Chapter 2

Xerostomia: An Update of Causes and Treatments

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Abstract

Xerostomia or dry mouth sensation is considered a complex condition that affects several stomatological functions that drives to the detriment of the quality of life of individuals who suffer from it. Often, xerostomia is accompanied by a decrease in salivary flow or hyposalivation, and this condition leads to oral health problems such as dental caries, candidiasis, and mucosal complications. Currently, the diagnosis and therapeutic methods for this condition are varied and it is difficult to achieve favorable results in all cases, since the etiology seems to be multifactorial where both local factors and systemic conditions would participate. This chapter presents, in a concise shape, the relevant data about etiology of xerostomia, such as age, autoimmune diseases, systemic diseases, infectious diseases, neuropathic complications, psychogenic factors and therapeutically consumption of drugs among others, and the current available treatments.

Keywords: xerostomia, etiology, diagnosis, clinical manifestation, treatments

1. Introduction

Xerostomia or dry mouth sensation is considered a complex condition that affects several stomatological functions and drives to the detriment of the quality of life of individuals who suffer from it. Often, xerostomia is accompanied by a decrease in salivary flow or hyposalivation with consequences such as oral lesions, alterations of taste, feeling of thick saliva, chewing problems, dental caries, dental demineralization, periodontal disease, salivary gland infection, cervical caries, fungal infections, and others [1]. Currently, the diagnosis and therapeutic methods for this condition are varied and it is difficult to achieve favorable results in all cases, since the etiology seems to be multifactorial where both local and systemic factors would participate [2–5]. Although xerostomia may occur frequently in the general population, clear and defined tools for diagnosis and treatment are still needed. Today, patients suffering from xerostomia visit numerous health professionals to solve this complex condition

that limits many functions of day-to-day life, and often does not find response or effective treatment. Regards the complexity of xerostomia and its importance in dental practice, this chapter reviews the relevant data about etiology, diagnosis, consequences, and the current available treatments to this condition.

2. Definition and evaluation

Xerostomia (dry mouth, oral dryness, and mouth dryness) is the dryness of oral cavity and can be caused by lower salivary flow or the complete lack of saliva [6]. Based on the etiology, the xerostomia can be classified as true xerostomia (xerostomia vera, primaria), caused by the malfunction of the salivary glands and pseudo xerostomia or symptomatic xerostomia (xerostomia spuria, symptomatica), which is described as the subjective sensation of oral dryness, despite normal secretory function of the salivary glands [7]. The xerostomia, as a symptom, is more common in older populations, but its causes are not related to aging. It has been shown it is related to some specific diseases, drugs, or therapies associated [8]. The prevalence of xerostomia varies from 13 to 28% in older populations, and increases up to 60% in patients living in long-term care facilities [9–11].

Xerostomia, although not considered a disease, may imply the presence of changes directly related to the salivary glands or be the result of systemic diseases [12]. In order for a suitable treatment to be instituted in a timely manner, it is important to carry out a thorough evaluation of the patient with the dry mouth condition, determining, if possible, the cause of the xerostomia. The patients with xerostomia, who are present with salivary gland hypofunction, are at risk of many oral complications; the persistence over time of low rates of salivary secretion causes changes in the oral environment and affects the hard and soft tissues of the mouth. Xerostomia can also be a consequence of systemic disease and its recognition is a valuable aid in the treatment [13]. It is a potentially debilitating condition that can affect up to 1 in 5 oncology patients, with higher prevalence in women and the elderly. There is evidence that the use of multiple medications may increase the risk of xerostomia [13]. This symptom represents a strong impact on the quality of life of the people affected. Over 87.6% of people with xerostomia were worried if they had to spend the rest of their lives with the dry mouth sensation [14]. The dry mouth (xerostomia) sensation has a higher incidence on individuals over 60 years old (12–40%), up to three times higher than on younger adults. It does not seem to be directly related to the normal aging process, but to some chronic diseases or treatments [15, 16]. It is estimated that about 20–30% of the 20-year-old population has xerostomia and the cause may be the increased use of antidepressants, since xerostomia is associated with depression and anxiety. In United States, up to 40% of the 20-year-old population may have xerostomia. The high consumption of antidepressants and other medications, as well as alcoholic beverages and tobacco may explain the increase in people with this condition [17].

