

Saliva

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Saliva serves multiple functions, and the importance of saliva in the maintenance of oral health becomes evident when saliva flow is reduced. Impaired salivary secretion and altered salivary composition, which can be caused by a variety of medical conditions and medications, increase the risk of oral diseases such as dental caries, dental erosion and oral candidal infections. Furthermore, the sensation of oral dryness (xerostomia) can have a negative impact on the patient's quality of life.

The salivary glands

Under normal physiological conditions we produce between 0.5-1.0 liter of saliva per day. The majority of saliva is produced by the three paired major salivary glands, that is, the parotid glands, the submandibular glands and the sublingual glands (Figure 1). The minor salivary glands, which are widely distributed on the inner mucosal surface of the lips, cheeks, palate and glossopharyngeal area, contribute about 10% of the total volume of saliva. However, the minor salivary

glands play an important role in the lubrication of the oral mucosa, since they secrete about 70% of the total volume of salivary proteins. The mixed fluid that covers the teeth and oral mucosa is designated whole saliva, and apart from saliva from both the major and minor salivary glands, it also contains gingival crevicular fluid, micro-organisms from dental plaque, leucocytes, discarded epithelial cells from the oral mucosa and food debris.

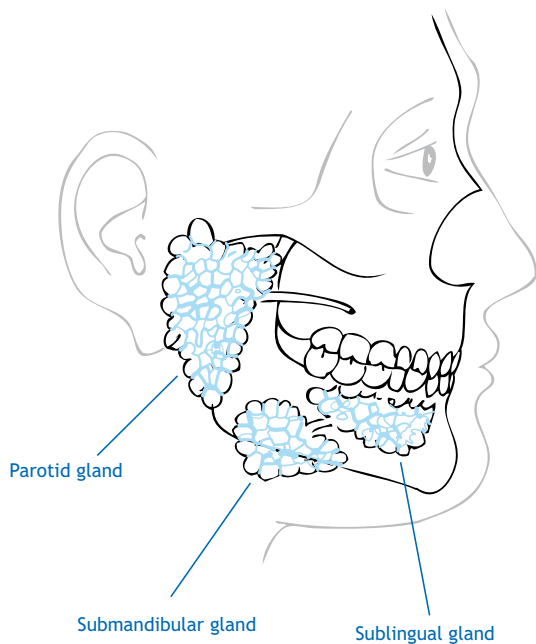
In healthy, non-medicated persons the unstimulated (resting) whole saliva flow rates usually vary within the range of 0.3-0.5 ml/min and the stimulated whole saliva flow rates within the range of 1.0-1.5 ml/min.

The salivary flow and thereby the composition of saliva display large variations during the day. The salivary flow rate typically increases during the day and peaks around noon, and is almost zero during sleep. In addition, several factors influence the salivary flow rate including the nature and duration of stimulus, the

emotional state and water balance of the body. In the unstimulated state, i.e. resting salivary secretion, the submandibular glands contribute about two-thirds of the volume of whole saliva, whereas the parotid glands account for at least half of the whole saliva volume, when salivary flow is stimulated, especially by mechanical stimulation (chewing). Only a small percentage of unstimulated or stimulated whole saliva derives from the sublingual glands.

Some of the salivary glands like the parotid glands and the minor lingual (von Ebner's) glands are purely serous glands. Upon stimulation they produce watery saliva with a high content of enzymes like amylase and lipase, respectively. Others are purely mucous like the minor palatal glands, which produce more viscous, mucin-rich saliva. Finally, some salivary glands are mixed serous and mucous gland types including the submandibular, sublingual and most of the minor glands.

