Understanding of Xerostomia and Strategies for the Development of Artificial Saliva

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Xerostomia is becoming a major issue in dental and medical clinics with an increase of aged population. Medication is the most common etiology of xerostomia, while the most severe xerostomia generally occurs in patients with a history of head and neck radiotherapy. Xerostomic patients usually suffer from diminished quality of life due to various symptoms and complications. Decreased salivary output is a definite objective sign, but oral mucosal wetness is a more reliable factor for the evaluation of xerostomia. At present there are no effective therapeutic methods for the treatment of xerostomia. Sialogogues may have problematic side effects and their therapeutic effects last only brief duration. Artificial saliva typically does not produce satisfactory results in therapeutic efficacy. Therefore, further research and development of better therapeutic modalities are necessary. The basic concept for the development of ideal and functional artificial saliva is the mimicry of natural human saliva. We need proper candidate molecules and antimicrobial supplements to simulate the rheological and biological properties of human saliva. We also need better understanding of the interactions between the ingredients of artificial saliva themselves and between the ingredients and components of human saliva both in solution and on surface phases. In addition, we need accepted measures to evaluate the efficacy of artificial saliva. In conclusion, for the development of ideal artificial saliva, research based on the understanding of pathophysiology of xerostomia and knowledge about rheological and biological functions of human saliva are necessary.

Key words: *xerostomia, dry mouth, artificial saliva, saliva substitute*

General aspects of xerostomia

Importance of saliva for oral health

Saliva plays a vital role in protecting the oral mucosa and teeth, as well as aiding oral essential function[1]. These functions depend on a number of salivary components, which are mainly proteins and glycoproteins such as mucins, agglutinin, lysozyme, peroxidase, lactoferrin, and immunoglobulins[2]. The role of several antimicrobial peptides present in saliva has also been reported[3]. The importance of saliva could be reflected by the condition of diminished saliva production, resulting in a number of oral changes and related behaviours that can negatively influence a patient's quality of life[4-6]. The importance of saliva has also been highlighted in aged populations. Dry mouth is a common condition in the elderly, with a prevalence of 12–40%[7,8], and dry mouth and its complications have become major concerns in geriatric dental and medical clinics.

Aetiology of xerostomia

Dry mouth has many etiologic factors, including medications, Sjögren syndrome, head and neck radiotherapy, radioactive iodine therapy, and other systemic conditions, and can also be idiopathic[6,9,10,11-15]. The most common cause of dry mouth is the use of medications; several hundred medications have been implicated in

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dry mouth[13,16]. Dry mouth caused by medications is usually functional, in which patients have some residual capacity in their salivary glands that can be stimulated by various agents or pharmaceuticals. Sjögren syndrome is an autoimmune rheumatologic disease that presents most commonly in middle-aged or elderly women. In this syndrome, salivary acinar cells are destroyed and replaced by lymphocytes. Dry mouth caused by head and neck irradiation is dosage-dependent. Dry mouth caused by Sjögren syndrome and head and neck irradiation is an organic disorder that gradually results in non-response, meaning that patients usually terminate in no signs of residual salivary flow. The systemic disorders or conditions may be either organic or functional in nature[17].

Signs and symptoms of xerostomia

Patients with dry mouth may present with complaints that include difficulties in eating, swallowing, and even speaking, which can seriously affect the quality of life in patients with a severe degree of dry mouth. Some patients may also complain of oral malodour, taste disturbances, a burning sensation, and intolerance to spicy food. Furthermore, decreased salivary production can lead to oral candidal infection, and increased risk of dental caries and periodontal diseases, which further worsen nutritional issues. Patients with dentures may have retention problems, oral soreness, and ulcers[9,10,18,19]. Consequently, inadequate saliva production can significantly diminish a patient's quality of life[20,21].

Patients with xerostomia display various degrees of discomfort according to aetiologies. Patients with a history of radiation therapy display the most significant decrease in salivary flow rates and the most severe clinical symptoms and behaviours. Patients with an unknown aetiology displayed relatively favourable symptoms and behaviors[22]. Although the severity of symptoms is obviously affected by the number of medications taken and type and degree of disease present[23,24], the effects of diseases and medications on salivary gland function were not mild in terms of severity and were almost comparable to those of Sjögren syndrome[22]. Dry mouth caused by radioactive iodine therapy is not as severe as beam irradiation, and there have been reports suggesting the recovery of damaged salivary gland function in patients with a history of radioactive iodine therapy[25,26].