Although xerostomia, as a symptom, entails many problems for patients who suffer from it, especially in relation to their quality of life, the decrease in the amount of saliva due to its multiple properties is what brings more consequences at the oral level. Saliva is composed of 99% water and electrolytes. The rest of the composition is organic and includes immunoglobulins,

digestive enzymes such as amylase and lipase, and antibacterial and antifungal enzymes, as well as mucins [14]. Ninety-three percent of its volume is secreted by the major salivary glands and the remaining 7% by the minor glands. Saliva production is controlled by the autonomous nervous system, mainly by parasympathetic nerve signals [18]. Saliva is very important for the preservation of general and oral homeostasis. It has a participation in digestives functions, cleaning, sense of taste, oral mucosa hydration, and defense of teeth trough pH control and its remineralizing potential. In addition, it has antimicrobial properties and controls the composition of oral microbiota by its antibacterial, antiviral, and antifungal capacities [14]. A summary of the Saliva components and functions can be seen in **Table 1**.

Several short and long-term conditions can interrupt salivary secretion, leading to xerostomia. Xerostomia can thus result from three basic causes:

(1) Factors affecting the salivary center: psychological problems (stress and anxiety), Parkinson's disease, Alzheimer's disease (changes in the ability to perceive oral sensations), menopause, and others;

(2) Factors that alter nerve stimulation of saliva: encephalitis, brain tumors, smoking and dehydration (resulting from the deficiency of water intake, vomiting, diarrhea and polyuria), as well as the use of some drugs, including antihistamines, opioids, antidepressants, antiepileptics, anxiolytics, anticholinergics, antimuscarinics, and others;

(3) Alterations in salivary gland function as a consequence of obstruction, infection (sialodenitis), glandular tumors, calculi (sialolithiasis), autoimmune diseases (Sjögren's syndrome-SS-, rheumatoid arthritis, uncontrolled diabetes mellitus and systemic lupus erythematosus), and chemotherapy or radiotherapy performed as cancer therapy for the head and neck area. The extent of injury induced by radiotherapy depends on the volume of irradiated glands and the total dose and technique used [15, 19–23].

Functions	Components
Digestion	Amylase, lipase, ribonucleases, proteases, water, mucins
Phonation	Water, mucin
Taste	Water, gustin
Lubrication	Mucin, proline-rich glycoproteins, water
Antimicrobial action	Lysozyme, lactoferrin, lactoperoxides, mucins, cystins, histatins, immunoglobulins, proline-rich glycoproteins, IgA
Maintaining mucosa integrity	Mucins, electrolytes, water
Cleansing	Water
Buffer capacity and remineralization	Bicarbonate, phosphate, calcium, staterin, proline-rich anionic proteins, fluoride
Preparing food for swallowing	Water, mucins Digestion Amylase, lipase, ribonucleases, proteases, water, mucins

Table 1. Saliva components and functions.

3. Diagnosis of xerostomia

The objective of the diagnosis is to provide treatment as early as possible, thus minimizing side effects in patients suffering from xerostomia. In order to establish a diagnosis of xerostomia, a clinical history is essential to identify the possible etiological factors [24]. It is necessary to investigate its causes. Thus, three orders of factors need to be known: the occurrence of systemic diseases, medication, and the history of radiation therapy. Questions are asked to the patient, trying to find out if he feels the dry mouth sensation, whether he needs to wet his mouth, if he can eat a wafer without drinking water, if the tongue chews the food and clings to the teeth, and the daily water intake daily among other issues [24, 25]. The qualitative clinical diagnosis of xerostomia is made through the observation of clinical signs such as palpation of the salivary glands, observation of the oral mucosa and its hydration, cracked lips, saliva under the tongue, appearance and texture of saliva, the identification of caries, candidiasis and burning sensation, and others [26].

