The impact of saliva on patient care: A literature review

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Decreased salivary flow results in a clinically significant oral imbalance that may manifest as increased caries, susceptibility to oral candidosis, altered taste sensation, or a host of other problems. This article reviews the role of saliva in oral health, highlights the causes and consequences of xerostomia, and outlines treatment modalities for patients with xerostomia. Journal articles were investigated through Medline, and relevant textbooks and handbooks were consulted. A summary of the literature pertinent to clinical prosthodontics is presented. (J Prosthet Dent 2002;88:337-43.)

Decreased salivary flow and alterations in salivary composition cause a clinically significant oral imbalance manifested by increased caries incidence; susceptibility to oral candidosis; burning mouth; sore tongue (glossodynia); difficulties with speech, mastication, and swallowing; altered taste sensation (dysgeusia); and halitosis.[1-5] Xerostomia is the subjective symptom or sensation of dry mouth; it reportedly affects 14% to 40% of all adults.[3,6] This article reviews the role of saliva in oral health and outlines clinical treatment modalities for the patient with xerostomia. A Medline database was compiled, and pertinent clinical articles and textbooks were selected for discussion.

SALIVARY GLAND CLASSIFICATIONS

Salivary gland function is mediated by the muscarinic M_3 receptor. Saliva is produced in response to afferent nerve impulses sent to salivary nuclei located approximately at the junction of the medulla and pons. These nuclei are excited by taste and tactile stimuli from the tongue and oral mucosa, as well as other cortical stimuli like smell, anxiety, and depression. The salivary centers in turn send impulses over external nerves of both sympathetic and parasympathetic divisions of the autonomic nervous system to the salivary glands, causing them to excrete saliva.[7]

Mean daily salivary output ranges from 500 to 1500 mL,[8] and the average volume of saliva present in the oral cavity is approximately 1 mL.[9] The rate of secretion follows a circadian rhythm, decreasing during sleep and increasing during the waking hours.[10] Pairs of extraoral or major glands are responsible for most salivary secretion. Those glands possess terminal secretory units composed of serous, mucous, and myoepithelial cells arranged into acini. Acinar secretions empty into an elaborate system of small, intercalated ducts leading into larger, striated excretory ducts to guide saliva into the oral cavity.[8,11]

The histochemistry of the secretions defines the commonly used basis for salivary gland classification.[12-14] The parotid glands are classified as serous glands and contribute up to 20% of the total unstimulated volume of saliva.[8,14] Major secretions of the serous cells include water, inorganic salts, and α-amylase (ptyalin), an enzyme responsible for starch digestion. Mucous cells, in addition to the substances secreted by cells of the serous type, secrete various glycoproteins that collectively are called *mucin*. Those secretions are viscous in nature and serve to lubricate a food mass. The submandibular and sublingual glands are classified as mixed serous and mucous. They contribute 60% and 5%, respectively, of the total unstimulated salivary volume. Each gland secretion has a unique composition. For instance, the secretion of the submandibular salivary glands contains approximately 50% more calcium than that of the parotid glands.[15] It has been hypothesized that the differences may account, in part, for caries resistance of the mandibular incisors. Many small groupings of minor glands also are present within the lips (mucous), buccal mucosa (mixed), posterior hard palate, soft palate and uvula (mucous), anterior tongue (glands of Blandin and Nuhn, mucous), and posterior tongue (von Ebners' glands, serous).[16]

SALIVARY FUNCTION AND DYSFUNCTION

Overall, saliva is composed of 99% water.[7] Inorganic ions such as Ca^{+2}, Mg^{+2}, Na^{+}, K^{+}, Cl^{-}, HCO_3^{-}, $H_3PO_4^{-}$, HPO_4^{-}, and F^{-} maintain osmotic balance and offer buffering and remineralization capacities. Other substances in saliva include albumin, ammonia, amylase, creatinine, cystatins, esterases, glucose, gustin, histatins, immunoglobulins (IgA, IgG, IgM), iodine, kallikrein, lactoferrin, lactoperoxidase, lactic dehydrogenase, lysozyme, mucins, nitrogen, proline-rich proteins, ribonucleases, serum proteins, sialic acid statherin, sulfates, thiocyanate, and urea.[3,8,17,18] The exact role of individual salivary constituents is not known, but as a