Diagnosis of xerostomia

Diagnosis of xerostomia starts with a comprehensive evaluation of symptoms, complete history of present illness, and past medical history pertinent to dry mouth symptoms. Potential oral complications should be assessed via thorough physical exam. Questionnaires have been used to determine subjective measures of dry mouth and clinically significant questions indicating salivary gland performance have been suggested[19,27]. The visual analogue scale, a categorical scale, and a binary yes/no scale have been used to evaluate symptoms. These questionnaires have also been effective in determining subjective measures of dry mouth, evaluating the relationship between subjective symptoms and salivary flow, and assessing treatment efficacy (Table 1)[27-29].

Diagnosis of xerostomia practically depends on reduction of salivary output. Sialometry is a simple but essential procedure used to evaluate dry mouth. Although measurement of individual glandular salivary flow surely provides valuable information, it is often impractical in patients with decreased salivary flow. Whole saliva is easily obtained and in most cases is a good indicator of oral dryness[30-33]. Salivary flow should be evaluated under both unstimulated and stimulated conditions. The flow rate of unstimulated whole saliva (UWS) reflects gland function in the absence of a local stimulus, while that of stimulated whole saliva (SWS) is a measure of the glands' functional capacity[34]. Hyposalivation is usually defined by a flow rate of UWS less than 0.1 mL/min, or that of SWS less than 0.7 mL/min[10]. When both flow rates of UWS and SWS are decreased, individuals are regarded as nonresponders. When only the flow rate of UWS is decreased, individuals are regarded as responders[17].

Diagnostic imaging modalities such as plain radiographs, sialography, sonography, computed tomography, magnetic resonance imaging, and salivary scintigraphy are utilised appropriately in indicated patients. Clinicians should be well informed of the advantages and disadvantages of each imaging modality. Blood examinations and minor salivary gland biopsy could be performed in patients presenting with symptoms suggestive of Sjögren syndrome. Psychological evaluation is also sometimes needed.

Table 1 Dry mouth questionnaire

Question	Answer
Oral dryness at night or on awakening (Dry-PM)	VAS (Visual Analog Scale)
Oral dryness at other times of day (Dry-day)	
Oral dryness while eating (Dry-eat)	
Difficulty in swallowing foods (Dif-swal)	
Amount of saliva in usual, everyday life (Am-sal)	
Effect of oral dryness on daily life (Eff-life)	
Awakening from sleep at night because of oral dryness (Night-awake)	(1) Never (2) 1-2/week (3) 3-4/week (4) 5-6/week (5) Everyday
Taking water to bed (H_2O-bed)	
Sipping liquids to aid in swallowing dry foods (Sip-liq)	(1) Never (2) Occasionally (3) Frequently (4) Always
Using candy or chewing gum because of oral dryness (Gum-candy)	
Dry mouth-associated complaints: • Burning mouth • Taste disturbance • Oral malodor	(1) Yes (2) No

Mechanisms of xerostomia

Relationship between salivary output and xerostomia

Although there are wide individual variations, an individual will usually begin to experience xerostomia when salivary secretion has decreased to half of its normal value[15]. Thus, when individuals visit to clinics with dry mouth or its related symptoms, salivary gland function has typically already been severely compromised. Most studies have shown that the flow rate of UWS is more important than that of SWS as a determinant of oral dryness[17,18,35,36], and an additional study found no association between stimulated salivary flow rate and xerostomia[18]. However, among patients with xerostomia who have very low salivary flow rates, the flow rate of SWS can be a more meaningful factor indicating the extent of gland dysfunction[34] and was more significantly associated with dry mouth-related symptoms than that of UWS[27].

A positive correlation has been reported between a reduction in the production of saliva and the perception of dryness[17,37]. However, the severity of dry mouth sensation does not correlate directly with reduction of salivary flow[38-40]. The rate of salivary flow necessary for normal oral function varies between individuals[41]. Some individuals may complain of oral dryness without reporting that there is not enough saliva in the mouth[19]. Previous studies suggest that the subjective feeling of dry mouth is directly related to the oral sensory perception of mucosal wetness, rather than salivary gland output changes[42,43]. Changes in quality of saliva also affect patients' discomfort and dry mouth sensation[17,42-44].