Figure 1



Localisation of the three paired major salivary glands.

mechanoreceptors in the periodontal ligament. The sensory signals from taste-activated chemoreceptors and chewing-activated mechanoreceptors are conducted to the salivatory nuclei (salivation centre) in the medulla oblongata of the brain (Figure 2). The conditioned reflexes are programmed in higher centres in the brain and can be activated not only by the sight, the smell and the thought of food but also by sounds related to cooking. Accordingly, the activation of salivary secretion is also culturally determined and based on each person's experiences with foods. Pavlov's dog experiment is a classical example of mentally conditioned salivary secretion. Salivary secretion is also influenced by impulses from other centres in the brain resulting in facilitation or inhibition of salivation. Anxiety and depressive conditions can cause diminished salivary flow, whereas mania can lead to increased flow. Furthermore, medications which act on the central nervous system like morphine and cocaine may influence the salivary secretion.

Nervous regulation of salivary secretion

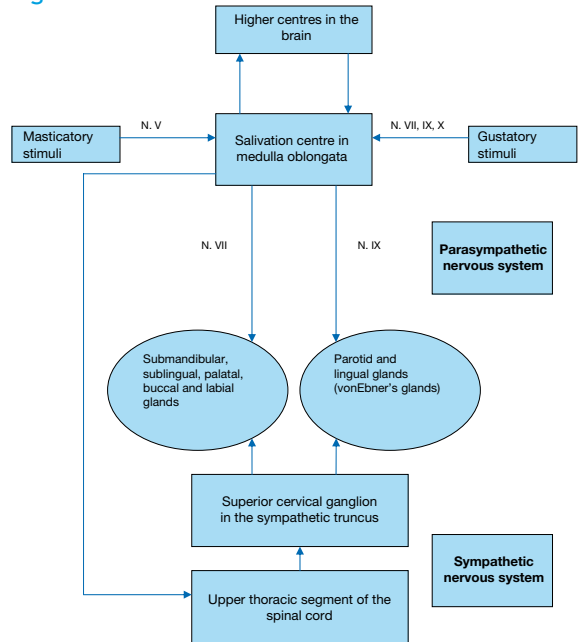
Salivary gland secretion is under autonomic nervous control and thus regulated by both the parasympathetic and sympathetic nervous system (Figure 2). Neural activation of the salivary glands initiates a cascade of events including initiation of water- and salttransport, secretion of proteins and

secretion of primary saliva into the duct system. The formation of saliva is based on unconditioned and conditioned reflexes comprising an afferent sensory part and an efferent secretory part. The sensory part of the unconditioned reflex is activated by stimulation of chemoreceptors in the taste buds and

In the salivation centre the sensory signals are integrated and the salivary nuclei direct signals to the efferent, secretory part of the reflex which consists of parasympathetic and sympathetic autonomic nerves that run along separate pathways to the salivary glands and initiate neural activation of the salivary secretion (Figure 2).

Stimulation of chemoreceptors in the taste buds gives rise to increased salivary secretion with high content of proteins, especially from the submandibular glands. Stimulation of mechanoreceptors by chewing leads to activation of the parasympathetic nerves which gives an increased secretion of watery saliva, particularly from the parotid glands. Unilateral stimulation of the periodontal ligament, masticatory muscles or temporomandibular joint primarily leads to ipsilateral salivation. Finally, activation of stretch-receptors in the stomach due to nausea and/or vomiting can give increased salivary flow via the vagus nerve (X).

Figure 2



Salivary secretion is under autonomic nervous control and is regulated by reflexes. The unconditioned reflexes are activated by stimulation of mechanoreceptors (chewing) and chemoreceptors in the taste buds in the oral cavity. The impulses from these receptors are carried to the salivation centre in the medulla oblongata via the trigeminal nerve (n. IV), facial nerve (n.VII) and glossopharyngeal nerve (n.IX). The conditioned reflexes are activated by the sight, sound and thought of food. In the salivation centre, which also receives impulses from higher centres of the brain, the afferent signals are integrated and directed to the efferent part of the reflex comprising parasympathetic (the facial, n. VII, and glossopharyngeal, n. IX, nerves) and sympathetic secretory nerves that initiate neural stimulation of the salivary glands.

