RECENT UPDATES ON SALIVARY SUBSTITUTES: AN OVERVIEW

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Abstract

Saliva plays a significant part in preserving the health of the oral cavity. It has a strong antibacterial effect and aids in lubrication and mastication. Water, glycoproteins, enzymes, antibacterial agents, and electrolytes are all present in human saliva. A decrease in salivary flow is one of the most common adverse reactions of diabetes, chemotherapy, radiotherapy, Sjogren syndrome, several systemic diseases, and patients with craniofacial deformities. The first line of therapy for increasing salivary flow is pharmacotherapy. Systemic use of cholinergic medications increases salivary flow. To sustain and enhance the salivary flow, salivary substitutes are also used. Saliva is a viscoelastic fluid with significant surface activity from a biophysical perspective. The biophysical characteristics of commercial artificial saliva used to treat issues affecting the salivary glands should be similar to that of natural saliva. This article aims to provide an overview of the various aspects of a salivary substitute.

Keywords: Salivary substitutes, oral dryness, saliva.

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1. INTRODUCTION

Saliva a noninvasive diagnostic fluid plays one of the most difficult and important roles in the body. 99% of saliva is made up of water. Ninety percent of the salivary secretion is from the major salivary gland and around 10% occurs through many minor glands that are scattered throughout the oral epithelium [(1)]. Electrolytes, proteins, enzymes, immunoglobulins, antimicrobial agents, glycoproteins, polypeptides, glucose, urea, and ammonia are the major constituents of saliva [(2).] It protects the oral mucosa and facilitates the taste. It also plays a role in lubrication and aids digestion. Saliva helps in the clearance of gram-negative bacilli from the oropharynx [(3)]. 0.5 to 1.5 liters of saliva is produced by a normal individual every day [(4)]. The unstimulated salivary flow rate ranges between 0.3 and 0.4 ml per minute. Its rate rises to roughly 4, 0-5, 0 ml/min during eating, chewing, and other stimulating activities respectively, and falls to 0.1 ml/min while sleeping. Hyposalivation is diagnosed when the stimulated salivary flow rate is between 0.5 and 0.7 mL/min and the unstimulated salivary flow rate is below 0.1 mL/min [(5)].

Qualitative and quantitative deficiency of saliva affects the quality of life. The degree of hydration, the body position, and the circadian rhythm are a few variables that have an impact on the salivary flow rate. It can increase due to masticatory, gustatory, and pharmacological stimulation. Salivary flow decreases with age, chronic ailments, autoimmune conditions, and the side effects of the various drugs taken to combat them. The side effects of cancer therapy can also affect the salivary flow. Many patients diagnosed with head and neck cancer often undergo high-dose radiotherapy, which targets extensive regions including the mouth, maxilla, mandible, and salivary glands. Radiation therapy leads to alterations in the function of the salivary glands, leading to reduced saliva production and changes in its quality. Various imaging techniques, including sialography, scintigraphy using technetium-99m, computed tomography scans, and magnetic resonance imaging, can be utilized to diagnose salivary gland dysfunction.

1. Dry Mouth:

When the salivary glands are unable to produce enough saliva, a condition called xerostomia develops, often known as dry mouth. External beam radiation therapy for head and neck cancer, Sjögren's disease, adverse effects of some drugs, and other medical conditions can all result in dry mouth. There is a decrease in saliva volume, decreased buffer capacity, increased viscosity, an acidic pH, and changes in mucoglycoprotein, total protein, and IgA levels [(6,7)]. Patients present with subjective complaints of dry mouth and an objective reduction in saliva production. They also experience difficulty in chewing and swallowing dry food, impaired vocalization, persistent dryness, and a burning sensation in the mouth. Additionally, they may encounter difficulty in tasting, which can be severe and lead to loss of taste, loss of appetite, and weight loss [(8)]. Some of the other symptoms of xerostomia include altered

taste, trouble wearing dentures in edentulous patients, dry, cracked lips, and ropy saliva. Patients with salivary gland dysfunction have a higher prevalence of developing dental caries, periodontal disease, non-caries tooth loss, halitosis, and opportunistic infection.