Several methods have been developed to evaluate the level of dryness of the mouth, the discomfort being the most used: sialography, sialochemistry, sialometry and scintigraphy, salivary gland biopsy, ultrasound, magnetic resonance, and computed tomography [19]. Sialography is a technique of imaging that involves the injection of a retrograde form of radiopaque material into the salivary duct system in order to define the anatomy of the glands. This test is very important to demonstrate the presence of nodules or sialectasis, but it has its disadvantages, such as: the difficulty of the technique, since it is invasive and the patient can react acutely or chronically with the contrast material. The biopsy of the major or minor salivary glands allows the detection of inflammatory infiltrations, acinar destruction and dilation of salivary channels with thick mucus, and sometimes fibrosis [27]. Ultrasound, magnetic resonance, and computed tomography are tests that may also contribute to the diagnosis of diseases of the salivary glands.

To establish the condition of the symptom or to evaluate a possible salivary glandular dysfunction, the most used mechanisms are the questionnaire of xerostomia developed by Fox et al. [11, 28] and the determination of salivary flow rate. Sialometry and scintigraphy (an imaging diagnostic method of nuclear medicine that allows the study of the physiology of the various organs) are complementary tests that must be performed in order to evaluate the involvement of the salivary glands in patients with xerostomia. Sialometry is a relatively common procedure in normal clinical practice and include determination of stimulated salivary flow rate (s-SFR), unstimulated salivary flow rate (u-SFR), palatal secretion (PAL), and parotid secretion (PAR). These measurements are the simplest methods of evaluating the salivary glandular function. It is essential to measure the salivary flow, that is, the amount of saliva produced per unit of time. Very low unstimulated and stimulated salivary flow rates or hyposalivation are defined as <0.1 and <0.7 mL/min, respectively [7]. At rest, secretion ranges from 0.25 to 0.35 mL/min and is mostly produced by the submandibular and sublingual glands [29]. Under stimulation, the parotids account for 50% of salivary volume [30]. Determining the stimulated and unstimulated salivary flow is a procedure to measure the amount of saliva it produces a person at a given time. Generally, the stimulated salivary flow is measured for 5 min and unstimulated salivary flow is measured for 15 min [31]. This

kind of measuring has the advantage of being easily implemented, low-cost, and could be available to most of the population at risk [32]. The diagnosis of salivary gland dysfunction is based on data derived from the symptoms reported by the patient, clinical examination leading to verification of the clinical signs and determination of stimulated salivary flow [33]. A severe decrease in salivary flow may lead to a poor health-related quality of life, as well as a risk condition for the development of oral pathologies such as periodontal disease, caries, and candidiasis [29, 34, 35].

4. Causes of xerostomia

The most severe conditions with effect on the salivary flow are SS and radiotherapy in the head and neck area, with the prevalence of xerostomia in almost 100% in these cases. These conditions are characterized by a progressive loss of secretory cells, and thus a progressive decline in saliva production [36, 37]. Less severe conditions may be dehydration, smoking, and inflammation or infection of the salivary glands [12]. In older people, the most common cause of xerostomia is the use of medications because the vast majority of the elderly are being treated with at least one drug that causes salivary hypofunction [32]. A summary of the main causes of xerostomia can be seen in **Table 2**.

4.1. Aging

The reduced salivary flow is commonly seen in the aging populations. This can be attributed to either age-related localized degeneration of salivary glands or systemic diseases [38, 39]. As the patient ages, the organs atrophy and often result in a decrease in salivary production. It was described that in older people the loss was about 30% of acinar cells, with substitution of secretory components by fibrous and adipose tissue [40]. Besides, there are changes in salivary levels of potassium, sodium, IgA, proline-rich protein, lactoferrin, and lysozyme in elderly [28, 40]. A reduction in salivary flow of older people was identified, even in those not using systemic drugs, suggesting a relation between salivary dysfunction and aging [41]. Smith determined that a stimulated salivary flow in healthy adults older than age 70 is lower than in adults under 50 [42].