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group product, saliva provides a fluid environment for lubrication of the oral cavity to aid in speech, swallowing, and cleansing of the oral tissues. Salivary proteins aid in the digestive process (amylase, lipase, proteases, nucleases, mucins, gustin); possess antibacterial properties for hydrolysis of cell membranes (lactoferrin, lysozyme, lactoperoxidase); and inhibit microbial adherence (immunoglobulins).[17-19] The principal anticariogenic properties of saliva include dilution and clearance of dietary sugars, buffer of plaque acids, and supply of calcium and phosphate ions for tooth remineralization.[3]

The composition of saliva varies in response to different stimuli. When dry foods are consumed, watery serous secretions are increased so as to clear the food bolus. Bicarbonate is the major salivary buffer; its salivary concentration increases with a concomitant increase in salivary flow. Salivary pH is very near neutral (6.7 to 7.4) and depends on the bicarbonate concentration. At low flow rates, less bicarbonate is released, and the pH and buffering capacity of saliva decrease.[20]

Clinical evidence of dry lips, dryness of buccal mucosa, absence of saliva in response to gland palpation, and a high number of decayed, missing, or filled teeth have been cited as an easily assessed set of clinical parameters for identifying most patients with salivary gland dysfunction.[21] Crow and Ship[22] investigated the relationship between gingival and periodontal health and salivary gland function. Their results indicated there was no consistent relationship between parotid flow rates and gingival bleeding, calculus, attachment loss, or severity of attachment loss. The authors concluded that periodontal disease was not an indicator of decreased salivary flow. Other clinically significant signs of dry mouth include fissuring of the dorsal surface of the tongue, angular cheilosis, candidiasis, denture stomatitis, and the presence of thicker saliva.[5,13,21]

As salivary glands age, acini decrease in number and are replaced with adipose and fibrotic tissues.[11] This finding is readily evident histologically, but its total impact on the measurable salivary output is argued in the literature. Although more than 50% of elderly subjects report occasional oral dryness,[13] research on healthy, unmedicated subjects has shown minimal or no changes in salivary flow directly related to the aging process. Several studies have shown no change in stimulated parotid saliva because of chronologic age.[23-25] Submandibular gland flow rate has been shown to either remain stable or decrease with age.[26,27] Some authors have accepted that salivary gland hypofunction and complaints of dry mouth should not be considered a normal consequence of aging.[11,28,29] Vissink et al[30] concluded that stimulated salivary flow rate in healthy adults did not demonstrate significant age-related changes, possibly because of a high reserve capacity within the glands. Sreebny[13] reviewed 14 studies that reported sample sizes greater than 100 and included only healthy, nonmedicated subjects. He concluded that, in most of these studies, the flow rate of resting, whole saliva decreased with age whereas the flow rate of stimulated saliva provided mixed results because most organs, when stimulated, compensate for parenchymal loss.

Studies have shown that complaints of oral dryness are not a reliable indicator of salivary gland performance. Some patients may have a significant decrease in salivary output and experience no discomfort, and some may not perceive decreased salivary output until the flow rate has decreased by 50%.[10] Ship et al[31] proposed that the normal range of salivary flow varies for each individual.[31] They noted wide ranges and considerable variability in flow rates and showed that, under normal circumstances, some healthy individuals require very little salivary fluid to maintain oral health.