1.1 Assessment and Clinical Oral Dryness Score and its Interpretation

The Clinical Oral Dryness Score (CODS) is a comprehensive 10-point scale. Each point on this scale corresponds to a specific characteristic associated with oral dryness. [10]

The ten characteristics are listed below:

1. The buccal mucosa becomes stuck with the mirror.
2. The tongue adheres to the mirror.
3. Saliva appears to be frothy.
4. There isn't any saliva collecting on the mouth's floor.
5. Depapillation of the tongue.
6. A modified or smooth gingival structure.
7. Oral mucosa, the palate, appears glassy.
8. A lobulated or fissured tongue.
9. Cervical caries that are active or have just returned (within the past six months more involving than two teeth).
10. Debris on the palate (excluding under dentures)

1.2 Interpretation of oral dryness

Oral dryness can be categorized as mild, moderate, and severe dryness. When an additive score of 1 to 3 is obtained, it is categorized as mild dryness. An additive score of 4 to 6 is obtained, it is categorized as moderate dryness. When an additive score of 7 to 10 is obtained, it is categorized as severe dryness.

Management of dry mouth

Several proposals have been put forward for the effective management of dry mouth in recent years, all of which seek to improve patients' symptoms and enhance salivary flow. Treatment depends on the output of saliva and should focus on restoring normal functions, relieving symptoms, and reducing unfavorable outcomes brought on by hypofunction of the salivary glands. It is viable to do this exogenously or endogenously. Pharmacological methods using pilocarpine, pilocarpine combined with anetholetrithione, cevimeline, and bethanechol; mechanical stimulation such as sugar-free chewing gum containing xylitol and sorbitol with antimicrobial effect; electrostimulation; acupuncture; and genetic solutions can all help to improve the function of the endogenous salivary glands [11]. It is possible to stimulate salivary production exogenously by encouraging the patient to consume water, applying moisturizing products, or using salivary substitutes [12].

Products and management procedures that offer a continuum of care all the time would be ideal for managing patients with dry mouths. Patients benefit greatly from the stimulation of their residual secretory capacity, as saliva plays a crucial role in lubricating and protecting various parts of the oral cavity. It is necessary to lubricate and wet the oral cavity by swigging, spraying, or applying oral rinses or gels. The substantivity of the product and its ability to remain in the mouth for an extended period of time are crucial factors that enhance its functionality. Therefore, the most effective products and management protocols differ from patient to patient. The chosen strategy also relies on the underlying cause of salivary gland hypofunction, which can be attributed to either the inhibition of salivary secretion or the destruction of gland tissue. In addition to this, patient preferences such as application, texture, and flavor play an important role.

The demand for relief may vary throughout the day due to diurnal fluctuations and patient lifestyle patterns. As a result, different medicines or formulations may prove useful at different times of the day. For instance, in the morning, oral rinses, lozenges, or chewing gum can provide aid. However, during the night, longer-lasting

solutions such as oral gels or molecularly strengthened substances may offer greater benefits. The extent of salivary gland dysfunction determines the level of stimulation required for secretion. Mild to moderate hypofunction may allow for some salivary secretions, whereas severe hyposalivation may prevent any secretion. Moreover, individuals with no saliva production may struggle more with the texture and thickness of palliative products compared to those with higher production levels. To cater to individual patient preferences and need, it is important to offer a range of dry-mouth products with different taste profiles. Additionally, patients with hyposalivation often experience reduced or altered taste sensations. As a result, since many patients rely on dry-mouth products continuously, sometimes indefinitely, it is crucial to have a diverse selection available (Table 1).

		Management
Mild dryness	Additive score of 1 to 3	• Sugar-free chewing gum chewed for 15-20 minutes twice a day • Advised with regard to the importance of maintaining hydration, especially for the elderly.
Moderate dryness	Additive score of 4 to 6	• Sugar-free chewing gum or mild sialagogues • Saliva substitutes • Fluoride toothpaste • Monitor at regular intervals • Substitutes with low viscoelasticity hydroxypropyl methylcellulose, and mucin, or low concentrations of xanthan gum and polyacrylic acid along with the gel.
Severe dryness	Additive score of 7 to 10.	• Saliva substitutes • Topical fluorides

Table 1: Management strategies for oral dryness based on Clinical Oral Dryness Score

This article focuses on providing an overview of salivary substitutes**.**

Salivary Substitutes

Salivary substitutes are oral rehydrating agents, which function as saliva [(13)]. They directly act on the oral mucosa and cannot directly stimulate salivary secretion. Salivary substitutes have drawn a lot of interest recently. They are available in various formulations. However, none of the products were able to mimic the properties of natural saliva as these substitutes were inedible. Preservatives are typically present in products that replace saliva. As a result, they can only be used in the oral cavity, and swallowing them is not advised [(14)]. This restricts the usage of salivary substitutes. In addition, these substitutes also lead to demineralization.