Systemic diseases	Sjogren's syndrome, diabetes mellitus, Parkinson's disease, encephalitis, brain tumors, Plummer Vinson disease, hypertension, HIV infection, systemic rheumatic diseases, sarcoidosis, Alzheimer's disease, cystic fibrosis, aplasia, chronic tuberculosis, primary biliary cirrhosis, hemolytic anemia, malignant lymphoma, systemic lupus erythematosus, scleroderma, dermatomyositis, pernicious anemia, hypothyroidism, amyloidosis
Other causes of xerostomia (no drugs or systemic diseases)	Radiotherapy and chemotherapy, infections, inflammation, tumors and sialolithiasis in salivary glands, salivary gland excision, vitamin A deficiency, menopause, stress, anxiety, dehydration, neurological disorders, senility, oral sensory dysfunction, iron deficiency, folic acid deficiency, uremia, polyuria, diarrhea, mouth breathing, bone marrow transplantation, endocrine disorders, pancreatic insufficiency

Table 2. Systemic diseases and other causes of xerostomia.

4.2. Drugs

The most common cause of xerostomia is the use of some systemic medications [43]. Several drugs are able to induce hyposalivation and xerostomia, but they rarely cause irreversible damage to the salivary glands. Over 400 medicines, many of them in common use, induce salivary gland hypofunction [44]. Some examples are: anxiolytics, anticonvulsants, antidepressants, antiemetics, antihistamines, antiparkinsonian, antipsychotics, bronchodilators, decongestants, diuretics, muscle relaxants, analgesics, sedatives and anti-hypertensives, and others (**Table 3**) [29]. The exact mechanisms whereby some drugs determine xerostomia or hyposalivation are still unknown. Salivary dysfunction associated to drugs may occur through anticholinergic, cytotoxic action, sympathomimetic, or by damaged ion transport pathways in the acinar cells [39, 45, 46]. Patients who consume a higher number of daily medications have been associated with complaints of xerostomia [47, 48]. The therapeutic and controlled doses of medications do not damage the salivary gland structure. For that reason, drug-induced xerostomia is reversible. The discontinued use of these drugs can restore salivary flow [49].

4.3. Systemic conditions

Xerostomia or hyposalivation may be caused by local factors, including salivary gland disease (sialadenitis) or salivary gland destruction associated with head and neck irradiation for the

Medicine group	Examples
Anxiolytics	Lorazepam, diazepam
Anorectic	Fenfluramine
Anticonvulsants	Gabapentin
Antidepressants—tricyclic	Amitriptyline, imipramine
Antidepressants—SSRI	Sertraline, fluoxetine
Antiemetics	Meclizine
Antihistaminics	Loratadine
Antiparkinsonian	Biperidene, selegiline
Antipsychotics	Clozapine, chlorpromazine
Bronchodilators	Ipratropium, albuterol
Decongestants	Pseudoephedrine
Diuretics	Spironolactone, furosemide
Muscle relaxants	Baclofen
Narcotic analgesics	Meperidine, morphine
Sedatives	Flurazepam
Antihyperptensive	Prazosin hydrochloride
Antiarthritic	Piroxicam

Table 3. Medicines and drugs with side effects on salivary secretion.