Hyposalivation may be caused by localized factors, including salivary gland disease (sialadenitis, sialolithiasis) or salivary gland destruction associated with head and neck irradiation for the treatment of carcinomas. The effects of radiation are dose, time, and field dependent. The parotid glands are the most radiosensitive, followed by the submandibular, sublingual, and minor glands.[14] Salivary gland tissue has a low mitotic index that usually reflects radioresistance. Unfortunately, radiation damage to salivary glands is severe. Radiation damage may be due to damage to the blood supply (endarteritis), interference with nerve transmission, or destruction of the gland itself.[3] Permanent gland damage can be expected if the radiation exposure exceeds 50 Gy.[32] Shannon et al[33] reported a 50% decrease in resting parotid flow within 24 hours after exposure to 2.25 Gy.[33]

Other systemic conditions also affect salivary flow; these include autoimmune diseases (Sjogren's, AIDS, systemic lupus erythematosis, rheumatoid arthritis, scleroderma); hormonal disorders (uncontrolled diabetes, thyroid dysfunction); neurological disorders (Parkinson's, Bell's palsy, cerebral palsy); and psychogenic illness such as depression. Overall, the most common cause of decreased salivary output is medicinal drug intake.[34] More than 400 medications have side effects that include xerostomia or salivary gland hypofunction.[35] Side effects appear to be more pronounced in the elderly, perhaps because of slower metabolism, delayed clearance of the drug, or decreased acinar volume.[11]

Mechanisms of xerostomic drug action may be due to drug interference with transmission at the parasympathetic neuroeffector junction, actions at the adrenergic neuroeffector junction, or the depression of central connections of the autonomic nervous system. Classes of drugs that affect gland function include anticholinergic and antiparkinsonian agents, antidepressants, systemic antihistamines, antipsychotic and antihypertensive medications, central nervous system stimulants, and sedatives. Other medications such as analgesics and diuretics

cause the sensation of oral dryness because of altered sensory function or mucosal and total body dehydration caused by increased urine output.[34]

Patients who consume a higher number of daily medications have been associated with increased complaints of xerostomia.[36] Navazesh et al[37] revealed that medicated persons with at least 1 systemic disease and those who had taken medication longer than 2 years had significantly lower salivary flow rates. At therapeutic doses medications do not damage actual salivary gland structure; drug-induced xerostomia therefore is frequently reversible. The discontinued use of xerogenic drugs can restore salivary flow.[14]

MANAGEMENT OF XEROSTOMIA

Prosthodontists often are the primary care givers in the management of xerostomia. Dental management of these patients begins with thorough patient education. To compensate for intraoral dryness, patients may stop chewing and prefer a liquid or semiliquid diet rich in fermentable carbohydrates. Because decreased mastication worsens the condition, patients should undergo nutritional counseling to limit the harmful effects of reactionary diet modifications. Patients should be reminded to chew, because periodontal mechanoreceptors and mechanical stimulation of the tongue and oral mucosa are vital stimuli for salivation.[8,14] Studies have shown increased parotid gland secretion and salivary pH in response to daily gum chewing.[38,39] The use of citrus sweet drinks or candies accelerates the caries process and must be discouraged. Sugar-free candies and gum are highly recommended.

Consultation with physicians and pharmacists is recommended if elimination or substitution of an offending medication is considered. The timing of the dose may be changed to correspond with meals, thus enabling salivary stimulation through the process of eating to counteract the drying effect of the drug. The use of medication before bedtime should be discouraged because this time of day coincides with the lowest salivary flow rate.[10]

A change in fluid intake also must be recommended. Most people do not drink enough fluids, which contributes to the problem. Patients should sip cool water throughout the day and drink milk with their meals. Water will cleanse and hydrate the oral tissues but, unfortunately, it is not a substitute for saliva. Water is a poor mucosal wetting agent that lacks buffering capacity, lubricating mucins, and protective proteins. Whole or 2% milk may serve as a better substitute because both contain moisturizing properties that can help patients swallow a food bolus. The use of olive oil swabbed onto the mucosa as a lubricant also has been recommended.[13] Citrus fruits can irritate the oral mucosa, and caffeine and alcohol (including alcohol-containing mouthwashes) cause dehydration and must be avoided.[11]

Other helpful tips include encouraging patients to sleep on their side to reduce mouth breathing and to apply petrolatum-based lubricants to their lips frequently during the day and especially at bedtime. A cool-air humidifier should be placed in the bedroom, started at least 1 hour before bedtime, and allowed to run through the night.