Ideal requirements:

The salivary substitutes have to perform the roles of natural saliva. It should provide rapid relief along with a sustained duration of its effect. It is preferable if the artificial saliva has the ability to stimulate and enhance salivary production. It should have a pleasant taste and should be non-irritating in nature. The constituents should not contain any alcohol and should be nonacidic in nature. This reduces the incidence of tingling or burning sensation in the mouth. It should not have any systemic side effects. It should be antimicrobial and aseptic in nature to avoid infection. If the salivary substitutes possess

remineralizing properties, it can reduce the incidence of dental caries. It should have lubricating properties to protect and reduce inflammation of the oral mucous membrane. The salivary substitute should have the key features of salivary molecules such as

a) Shape and confirmation of particles for fulfilling biological functions.
b) Multifunctional
c) It should compensate for any deficient components.
d) Amphifunctionality.

Composition:

Most of the salivary substitutes contain two or more of the components as shown in Figure 1.

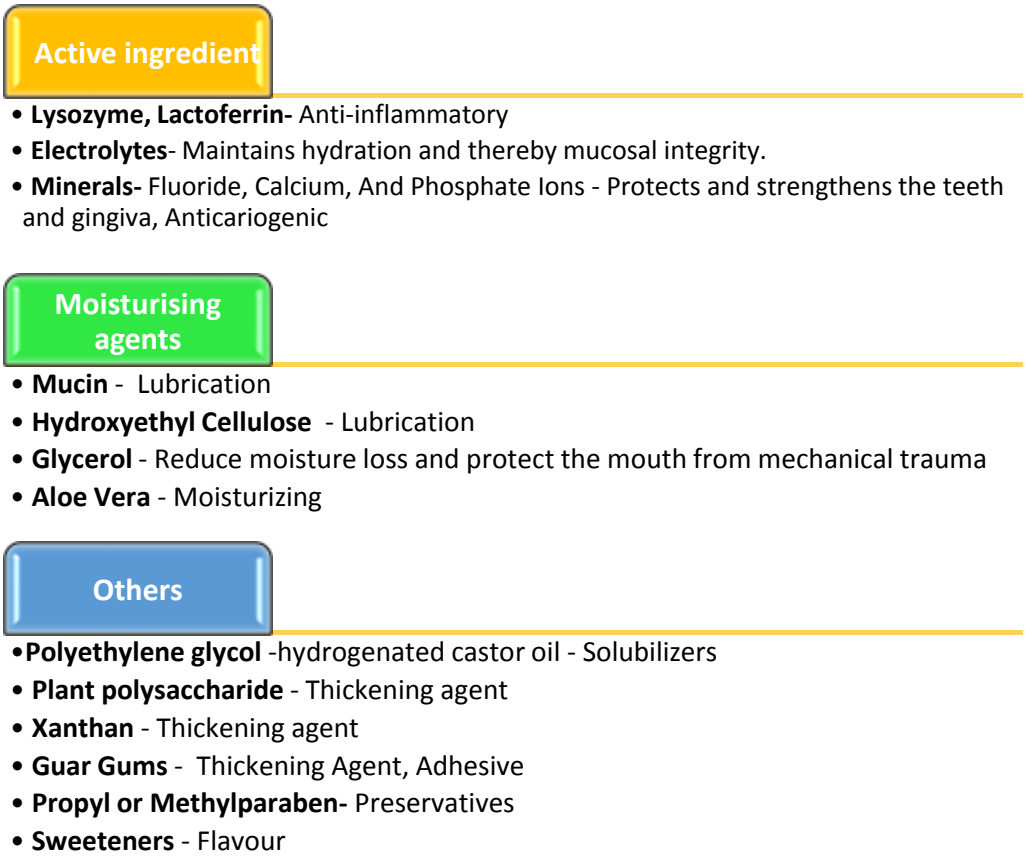

Figure 1: Components in salivary substitute and their function

Types of Salivary Substitutes

1. Based on the mode of dispensing

a) Home remedies

Salivary substitutes can be prepared at home. Juan et al. evaluated various salivary substitutes and the study revealed that homemade salivary substitutes have proven to be more effective in alleviating the discomfort of burning tongue sensations compared to commercially available alternatives. Specifically, a homemade salivary substitute made from chamomile flower and flax seed offers a cost-effective, practical, user-friendly, noncytotoxic, and highly efficient solution for relieving the symptoms of xerostomia. The flax seed extract contributes lubricating and wetting qualities, while the chamomile flower brings anti-inflammatory, antispasmodic, and sedative properties, further enhancing the effectiveness of this natural replacement. (15)

b) Commercially Available Products

There are numerous artificial saliva brands and types in the market, some of which are available without a prescription. The most well-known brands are succinctly described below [16,17].