treatment of cancer [11, 50]. The effects of radiation are dose, time, and field dependent. When the damage of salivary glands by radiation happens is severe [39] permanent gland damage can be expected if the radiation exposure exceeds 50 Gy [50, 51]. Other systemic conditions that also affect the salivary flow are autoimmune diseases (SS, rheumatoid arthritis, AIDS, systemic lupus erythematosis, and scleroderma), neurological disorders (Parkinson's), psychogenic illness such as depression and hormonal disorders (thyroid dysfunction and diabetes mellitus) [9]. Regarding diabetes, we will refer more deeply about it since it is the most frequent metabolic disease in the world and the trend demonstrates that it continues to grow. Both diabetes mellitus (DM) type 1, as type 2 have been associated with xerostomia. In diabetic subjects were shown that salivary flow was significantly lower than in nondiabetic subjects [49]. The causes of low salivary flow may be due to direct injury in the gland parenchyma, changes in the microcirculation to the salivary glands, glycemic control disorders, and dehydration. Some studies consider that this decrease in salivary flow in diabetic subjects is related to an increased diuresis or polyuria, involving a decrease in extracellular fluid and consequently in saliva production [10]. Others explain this as a consequence of dehydration from glycosuria that would be more evident in cases of metabolic decompensation [52]. Regarding neurological diseases, studies have demonstrated that the salivary flow is lower in Parkinson's disease patients. This phenomenon could contribute to dysphagia, which affects up to 75% of patients with this disease [53]. Autonomic dysfunction could explain the decrease in salivary flow in subjects with this disease and the drugs used to their treatment could increase the problem [54]. One of the diseases most associated with a xerostomia is SS, a condition that involves dry mouth and dry eyes and that may be accompanied by rheumatoid arthritis or a related connective tissue disease. The oral manifestations observed in this disease are attributed to the involvement of the salivary glands, which leads to a decrease in salivary secretion [31, 39]. Patients with depression can have hyposalivation medication-induced. However, xerostomia may be of psychological origin. A study observed that subjects with a subjective sensation of dry mouth were significantly more depressive than non-depressive subjects [55]. Another study indicates the possibility of depression as an underlying factor of the sensation of dry mouth [56].

5. Consequences of xerostomia

Patients with xerostomia may have oral and dental consequences. Xerostomia can seriously impact quality of life and may alter speech, eating, and swallowing [13]. The most common complaints of patients with xerostomia include oral discomfort, difficulty speaking, dysphagia, dysgeusia (decreased taste), feeling of thick saliva, and generally, chewing issues, dental caries, dental demineralization, periodontal disease, salivary gland infection (sialodenitis), oral microflora alterations, burning sensation, mucosal inflammation, sore throats, hoarseness, ulcerations, halitosis, mucosal dehydration, reduced lubrication, painful tongue (glossodynia), enlarged parotid gland, oral mucosal fracture, inflammation and fissures of the lips (cheilitis). The reduction of rates of elimination of substances can affect the palate and be associated with changes in the mouth microbiota. The reduction of rates of elimination of substances can affect the palate and be associated with changes in the mouth microbiota. From the mouth, alterations of taste and intolerance to acidic or spicy foods, dry foodstuffs like biscuits can be very uncomfortable for them, and oral cavity examination may exhibit signs such as fissures on the tongue and

lips, angular cheilitis, and dry mucosa. Also, caries, candidiasis, halitosis, or loss of appetite and weight could be observed [25, 57, 58]. This collection of clinical parameters has been indicated as simply estimated for recognizing most patients with xerostomia [38, 47].

The side effects associated with xerostomia are microbial colonization and proliferation in the oral cavity, dental or decreased demineralization, accumulation of stones in the teeth, dehydration of the mucosa, reduction of rates of elimination of substances from the mouth and lubrication of the oral mucosa reduced [13]. When the production of saliva decreases, the buffering capacity of the saliva is reduced, and thus the environment of the oral cavity is vulnerable to acidification, which in addition to determining changes in the normal flora (ecological imbalance) has contributed to the increase in the number of some microorganisms such as *Candida albicans* (a salivary flow less than 0.1 mL/min may cause an increase in the incidence of this fungus) and *Streptococcus mutans* (Gram-negative bacteria). A higher proportion of these microorganisms results in greater acidification of the oral cavity environment, and thus contribute to the enamel demineralization and caries progression. There is a study related to it in which subjects with low salivary flow rate also had significantly more dental caries compared to those with a higher saliva flow rate [58]. In addition, high caries prevalence has been reported to be associated with significantly poorer quality of life compared to low caries prevalence [13].