Medication capable of stimulating the salivary glands also may be prescribed for certain individuals. The efficacy of pilocarpine (Salagen 5 to 10 mg administered 3 or 4 times daily, 30 minutes before meals; MGI Pharma, Bloomington, Minn.) in patients who have undergone radiation and patients with Sjogren's syndrome has been documented.[40,41] Pilocarpine ophthalmic solution used in the treatment of glaucoma is available in various strengths and can be administered dropwise, allowing the drug to be titrated to the minimum effective dose. Drops may be placed on a stick of gum or added to a small amount of water and ingested 3 to 4 times daily.[42,43] Pilocarpine is a potent, naturally occurring cholinergic agonist that stimulates muscarinic receptors, resulting in secretion of water and electrolytes when a sufficient amount of functional salivary tissue remains. Cemivaline (Evoxac 30 mg, tid; SnowBrand Pharmaceuticals/Daiichi Pharmaceutical Corp, Tokyo, Japan) is a novel cholinergic agonist approved for the treatment of dry mouth in patients with Sjogren's syndrome.[44] No clinical trials comparing cemivaline to pilocarpine are available.

The most common side effect of cholinergic agents is increased sweating. Other central nervous system adverse effects include increased heart rate and blood pressure, chills, headaches, and dizziness. Possible cardiovascular and pulmonary side effects limit the routine use of cholinergic agonists for other populations. At this time the Federal Drug Administration has not approved these drugs for use in drug-induced xerostomia.

Other medicinal remedies such as saliva substitutes manufactured in spray or gel forms are widely available (Table I).[45,46] Levine et al[47] defined the ideal artificial saliva substitute as long-lasting, capable of providing lubrication to wet and protect oral tissues, and able to inhibit the colonization of cariogenic bacteria. To date, an ideal substitute has not been marketed. Commercially available products contain salts, carboxymethyl cellulose derivatives, or animal mucins to increase viscosity, parabens to inhibit bacterial growth, and sugar-free flavoring agents (sorbitol or xylitol). Xylitol sweeteners have been associated with a greater decrease in caries than sorbitol, possibly because of the limited fermentation of sorbitol by *Streptococcus mutans*.[48] Clinical trials have reported increased patient satisfaction with mucin-containing saliva substitutes over carboxymethylcellu-

Table I. Artificial saliva substitutes and stimulants

Material	Manufacturer	Ingredients
Saliva substitutes		
Entertainer's Secret (spray)	KLI Corp, Carmel, IN	NaCMC, Na_2HPO_4, KCl, parabens, aloe vera, glycerin
Moi-Stir (solution)	Kingswood Laboratories, Indianapolis, IN	NaCMC, Na_2HPO_4, $CaCl_2$, $MgCl_2$, KCl, NaCl, parabens, sorbitol
MouthKote (spray)	Parnell Pharmaceuticals, Larkspur, CA	xylitol, sorbitol, yerba santa, citric acid, ascorbic acid, sodium benzoate, sodium saccarin
Oralbalance (gel)	Laclede Inc, Rancho Dominguez, CA	hydroxyethyl cellulose, hydrogenated starch, glycerate, polyhydrate, KSCN, glucose oxidase, lactoperoxidase, lysozyme, lactoferrin, aloe vera, xylitol
Saliva Substitute (solution)	Roxane Laboratories, Columbus, OH	NaCMC, sorbitol, methylparaben
Salivart (spray)	Gebauer Co, Cleveland, OH	NaCMC, sorbitol, KCl, NaCl, $CaCl_2$, $MgCl_2$, K_2HPO_4
Saliva Orthana* (spray)	Nycomed UK Ltd, Birmingham, UK	porcine mucin, xylitol, methyl paraben, EDTA, benzalkonium chloride, NaF, KCl, NaCl, $MgCl_2$, $CaCl_2$, K_2HPO_4
Saliva stimulant		
Salix SST (lozenge)	Scandinavian Naturals, Perkasie, PA	hydroxypropyl methylcellulose, CMC, $Ca_2H_2(PO_4)_2$, malic acid, citric acid, hydrogenated cottonseed oil, sodium citrate, SiO_2, sorbitol

*European formulation, not available in the United States.

lose-type products.[49,50] Patients with a para-aminobenzoic acid allergy should seek a paraben-free product.