Transmission of nerve stimuli

Stimulation of the parasympathetic nervous system leads to release of the neurotransmitter acetylcholine from the peripheral postganglionic nerve endings, and thereby secretion of copious, watery, amylase-rich saliva with very low content of glycoproteins (mucins). Sympathetic stimulation leads to release of noradrenaline and secretion of viscous saliva with high concentration of proteins and glycoproteins, but low content of water. Salivary secretion is not only mediated by these two classical neurotransmitters, but also by a wide number of neuropeptides such as vasoactive intestinal polypeptide (VIP) and substance P, which are co-released from the peripheral autonomic nerve endings surrounding the salivary glands.

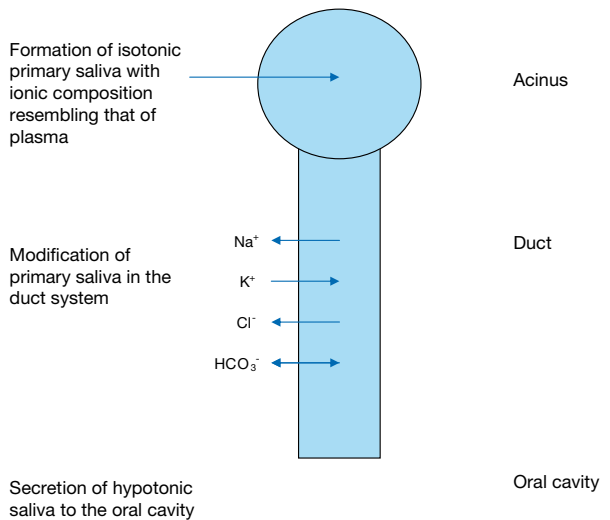
Formation of saliva

The salivary glands contain secretory end pieces consisting of polarized acinar cells, which surround a central lumen connected to a duct system. Salivary secretion is evoked by the binding of neurotransmitters

(acetylcholine and noradrenaline) and neuropeptides (such as VIP and substance P) to specific receptors on the plasma membranes such as muscarinic cholinergic receptors, α - and β -adrenergic receptors and peptidergic receptors for VIP and substance P. The binding

of transmittersubstance to receptors elicit a cascade of intracellular signalling- and transport- mechanisms, which result in secretion of isotonic primary saliva from the acinar cells, having an ionic composition similar to that of plasma (Figure 3). The intracellular mechanisms include activation of the

Figure 3



The formation of saliva takes place in two stages. In the first stage, the secretory endpieces (acini) produce isotonic primary saliva with ionic composition similar to that of plasma. In the second stage, the primary saliva is modified as it passes through the duct system by selective reabsorption of Na^+ and Cl^- (but not water) and some secretion of K^+ and HCO_3^- . The final saliva secreted into the mouth thus becomes hypotonic with salt concentration below that of primary saliva.

inositolphosphate metabolism in the plasmamembranes resulting in formation of the intracellular second messengers, diacylglycerol (DAG) and inositol 1, 4, 5 trisphosphate (IP3). DAG activates protein kinase C, another mediator of cellular protein synthesis and secretion of phosphorylated proteins by exocytosis. IP3 binds to specific IP3-receptors on the endoplasmic reticulum which induces calcium (Ca^{2+}) release from intracellular calcium stores, giving rise to an increase in the free intracellular Ca^{2+} concentration. This results in opening of ion channels and thereby loss of intracellular potassium (K^+), chloride (Cl^-) and water from the acinar cells, and subsequently shrinking of the cells.

Activation of the β -adrenergic and VIP-peptidergic receptors (by noradrenaline) results in synthesis of 3', 5'-cyclic adenosine monophosphate (cAMP) from adenosine triphosphate (ATP). The cAMP pathway is implicated in protein synthesis, protein phosphorylation and in

exocytosis of proteins such as amylase and mucin from the cell to the primary saliva.