The infection of the oral mucosa with *C. albicans* affects the lubrication of oral tissues, favoring an increase in the risk of caries and severity of periodontal disease. Candidiasis can also cause burning sensation, glossodynia, glossitis, and angular cheilitis (in areas where the lips are dry or cracked). Patients with prostheses may have reduced retention of the prostheses, pain, and ulcers [59]. The prevalence of oral Candida in the normal population has been estimated to range from 23 to 68% and 68 to 100% among SS patients. Studies have attributed the higher prevalence of oral Candida carriage in this disease to xerostomia [60].

6. Treatments

Treatment design to alleviate dry-mouth symptoms should be personalized to the individual patient, based on available treatment. The treatments of xerostomia can be classified into the following categories: (1) patient education, (2) prevention, (3) symptomatic treatment, (4) systemic and topical salivary stimulants, and (5) regenerative and gene therapies.

6.1. Patient education

Patients should receive detailed information about the potential causes of dry mouth and the potential sequelae of impaired salivary secretion, such as dental caries, candidiasis, and mucosal complications. Therefore, patients should be encouraged to have preventive oral health care such as dental hygiene habits and regular dental visits [61]. Another palliative action to minimizing symptoms and preventing oral complications is water intake, drinking water frequently, and remaining hydrated is an important treatment for symptoms of dry mouth [1].

6.2. Preventive therapies

Pharmacological interventions for the prevention of radiation-induced salivary gland dysfunction have been studied. The use of chemical radioprotectors represents an obvious strategy to improve the therapeutic index in radiotherapy. However, the vast majority of these are either too weak in terms of radioprotection, too toxic, or without any apparent mechanisms to ensure selective normal tissue protection [62]. The sulfhydryl compound amifostine (WR-2721; 2-[(3-aminopropyl) amino] ethylphosphorothioic acid), is an oxygen scavenger that may protect salivary glands from free-radical damage during radiation therapy without attenuation of the anti-tumor effects in many experiments performed [63]. Amifostine has been approved for prevention of xerostomia, in head and neck squamous cell carcinoma patients undergoing radiotherapy [64]. A recent systematic review that included randomized controlled trials suggested that the drug amifostine prevents the feeling of dry mouth in people receiving radiotherapy to head and neck (with or without chemotherapy) in the short- (end of radiotherapy) to medium-term (3 months after radiotherapy) [65]. However, amifostine has adverse effects such as nausea, vomiting, hypotension, transient, hypocalcemia, and allergic reactions [66]. Then, the benefits of amifostine should be weighed against its high cost and side effects. Another cytoprotective compound described in literature is the bioactive factor Keratinocyte growth factor-1 (KGF-1, also known as FGF-7) [67]. In a phase II Study, recombinant KGF (Palifermin) appeared to reduce mucositis, dysphagia, and xerostomia during hyperfractionated radiotherapy but not standard radiation therapy [68].

Current preventative therapies also include surgical salivary glands relocation outside the radiation field [69]. Jha et al. described a surgical transfer of a submandibular salivary gland to the submental space in order to prevent radiation-induced xerostomia in patients with neoplasias of the pharynx and larynx [70].

6.3. Symptomatic treatment

Saliva substitutes can provide some relief since provide higher viscosity and protection to the oral mucosa [39]. An ideal saliva substitute must simulate natural human saliva, providing long lasting and intense hydration of the oral mucosa, be inexpensive, edible, easy-to-swallow but retainable in the mouth and should allow a minimal number of applications [71]. Saliva substitutes are available in various formulations, e.g., lozenges, sprays, mouth rinses, gels, oils, chewing gums, or toothpastes. Most available in the market contain carboxymethylcellulose (CMC), mucins, xanthan gum, hydroxyethylcellulose, linseed oil, or polyethylene oxide [72]. Subjective impressions of patients suffering from severe xerostomia showed that artificial saliva containing mucins and xanthan gum are better in their rheological and moisturizing properties than those with CMC [73], because mucin-based substitutes had viscosities that were more similar to natural saliva. Recently, it was reported that a polysaccharide-based oral rinse was effective in symptom control in patients with xerostomia and may lead to an increase in saliva production [74]. Other studies include the use of natural products, in this line, a recent double-blinded, placebo-controlled clinical trial, evaluated the efficacy of topical lycopene-enriched virgin olive oil. It showed an improvement of oral quality of life and reduction of xerostomia symptoms [75]. Also, gelatinous substitutes of saliva showed a significant reduction of the