The Biotene Oralbalance product line for dry mouth irritation (Laclede, Rancho Dominguez, Calif.) claims antibacterial action through a combination of glucose oxidase, lactoperoxidase, lysozyme and lactoferrin.[51] The enzymes glucose oxidase and lactoperoxidase combine with potassium thiocyanate to produce a hypothiocyanate ion to inhibit growth and acid production of bacterial plaque. Lysozyme inhibits bacterial adherence through cell wall lysis. Lactoferrin is an iron-binding protein capable of inhibiting bacterial growth by depriving bacteria of iron (according to Laclede product information). Regardless of their mechanism of action, current commercial saliva substitutes are short-acting and require constant reapplication. In addition, their cost generally leads to poor patient acceptance.

Some patients may be interested in and pursue alternative treatment modalities. Acupuncture reportedly is capable of increasing parasympathetic activity, which results in neuropeptide release that stimulates salivary gland blood flow and secretions.[52,53] Gamma-linoleic acid (evening primrose oil, 2000 units daily, ingested over a minimum of 6 weeks) also has been recommended to increase parotid and submandibular gland salivary flow, although its mechanism of action is not clearly understood.[54]

DECREASED SALIVA AND DENTAL DISEASE

Practitioners must be prepared to manage dental disease associated with decreased saliva. The occurrence of dental caries is known to vary inversely with salivary flow rate.[55,56] Patients should be advised to maintain impeccable hygiene, schedule frequent recalls, and use topical fluoride regimen. The choice of a fluoride-delivery system varies with clinical need and patient compliance. Common sources of fluoride in toothpaste are sodium monofluorophosphate and sodium fluoride. Research has shown that fluoride from sodium fluoride becomes readily available in oral fluids, whereas fluoride in monofluorophosphate requires a hydrolysis step to be released. This finding may explain the stronger anticariogenic effect of NaF toothpaste.[57,58] Sodium lauryl sulfate, a strong denaturing agent with high protein affinity, is commonly used as the foaming agent in toothpaste and oral rinses (Plax; Pfizer, New York, NY). The use of SLS-Sodium lauryl sulfate-containing toothpastes is discouraged for patients with oral mucosal diseases and dry mouth.[59]

Over-the-counter fluoride dentifrices contain less than 1500 ppm fluoride; therefore patients who continue to demonstrate a high caries rate may receive a greater benefit from prescription fluoride dentifrices (PreviDent 5000; Colgate Oral Pharmaceuticals, Canton, Mass.) or topical, neutral sodium fluoride gels (1.1%) within a custom tray.[13,29,60,61] Stannous fluoride and acidulated phosphate gels may not be well tolerated because of tissue irritability, altered taste, and discoloration or etching of tooth-colored restorations.[29,62]

When carious lesions are restored, the use of fluoride-releasing restorative materials can be considered if it is kept in mind that both the handling and physical properties of a material contribute to the ultimate success of