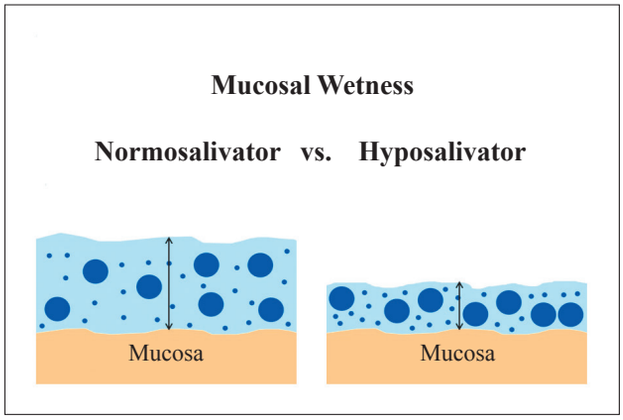

Fig 1 Mucosal wetness in normosalivators and hyposalivators. Mucosal wetness refers to the thickness of the water layer covering the oral mucosal surfaces.

Importance of oral mucosal wetness

Residual saliva is empirically defined as the salivary film coating on soft and hard oral tissue surfaces. These salivary films function as a moisture retainer, a protective barrier, a lubricant, and a determinant for microbial colonisation[45-47]. The degree of wetness correlates with the film thickness, which varies with location of the intraoral tissues. The sensation of dry mouth is perceived when there is insufficient mucosal wetness, i.e. decreased film thickness (Fig 1)[42,48,49]. A relationship between oral mucosal film thickness and the flow rate of UWS or the severity of dry mouth has been reported[42,43,50]. Due to their location, secretions from minor salivary glands may directly contribute to oral mucosal wetness. Therefore, despite the small amount of secretions produced from minor salivary glands, they may play a key role in protecting oral mucosa from drying out[43,51].

It has been suggested that the measurement of oral mucosal wetness could be used as one of the diagnostic modalities for assessing dry mouth[43]. A concurrent change in the composition of residual saliva associated with reduction of volume was observed in hyposalivators compared to normosalivators. Therefore, the information about composition as well as the amount of residual saliva is important for understanding the functional role of the residual saliva in the oral environment[42,43,50,51]. As in whole saliva, proteins and glycoproteins are also key components in residual saliva[52,53]. A negative correlation between mucosal wetness and the protein concentration of the mucosal film layer has been reported in both normo- and hyposalivators[43,51]. These results denote that increased protein concentration could be a result of a decreased volume of residual saliva.

Salivary glycoproteins play a major role in mucosal defence and provide mucosal surfaces with viscoelastic properties[45,54-56]. In particular, salivary mucins – bearing high levels of carbohydrate – may form complexes with other important salivary proteins with antimicrobial activities[57-59]. In this way, they might function as a vehicle to concentrate these molecules on the oral mucosal surfaces. This could lead to the composition of concentrated proteins present on the surface of the oral mucosa, differing from that of whole saliva[60]. In fact, the concentrations of total protein, important antimicrobials, and carbohydrates, including sialic acid, are elevated in residual saliva compared to whole saliva in normosalivators. The elevated carbohydrate to protein ratio in residual saliva suggests an increased amount of glycoproteins in the residual saliva[60]. However, there is no information currently available on the composition of residual saliva in patients with dry mouth.

Management of xerostomia and its limitations

Both intrinsic and extrinsic approaches are used to address the symptoms of xerostomia[61]. The intrinsic approach is to employ parasympathomimetic sialogogues, such as pilocarpine and cevimeline, in order to stimulate hypofunctional glands[9,62,63]. The effectiveness of these medications has been studied in patients with Sjögren syndrome and patients with a history of radiation therapy. These medications can provide a real help for the patients, but they are not always effective and have side effects that are not uncommon in older populations.

If saliva stimulants are ineffective, the extrinsic approach – treatment with artificial salivas or saliva substitutes – may be helpful[9,34,61,64-66]. Mouth rinse solutions containing sodium carboxymethylcellulose (CMC) or animal mucins have been extensively used and evaluated[67-72]. Although these saliva substitutes may decrease some symptoms of oral dryness in xerostomic patients, the alleviating effects of commercially available substitutes are short-lived and, therefore, of limited benefit to patients[64,73]. Several studies have reported that mucin-based saliva substitutes are more effective than their CMC-based counterparts[68,72,74]. As expected, there have been previous studies about the efficacy of artificial saliva, which reported a more

significant reduction of dry mouth-related complaints in the patients suffering from a more severe degree of xerostomia[29,65,75]. In fact, the CMC-based artificial saliva demonstrated significantly better effects in non-responders whose flow rates of SWS were undetectable. This indicates that CMC-based artificial saliva has significantly better effects in patients with very severe dry mouth in which the functional capacity of salivary glands is severely compromised[29]. Other commercial products are moisture containers, which include antimicrobial boosters to supplement the decreased antimicrobial activity of the oral cavity of patients with dry mouth[66]. The most common antimicrobials that have been used are lysozyme, peroxidase, lactoferrin, and IgA.

