial medication and is also used to decrease inflammation in systemic lupus erythematosus as well as rheumatoid arthritis and Sjögren's Syndrome (all rheumatic disorders) [62].

PREVENTION OF RADIATION-INDUCED XEROSTOMIA

Several strategies have been developed to avoid radiation-induced salivary dysfunction without compromising oncologic treatment. They include parotid gland sparing RT, cytoprotectants and surgical salivary gland transfer. However, each of these approaches have some limitations.

a) Parotid-gland sparing radiotherapy. This therapeutic approach focuses the radiation beams to the target tumour tissue with aim to avoid unnecessary radiation of sourrounding salivary gland. This was enabled by the implementation of 3-dimensional (3D) conformal RT (3D-CRT) and intensity modulated RT (IMRT) techniques in clinical practice. IMRT is based on computer-optimized treatment planning and a computer-controlled treatment delivery system. The computer-driven technology generates dose distributions that sharply conform to the tumor target while minimizing the dose delivered to the surrounding or contralateral normal gland tissues. Multiple studies have demonstrated that the parotid gland sparing effect of this treatment modality resulted in significant objective and subjective improvement of xerostomia. However, in patients who have tumours that originate from the midline or that cross the midline, or in patients with contralateral lymph node metastais it is not possible to use this technique [54,63].

b) Cytoprotectants - several agents have been developed to protect normal tissue against cytotoxic effects of RT and/or chemotherapy among which the most investigated is radioprotector amifostine. In active form it enters into the cells and nuclei where it acts as a scavenger against free radicals thus preventing radiation damage of DNA. Evidences from the recent studies show cytoprotective effect of amifostine:
- on the salivary gland during RT (amifostine is effective in preventing acute and late xerostomia in head and neck cancer patients);
- on oral health (unchanged DMFT (Decayed-Missing-Filled Teeth) index 1 year post-RT; trend to decreased incidence of oral candidiasis during amifostine cytoprotection; together with reduced xerostomia, amifostine may concomitantly help delay the onset of severe mucositis) [63].

However, a high rate of serious adverse events, including hypotension and gastrointestinal disturbances, results in discontinuation of amifostine and limits its use.

c) Salivary gland transfer – this technique propose surgical transfer of 1 submandibular gland to the submental space outside the path of radiation. This procedure has limitations: if patient refuse surgical treatment; if patient is not planned to receive postoperative RT; and if submental space is involved with tumour [64].

PREVENTION OF XEROSTOMIA COMPLICATIONS

Prevention of complications is carried out in all patients with dry mouth, and aims to prevent development of caries, oral fungal infection and stomatitis.

Caries

Fluoride preparations for control of dental caries should be prescribed to all individuals who have natural teeth. Patients with significant xerostomia should be closely monitored for the development of dental caries, which may be prevented by the daily use of *1.1%* sodium fluoride (NaF) dentifrice or gel. Application of fluoride should be adjusted accordingly to the severity of the gland dysfunction, the degree of development of caries and the underlying disease or the cause that led to the dryness of the mouth. Studies have demonstrated that fluoride preparations alone are not sufficient to prevent caries and remineralization of damaged teeth, particularly in patients with dry mouth who underwent radiation therapy [65-67]. A study evaluated the use of *calcium phosphate supersaturated remineralizing rinse* in

tandem with 1.1% NaF for daily use in patients at high risk for caries due to xerostomia [67]. Artificial saliva, supersaturated remineralizing rinse based on calcium and phosphate ions (Caphosol® ,EUSA Pharma, USA) was developed to treat patients on radio-and chemotherapy and to prevent the development of mucositis [65].

In a xerostomic group, a regimen of Caphosol® used daily with 1.1% sodium fluoride dentifrice, and fluoride varnish treatments every 3 months was effective in preventing the progression of both root and coronal caries and significantly increased net reversals or remineralization [66,67].

Fungal infections (candidosis)

Treatment of oral candidosis with topical antifungal medications from polyenic group such as nystatin and amphotericin B proved to be successful at the beginning of the therapy. During the treatment, adverse effects of drugs were observed in some patients, and in patients treated with anticoagulant drugs and antidiabetics the use of antifungal drug myconazole is contraindicated. In xerostomic patients after cesation of the antifungal therapy relapses of oral infection are common [20]. A combination of antifungal drugs and application on the surface of dentures was described in patients with dentures and denture stomatitis. Other studies have shown that pretreatment isolates of C. albicans with polyenic antifungals reduces its ability to adherence to denture acrylic surfaces, and also prevents the adhesion of Candida to buccal epithelial cells [20].