Table II. Topical and systemic treatments for candidosis

	Drug name/Strength	Quantity	Instructions	Notes
Mouthrinses	Amphotericin-B 25 mg/mL oral suspension*	14-day supply (240 mL)	Rinse with 5 mL for 1 min, expectorate, after meals and before retiring, nothing by mouth ½ hour	Pleasant tasting; can gargle and swallow if pharyngeal involvement is present
	Nystatin 100,000 units/ml oral suspension	14-day supply (240 mL)	Rinse with 5 mL for 1 min, expectorate, after meals and before retiring, nothing by mouth ½ hour	Products contain 30-50% sucrose; can gargle and swallow if pharyngeal involvement is present
	Clotrimazole 10 mg/mL oral suspension*	60 mL	Swab 1-2 mL on affected area, 4 times a day, after meals and before retiring, nothing by mouth ½ hour, shake before use	Useful for debilitated patients who cannot rinse
Ointments and creams	Nystatin 100,000 U/g ointment (Mycostatin, generic)	15 g	Apply thin film to inner surface of dentures and angles of mouth, 4 times daily, after meals and before retiring, nothing by mouth ½ hour	Works well under dentures; yellow color may be objectionable for angular cheilitis
	Ketoconazole 2% cream (Nizoral, generic)	15 g	Same as above	Anti-inflammatory property, excellent choice for cheilitis
	Clotrimazole 1% cream (Lotrimin, generics)	15 g	Same as above	Less expensive than Nizoral cream; has slight anti-staph activity
Lozenges	Clotrimazole 200 mg (Gyne Lotrimin vaginal tabs)	9 tabs	Dissolve ½ tab in mouth twice a day, nothing by mouth 1 hour	Over-the-counter
	Clotrimazole 10 mg (Mycelex) oral troches	50 tabs	Dissolve 1 tab in mouth every 3 hours while awake, (5 tabs/day), nothing by mouth ½ hour	2× cost of vaginal tabs
Systemic	Ketoconazole 200 mg (Nizoral, generic)	10–14 tabs	1 tab daily. Do not take antacids within 2 hours	Requires acidic stomach; avoid for patients on H_2 blockers, antacids, proton pump inhibitors
	Fluconazole 100 mg (Diflucan)	11–15 tabs	1 tab 2 times daily on first day, 1 tab 4 times daily for 10–14 days	Expensive; fewer drug interactions

*Compounded by pharmacist.

any restoration.[63,64] An ideal material does not exist at this time. Resin composite restorations require multiple placement steps, are operator sensitive, and are not cariostatic. Moreover, resin composites are susceptible to polymerization shrinkage, which results in marginal gaps and subsequent recurrent caries. The dentinal adhesion of conventional glass ionomer restoratives is advantageous in the unretentive, Class V root surface lesion and glass ionomers exhibit sustained, rechargeable fluoride release.[65] However, their chemical polymerization reaction proceeds slowly, is susceptible to dessication and acid erosion, and may not endure an arid environment.[66] Light-polymerized, resin-reinforced glass ionomer restoratives were formulated with improved physical properties and handling characteristics. These materials bond to dentin, possess a coefficient of thermal expansion similar to tooth structure, and are less sensitive to water and dessication.[67] Silver amalgam restorations require retentive preparations but should be used whenever the restoration must withstand occlusal loads. Amalgam can be used with a fluoride-releasing liner.[63,68-70]

In the partially or fully edentulous patient, susceptibility to mucosal ulcerations and fungal infections may increase because of decreased salivary flow. Patients should be made aware of the importance of a well-fitting prosthesis and minimize denture use at times when decreased salivary flow is noted. Dentures must be soaked in water overnight. The oral mucosa and intaglio surface of a prosthesis can be sprayed throughout the day with artificial saliva. Various authors have described prostheses with incorporated chambers to serve as artificial saliva reservoirs.[71-73] Those prostheses have demonstrated shortcomings,

including food particle accumulation in the reservoir and short release time of the wetting agent.

Pharmacologic treatments for candidosis include mouth rinses, creams, lozenges, and systemic agents (Table II).[42,43] Topical mouth rinses and ointments are effective on contact, which makes the manner in which the medication is used critical. Patients should be advised to avoid anything by mouth for 30 minutes to 1 hour after use to prolong medication contact time. Nystatin, a commonly prescribed mouth rinse, contains up to 50% sucrose and may impact the caries rate. Patients with xerostomia may not tolerate antifungal agents in lozenge form because of mucosal trauma.[63] Systemic antifungal agents may interact with other medications (Table II).

SUMMARY

Xerostomia is a significant clinical finding that creates unique challenges for the clinician. Treatment requires communication between health care providers and a strict regimen to maintain patient comfort, as well as soft and hard tissue health. Patients must acknowledge the potential chronicity and morbidity of their condition and make appropriate lifestyle changes to minimize the detrimental impact of xerostomia on dental and total body health.

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