Recently, the efficacy of electrical nerve stimulation by means of an oral appliance or a dental implant containing an electrostimulator has been reported. This method does not appear to increase the risks of polypharmacy, but studies of long-term efficacy are still needed[76,77].

Despite the development of treatment modalities, each treatment has limitations, and the satisfaction levels of patients with dry mouth are low. We need new medications with greater efficacy and fewer side effects. In addition, we need further research to understand the potential regeneration of damaged salivary glands.

Development of artificial saliva

Developmental strategy

The development of effective saliva substitutes requires understanding of the rheological and biological properties of human saliva, which saliva substitutes should mimic[64,78,79]. An ideal saliva substitute composed of important salivary macromolecules purified or genetically manufactured is theoretically possible, but practically, the addition of antimicrobials to a solution with otherwise similar rheological properties to human saliva may be a better approach[80-83]. Animal or plant substances have been suggested as candidate base molecules. Antimicrobials from animal origins similar to innate defence molecules in human saliva have been used as antimicrobial supplements[80-82,84]. Since various molecules in saliva substitutes and host-derived antimicrobial salivary molecules exist simultaneously in the whole saliva of patients with salivary hypofunction, interactions between these molecules may occur. Indeed, such interactions are reported to induce an increase or decrease in enzymatic activities of antimicrobial molecules[85-90]. These molecular interactions could also affect the rheological properties of saliva substitutes.

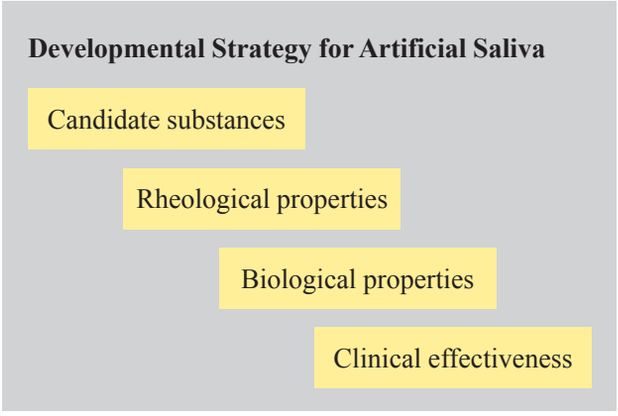

Fig 2 Developmental strategy for effective artificial salivas. We need candidate substances, rheological and biological knowledge about base and supplemental molecules, information about interactions between the molecules, and methods to evaluate the efficacy of developed artificial salivas.

Moreover, these interactions could occur on the surfaces of tooth or dental biomaterials as well as in the solution phase of saliva or saliva substitutes; therefore, information about these interactions in solution and on surface phases is also necessary. In addition, we need scientific methods to evaluate the efficacy of developed saliva substitutes. These methods include questionnaires to evaluate subjective satisfaction and other objective measurements. We need candidate substances, rheological and biological knowledge on base and supplemental molecules, information regarding the interactions between these molecules, and methods to evaluate the efficacy of developed artificial salivas (Fig 2).

Importance of rheological aspects

Quality as well as quantity affects saliva function[91-93]. Patients sometimes complain about changes in saliva quality, which might be due to changes in salivary composition. Thus, developing artificial salivas that have similar viscoelastic properties to human whole saliva is important for patients' satisfaction. However, previous studies on the effectiveness of saliva substitutes have largely focused on the evaluation of only subjective satisfaction or preferences of patients with xerostomia[68,72,73]. There have been few objective results regarding the rheological properties of saliva substitutes, such as viscosity and film-forming wettability, and the

relationships between these rheological properties and patients' satisfaction.

Human saliva has non-Newtonian viscoelastic properties, which is attributed to salivary glycoproteins, mainly mucins[75,80]. The shear forces produced during normal oral function are 60 to 160 s^{-1} for speaking and swallowing[78]. Thus, the efficacy of artificial saliva as a lubricant is partially dependent on its viscosity and how this changes with shear rates[92]. An artificial saliva without or with lower viscoelastic properties cannot adhere and therefore cannot protect oral tissue surfaces. However, considering that mucin-based saliva substitutes were preferred to traditional CMC-based ones that had relatively higher viscosity values[63,79,94], higher viscosity is not always desirable in terms of the function of the salivary substitute. Although there are different preferences according to the individual patient, an excessively sticky salivary substitute may be unpleasant and give rise to difficulty in masticatory function[79,95].