• **Aquoral:** This oral spray, which is lipid-based, should be used three to four times a day. 400 sprays are provided by each canister.

• **Oralbalance moisturizing gel (Biotène Oralbalance):** This flavorless, alcohol-free gel with no added sugar relieves the signs and symptoms of dry mouth for up to 4 hours. The moisturizing gel is available over the counter [18].

• **Mouth Kote dry mouth spray:** Nonprescription oral spray that contains xylitol offers up to five hours of relief from the symptoms of dry mouth. It has a citrus flavour with no sugar or alcohol content.

• **NeutraSal:** It is a prescription-only salivary substitute that can be used 2–10 times per day. It is a powder that dissolves when combined with water. It is packaged for single use.

• **Oasis mouth moisturizing spray:** This is an oral spray for dry mouth. It is used as often as needed up to thirty times per day. It provides relief for up to two hours.

• **XyliMelts:** They are discs that adhere to the teeth or gingiva. Once in place, it gradually releases xylitol to provide relief from the symptoms.

• **Oral moisturizing jelly (OMJ)** is a novel substitute that is edible. It can be compared to other commercially available salivary [19].

• **Alcea digitata and Malva sylvestris herbal powder:** It has been compared to an artificial saliva Hypozalix [20].

•**Immunologically active saliva substitutes:** This substitute contains lactoperoxidase, lysozyme, glucose oxidase, and lactoferrin [21].

• **Carboxymethylcellulose (CMC)**: It is a polymer that is available commercially and is generated from natural cellulose. It functions as a thickening ingredient in saliva substitute formulations [22].

• **BioXtra gel**: It is a lactoferrin, lysozyme, and lactoperoxidase-based commercial saliva substitute [23].

• **DC161-DP0292 aqueous solution:** This solution from Pierre Fabre Medical Devices, which contains glycerol, povidone K30, copovidone, xanthan gum, potassium chloride, xylitol, marshmallow concentrated hydroglycerined extract, anhydrous disodium hydrogen phosphate, potassium dihydrogen phosphate, macrogol glycerol 40 hydroxy stearate, potassium sorbate and benzylic alcohol [24].

2. Based on the components

a) Polycarboxylcellulose-based salivary substitute (CMC):

It is a natural cellulose that acts as a thickening agent by substituting saliva. Despite the fact that CMC does not quite match the viscosity, sheeting, stringing, and flexibility of human saliva, CMC-based saliva substitutes have been widely utilized and well-tested. The symptoms of dry mouth can be reduced with CMC-based saliva replacements [22]. It has been demonstrated that CMC-based saliva substitutes have few adverse effects and can lessen the intensity of xerostomia-related symptoms.

b) Mucin-based salivary substitute:

The various surfaces of the oral cavity are in a perpetual state of contact. One of the primary functions of salivary proteins is to establish a lubricating layer on delicate mucous membranes and the teeth themselves, ensuring smooth movement

and protection. The mucus glycoproteins, often known as mucins, are principally in charge of giving human saliva its lubricating and film-forming qualities. The viscosity and viscoelastic behavior of solutions containing bovine submandibular mucin or a combination of bovine submandibular and pig gastric mucin closely resemble those of human saliva. These findings align partially with the research conducted by van der Reijden et al., who explored the rheological properties of various polysaccharides (such as guar gum, alginic acid, scleroglucan, xanthan gum, hydroxyethylcellulose, and carboxymethylcellulose) in relation to a solution of pig gastric mucin, a commercially available mucin-based saliva substitute called Saliva Orthana, and human whole saliva. The shear rates examined in the study ranged from 1 to 1000 s^{-1}. The viscosity and elastic behavior of pig gastric mucin solution, known as Saliva Orthana, exhibit shear rate dependency. At high concentrations of mucin, it displays elastic or pseudoelastic behavior, similar to that of human whole saliva. From a rheological standpoint, bovine mucin, bovine serum albumin solutions, and xanthan gum could serve as effective components for artificial saliva substitutes[17]. According to Parl et al., mucin-based saliva substitutes are more effective compared to those based on carboxymethylcellulose. At shear rates of 90 and 225 s^{-1}, mucin concentrations of around 5 mg/mL showed comparable viscosity to stimulated saliva, demonstrating the acceptability of animal mucin solutions as substitutes for human saliva in terms of viscosity [25]. According to Aguirre et al., a mucin-based substitute (Saliva Orthana) demonstrated the highest degree of similarity to human saliva viscosity [12].