dryness-related complaints in patients suffering from severe xerostomia [76]. A randomized, double-blind, crossover study in patients affected by medication-induced xerostomia showed that two commercial mouthwash plus gel (GUM® Hydral versus Biotène® Oralbalance) achieve a significant improvement in oral health and xerostomia-related quality of life [77]. Recently, a novel edible saliva substitute, oral moisturizing jelly (OMJ), showed a higher grade of satisfaction than a commercially available saliva gel [78]. In addition to the persistent feeling of dry mouth, people who suffer from xerostomia are very susceptible to bacterial, fungal, and other transmittable mouth infections. It is important that products also include human saliva's enzymes (lactoperoxidase, lysozyme, and lactoferrin). Other important feature is to obtain a continuous oral lubrication. In this context, advances in hydrogel technologies and development of buccal mucoadhesive polymers, allows the continuous release of substances that maintain oral hydration and also offer dental-care benefits for its use in treatment of xerostomia [79]. Other strategy involves the use of modified prosthetic structure designed to retain saliva or substitutes in patients who usually wear a dental prosthesis [4, 80].

6.4. Systemic and topical salivary stimulants

Pilocarpine and cevimeline are two systemic US Food and Drug Administration-approved systemic sialogogues for treatment of dry mouth; both can increase secretions and diminish xerostomic complaints in patients, although they must have functional salivary gland cells. Pilocarpine is a cholinergic parasympathomimetic agent that stimulates muscarinic cholinergic receptors on the surfaces of exocrine glands [81] and has been indicated for the treatment of xerostomia [2, 82]. The usual oral dosage for pilocarpine is 5–10 mg three times per day. The initial recommended dose is 5 mg three times per day oral route (OR), which can be increased up to 30 mg/day depending on response and tolerance. The onset of action is 30 min, and the duration of action is approximately 2–3 h. Common side effects include gastrointestinal upset, sweating, tachycardia, bradycardia, increased pulmonary secretions, increased smooth muscle tone, and blurred vision. Contraindications include gall bladder disease, angle closure glaucoma, and renal colic [39, 83]. Cevimeline is a salivary gland stimulant with a stronger affinity for M3 muscarinic receptors [84]. Since it has no effect on M2 receptors, it shows fewer adverse effects when compared to pilocarpine, and besides, it has a long lasting action. The recommended dose is 30 mg three times a day OR, and the most common associated side effect is dyspepsia. Bethanecol is another drug whose action mechanism is on M3 receptors. It has been used to decrease unwanted effects caused by antidepressant and antipsychotic drugs [85]. The dose indicated is four times a day in doses from 10 to 50 mg OR. Adverse effects, despite being infrequent, include nausea and diarrhea. Other drugs that have been put forward include drug with mucolytic properties such us bromhexine improved salivary secretion in patients with SS [86, 87]. Nizatidine, an H2 receptor antagonist alone or in combination with cisapride, showed a significant increase in salivary secretions of dry mouth patients [88, 89]. In addition, other drugs, such as neostigmine, distigmine, yohimbine, nicotinic, and malic acid have also been attributed positive effects in the treatment of xerostomia [3]. Medicinal herbs, such as jaborandi, betel nut, Iceland Moss and Longo Vital, also can stimulate salivary secretion [4].

In the case of tissue autoimmune-related xerostomia, immunologic agents have been used. Interferon alpha (IFN-α), a protein with antiviral and immunomodulating traits, was an

effective treatment for xerostomia linked to SS, improved salivary output and decreased complaints of xerostomia without causing significant adverse medical events [7, 90]. Rituximab (anti-CD20 monoclonal antibody) and infliximab (anti-tumoral necrosis factor—TNF—monoclonal antibody) improved subjective and objective symptoms related to primary SS [91].