Because the oral cavity surfaces are in continual moving contact, a fundamental function of salivary macromolecules is to provide a lubricating film on the hard and soft oral tissues. This lubricating film provides smooth moving surfaces with minimal friction between tissues and allows food to travel easily through the upper gastrointestinal tract[96]. Like in viscosity, salivary mucins are primarily responsible for the lubricating and film-forming properties of human saliva[45,97-99]. The wettability of oral tissues and dental biomaterials is also indispensable for the maintenance of lubrication and denture retention. Thus, film-forming properties as well as viscosity seem to be essential to the clinical efficacy of saliva substitutes[80,81,99,100].

The rheological properties mainly depend on the molecular weight and concentration of a base molecule comprising artificial salivas[80-83], but addition of other supplemental substances and subsequent molecular interactions between components also affect the rheological properties of artificial salivas. Thus, changes in the components themselves, their concentrations, and ionic strength and pH of solution may affect the rheological properties of artificial salivas.

Importance of biological aspects

Of the various antimicrobial molecules identified in saliva, lysozyme and peroxidase are prominent antibacterial and antifungal components. These molecules are widely distributed in various biological fluids including saliva, tears, milk, and cervical secretions[101,102]. Lysozyme has antimicrobial activity through a muramidase activity, cationic properties, and structure-related bactericidal mechanisms[103,104]. Peroxidase in the form of the peroxidase system, provides antimicrobial activity and protection of oral tissues from oxygen toxicity through oxidation of SCN and consumption of H_2O_2[102,105]. In fact, lysozyme or lactoperoxidase from animal origins, either alone or in combination with other molecules, has been incorporated in oral health care products to restore the reduced antimicrobial capacity of saliva in patients with dry mouth[84]. Instead of the peroxidase system, the glucose oxidase-mediated peroxidase system has been applied in oral health care products, which has another advantage of utilising glucose in saliva, therefore decreasing chances of glucose utilisation by oral microorganisms[90,106].

Since candidate base molecules and antimicrobial supplements for saliva substitutes and host-derived antimicrobial salivary molecules exist simultaneously in whole saliva and tooth- or mucosal-pellicles of patients with salivary hypofunction, interactions between these molecules may occur. For example, interactions have been reported between sIgA and peroxidase[107], lactoferrin and peroxidase[108,109], lactoferrin and lysozyme[110], lysozyme and histatins[111], and lysozyme and peroxidase[88]. Interactions between base molecules and supplemental antimicrobials have also been reported[81,82,86,87,89,90]. Such interactions in vitro result in additive, synergistic, or inhibitory effects on mutans streptococci, lactobacilli, or fungi[89,90,112-114]. Although these observations are from in vitro experiments, it is very likely that such concerted effects exist also in vivo in whole saliva or in oral health care products.

Because molecules may change their conformations on surfaces, which may affect their biological activities, interactions may modify the antimicrobial activities of the supplemented innate defense molecules in distinct ways in solution or on surface phases. These effects on the surface could even be surface-specific[115,116]. Thus, information about interactions between possible components of saliva substitutes on hydroxyapatite surfaces, as well as in solution, have been reported[82,83,86,87].

Evaluation of clinical efficacy

Although the rheological and biological properties of artificial salivas are important, the most important factor is patients' satisfaction. The most typical strategy for measuring patients' response is via questionnaires[19,27,29]. Another objective technique is to evaluate mucosal wetness after applying developed artificial saliva[42,43]. A standardised protocol comprised of both subjective and objective measures needs to be established.

Barriers to development

There are still many limitations that should be overcome to develop an effective artificial saliva. First, we have to find a way to increase the substantivity, retention time of artificial saliva in the oral cavity. To find or develop molecules with better bioadhesiveness to oral tissue surfaces is one of the solutions. Second, we need to develop better delivery methods for artificial saliva, which is particularly important for handicapped patients, as well as usual patients with dry mouth. Third, we have to find a way to customise artificial salivas to fit the individual needs of patients. Moreover, individualised artificial salivas could be used by normal healthy populations for maintenance and improvement of oral health.

Conclusions

With an aging society, the need to relieve xerostomic symptoms is increasing, but, at present, effective machinery for the treatment of dry mouth is not available. Sialogogues have side effects and are not always effective. The effects of saliva substitutes are limited and the satisfaction level of patients is usually low. Therefore, the development of novel sialogogues and artificial salivas with reduced side effects and prolonged therapeutic effects is needed. For the development of effective artificial salivas, a scientific approach based on a thorough understanding of the pathophysiology of xerostomia and the rheological and biological functions of human saliva is necessary.

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