c) Glycerol based: The tribological and biological activities of human salivary secretions should be replicated in an ideal artificial saliva. Glycerol-based salivary substitutes provide only temporary relief of oral discomfort.

d) Lineen seed based: Linseed-based saliva substitutes have also been extensively researched. The therapeutic effectiveness of a linseed-based saliva substitute (Salinum) was evaluated by Johansson et al. over the course of 1 week [12]. They reported a significant reduction in symptoms of xerostomia for patients as well as varying improvements in speech, taste, chewing, and swallowing [12,26].

3. Based on the various formulations

a) Gels: Sugiura et al. evaluated the antibacterial properties of Biotene OralBalance, a novel saliva substitute gel that contains the immunologically active enzymes lysozyme, lactoferrin, and lactoperoxidase[23]. A sizable zone of inhibition was identified surrounding the substitutes for all bacterial species highlighting the antimicrobial property of OralBalance. Regelink et al. investigated the effectiveness of Biotene OralBalance over a three-month period in 25 individuals with moderate and severe xerostomia. Patients who had significant xerostomia reported significant relief upon using moisturizing gel. It was found that patients with severe xerostomia experienced longer moisturizing. Epstein et al. compared the Biotene product family (toothpaste and gel for Biotene Oral Balance) to a placebo (gel made of carboxymethyl cellulose and regular toothpaste), and they found that the Biotene products generally improved xerostomia symptoms more than the placebo, especially in terms of taste and consistency.

b) Solutions: Salivary substitutes in the form of solutions are available as mouthwashes and oil. A decrease in the symptoms associated with xerostomia and an improvement in the oral quality of life was seen in subjects when lycopene–enriched virgin olive oil was used as a

topical agent. A study conducted by Warde et al. revealed that 54% of the patients reported a significant improvement in the sensation of dry mouth when Biotene mouthwash was used.

c) Sprays: The sprays include Biotene mouth spray, Glandosene (50 ml), Aqua oral (40 ml to be sprayed inside cheek 3–4 times daily), Saliveze (50 ml), and Xerotin (100 ml).

d) Devices: Salivary Substitute can be delivered intraorally using various devices. Discs, built-in prostheses, and mucoadhesive polymer can be used to deliver salivary substitutes. A 1cm diameter disc called Ora Moist is available in the market. It contains lubricating agents, enzymes, gustatory and flavoring agents, and antibacterial agents. It sticks to the oral mucosa and delivers the salivary substitute [(27)].

e) Recent advances: Current research focuses on developing treatments for dry mouth. Regenerative therapies are dedicated to mitigating salivary gland dysfunction, whereas stem cell and gene therapies strive to repair or prevent salivary gland damage through gene transfer.

- **Stem cell therapy:** Restoring damaged glands at the cellular level is now achievable. Through the transplantation of human salivary stem cells or progenitor cells derived from the major salivary glands, patients who have undergone radiotherapy can experience remarkable self-renewal and differentiation capabilities, leading to the successful restoration of glandular function. [(28)]**.**

- **Gene therapy:** Baum BJ et al. reported that treatment with the cDNA of the human aquaporin-1 (Haqp1) using an adenoviral (Ad5) vector (AdhAQP1) led to an increase in salivary flow from the parotid gland as well as a reduction in the side effects of radiation. In mice, other genes such as Gli1, human keratinocyte growth factor, and Tousled-like kinase 1B produce positive effects. It was discovered that radiotherapy-induced salivary gland apoptosis could be prevented by gene silencing using small interfering RNA (siRNA) [(29)].

- **Recombinant supercharged polypeptides:** They have shown an improvement in the functionality of naturally occurring salivary proteins, which create a layered architecture by electrostatic bond formation to stabilize and produce salivary conditioning films, and mucin recruitment, which decreases water evaporation [(29)].

2. CONCLUSION

Earlier it was assumed that dry mouth in the elderly population was due to aging but later it was accepted that it could be due to other factors like side effects of medications, systemic diseases, or radiation therapy. Saliva has several functions and a decrease in its production could affect the oral functioning and development of infections in the oral. Dentists play a crucial role in managing patients with oral dryness by tailoring to individuals' concerns, preferences, and oral health needs thereby, providing them with better quality of life.

Conflict of Interest:
The authors have no conflicts of interest regarding this investigation**.**

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