Topical salivary stimulants includes sugar-free chewing gum and jellybeans, they can increase salivary secretion by mechanical stimulation and improve the sensation of dry mouth. These products usually contain fluoride, chlorhexidine, calcium phosphate, and xylitol releasers [92, 93], which inhibits the growth of cariogenic bacteria and reduces the incidence of caries [94]. Direct stimulation with electrostimulating device mounted on an intra-oral removable appliance has been used in patients with salivary dysfunction with good results and no significant side-effects [95, 96]. Moreover, non-invasive electrical stimulation systems such as transcutaneous electrical nerve stimulation (TENS) was highly effective in stimulating whole salivary flow in patients with xerostomia and hyposalivation caused by DM and postmenopausal condition [97, 98]. Acupuncture as a method of xerostomia treatment is also cited, a recent randomized and controlled pilot trial of acupuncture showed that acupuncture has beneficial effects on SS symptoms [99]. Other pilot study showed a preliminary evidence that auricular acupressure therapy may be effective in reducing xerostomia intensity in maintenance hemodialysis patients [100].

6.5. Glandular regeneration and gene therapy

Stem cell replacement therapy may be a good option to treat radiation-induced hyposalivation. Stem cell therapy attempts the repair of damaged salivary glands at the cellular level. In this regard, bone marrow stem cells, adipose tissue-derived stromal cells, dental pulp cells have been tested as a form of treatment for hyposalivation after radiotherapy [39]. Interestingly, human salivary stem/progenitor cells (hSSPCs) (derived from parotid and submandibular glands) can be cultured using the salisphere technique and can be introduced to a damaged salivary gland tissue to replace dead or damaged cells. In this context, Pringle et al. showed the presence of SSPCs in cultured human salipheres [101]. These cells were capable of self-renewal and differentiation, which when transplanted into irradiated recipients and restored glandular function. Considering that an ultimate goal is to develop fully functioning bioengineered organs to replace lost or damaged. It was recently reported that a population of SSPCs can be reliably isolated and expanded in sufficient number, suitable for use in a unique 3D hydrogel model of a human implantable salivary gland [102]. However, independent and collaborative work in stem cells research and tissue engineering is still necessary to have fully functional human salivary glands.

Gene therapy involves injecting a vector with genetic information into a tissue to result in some beneficial change. Originally, gene transfer was considered for use in treating congenital genetic disorders, but the basic principles have now been applied virtually to every organ, for acquired as well as inherited disorders. Regarding salivary glands, Baum et al., in phase I/II study, showed an increased saliva flow rate from the targeted parotid gland, as well as a reduction in symptoms related to the radiation-induced xerostomia in subjects treated with the transferring of cDNA for human aquaporin-1 (hAQP1) through an adenoviral (Ad5) vector (AdhAQP1) [103]. Additionally, others genes (Gli1, human keratinocyte growth factor, and Tousled like kinase 1B) have been targeted and have shown promise in preventing salivary

hypofunction in a preclinical mouse [104, 105]. On the other hand, the use of small-interfering RNA (siRNA)-based gene silencing has provided protection of salivary gland from radiation-induced apoptosis at preclinical level [106].

7. Conclusion

Patients with xerostomia are often a challenge regarding diagnosis and treatment, because although xerostomia is not considered a disease, it has a potential devastating effect on the oral cavity. Since dentists are generally challenged with this problem, it is important to have an appropriate comprehension of diverse causes of xerostomia to develop a systematic approach that includes collaboration with physicians to facilitate interdisciplinary patient care, which involves its systemic conditions and medication. Furthermore, a comprehensive management of xerostomia is also necessary and it should incorporate patient education, lifestyle modifications, and adequate pharmacological and non-pharmacological therapies to improve the patient's quality of life. Since most of the successful therapies are depending on the parenchymal gland affection, it is essential to know new therapeutic approaches to fully recover *in vivo* the gland's function or to develop new bioengineered salivary tissues.

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