In recent study the effect of supersaturated solution of calcium and phosphate (Caphosol®) on oral yeast infection in patients with dry mouth was investigated. Supersaturated solution of calcium and phosphate increased the amount of saliva and significantly reduced oral fungal infection, in comparison with a solution of sodium bicarbonate. Compared with myconazole and in combination with it, no significant differences were found [68].

Dentures wearing

In dentures wearing patients wetting dentures before placing them into the mouth and spraying protheses with artificial saliva before applying denture adhesives [15] will help in reducing the discomfort. Use of salivary substitutes (e.g.marshmallow tea) and artificial saliva will help in adhesion, stability and denture retention. Wetting dentures before meals and taking more fluids during mealtime will aid in mastication and swallowing [1-3,20,24,34]. Adapted denture fabrication (split denture technique and flexible complete denture construction) will help in alleviating dyscomfort [55,56].

CONCLUSION

Oral health and function depend on salivary function. Although xerostomia is common in elderly patients it is frequently not assessed and managed on time. Due to serious complications of dry mouth which affects oral and general health the quality of life of these patients is decreased. Therefore, the assessment of salivary gland hypo-function, early recognition, prevention and treatment of xerostomia and its complications will need to be incorporated into everyday clinical dental practice.

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Sažetak

Kserostomija – dijagnostika i liječenje

Kserostomija je subjektivan osjećaj suhoće usta koji nastaje zbog smanjenog lučenje sline ili hiposalivacije. Smanjeno lučenje sline je posljedica oštećenja žlijezda slinovnica koje uzrokuju određeni sustavni poremećaji, brojni lijekovi i liječenje zračenjem tumora u području glave i vrata. Raznolikost uzroka hiposalivacije, stupanj oštećenja slinovnica te popratni oralni morbiditeti kao komplikacije suhoće usta, čine terapiju kserostomije složenom, a često i refraktornom.

Liječenje kserostomije ovisi o uzroku i stupnju oštećenja slinovnica i obuhvaća simptomatsko liječenje, lokalnu i sustavnu stimulaciju žlijezda slinovnica i prevenciju komplikacija. Izbor liječenja ovisi o stanju slinovnica i mogućnosti stvaranja sline. U osoba u kojih je funkcija slinovnica očuvana, provodi se stimulativna terapija dok se u osoba u kojih su slinovnice ireverzibilno oštećene i koji nemaju sline provodi nadomjesno liječenje umjetnom slinom i simptomatsko liječenje. Kserostomija je jedna od prvih i teških komplikacija liječenja zračenjem raka glave i vrata i kemoterapije.

Prevencija kserostomije obuhvaća djelovanje na uzrok kserostomije i održavanje salivarne funkcije i prevenciju komplikacija. U prevenciji radijacijske kserostomije razvijeno je nekoliko strategija liječenja koje uključuju sofisticirane kirurške tehnike, citoprotektivna sredstva i posebne tehnike ozračivanja pri čemu se štedi tkivo slinovnica a istodobno ne ugrožava onkološko liječenje. Međutim, ovi preventivni postupci ne mogu se primjeniti u svih pacijenata pa u konačnici jedini izbor je liječenje suhoće usta. Dostupni načini liječenja kserostomije obuhvaćaju više kategorija, a izbor terapijskog postupka ovisi o tome da li slinovnice mogu stvarati slinu ili ne. U nemogućnosti stvaranja sline primjenjuju se nadomjestci sline i umjetna slina. Terrapija kserostomije uz lokalnu i sustavnu terapiju uključuje i fizikalne metode stimulacije slinovnica kao što su laser, akupunktura i elektrostimulacija.

Ključne riječi: suhoća usta; kserostomija; hiposalivacija; sijalometrija; kserostomija/oralne komplikacije; kserostomija/etiologija; kserostomija/prevencija; kserostomija/liječenje; umjetna slina; prezasićena remineralizirajuća otopinakalcija i fosfata.

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