Ductal modification of primary saliva

During its passage through the duct system, the primary saliva is modified by selective reabsorption of Na^+ and Cl^- (but not water) and some secretion of K^+ and HCO_3^- , whereby the final saliva secreted into the mouth becomes hypotonic (Figure 3). The secretion rate as well as the volume of the final saliva is determined directly by the formation rate of primary saliva by the acinar cells. Furthermore, the metabolic activity in the duct system is also of importance for the composition of saliva secreted into the mouth.

The composition and functions of saliva

Saliva not only protects the teeth and oral mucosa, facilitates mastication, swallowing and speech, but also acts in the initial digestive processes that take place in the upper parts of the gastrointestinal tract. Table 1 shows some of these important functions related to

the fluid characteristics and other specific components of the saliva.

Normally saliva is composed of more than 99% water and less than 1% of solutes such as proteins and salts. These salts primarily comprise sodium, potassium, chloride, bicarbonate, calcium, phosphate and magnesium. As mentioned previously, the final composition of saliva in the mouth is dependent on the rate by which it is secreted from the acinar cells to the duct system, since the salt concentration and the osmolarity increase as the flow rate increases.

Oral clearance

One of the important functions of saliva is maintenance of oral hard tissue integrity by providing mechanical cleansing, buffering effect, antimicrobial actions and maintaining saturation with respect to hydroxyapatite (calcium and phosphate) in the saliva. Saliva dilutes and eliminates dietary sugars and acids as well as oral micro-organisms from the mouth by a process referred to as oral clearance. This process is dependent

Table 1.
The most important functions of saliva related to the each salivary component.

Functions	Component in saliva
Protection of teeth and oral, pharyngeal and oesophageal mucosa	
Mechanical cleansing of teeth and mucosa	Water
Lubrication of teeth and mucosa	Water, mucins
Keep oral mucosa intact, soft and moistened	Water, mucins, salts, epidermal growth factor, fibroblast growth factor, nerve growth factor
Prevent tooth demineralisation	Proline-rich proteins, statherins, cystatins, histatins, calcium and phosphate
Buffer capacity	Bicarbonate, phosphate and protein
Antimicrobial activities	
Antibacterial functions	Amylases, cystatins, histatins, mucins, peroxidase, lysozyme, lactoferrin, calprotectin, immunoglobulins, chromogranin A.
Fungicidal functions	Histatins, immunoglobulins, chromogranin A
Antiviral functions	Cystatins, mucins, immunoglobulins
Digestive properties	
Formation of food bolus	Water, mucins
Facilitation of mastication and swallowing	Water, mucins
Initial digestion	α -amylases, lipases, ribonucleases, proteases, water, mucins
Dissolution of taste compounds	Gustin (carbonhydrase), zinc (Zn^{2+}), water
Facilitation of speech	Water, mucins

on the salivary flow rate and the swallowing frequency. Thus, if the salivary flow rate is reduced, the oral clearance rate is also reduced. In the latter case, the elimination of food substances including acids is prolonged resulting in a more acidic environment in the oral cavity and in the dental plaque leading to an increased risk of dental erosion and caries. It has been shown that oral sugar clearance becomes extensively prolonged, when the unstimulated whole saliva flow rate is below 0.2 ml min/l.

Saliva buffer capacity

Another important function of saliva is its ability to buffer acids, which is essential for maintaining pH values in the oral environment above the critical pH for hydroxyapatite. The saliva buffer capacity includes the bicarbonate, phosphate and protein systems. The concentration of bicarbonate in saliva and the salivary pH are highly dependent on the salivary flow rate, and the pH can under normal physiological conditions

vary from 6.0 to 7.5. The bicarbonate concentration and thereby the pH in saliva increases when the salivary flow rate increases and vice versa. The concentration of bicarbonate is highest in parotid saliva and lowest in the minor salivary glands. In unstimulated state, the bicarbonate and phosphate contribute almost equally to the buffer capacity in whole saliva. In stimulated whole saliva, the bicarbonate buffer system is responsible for approximately 90% of the buffer capacity. At very low salivary flow rates and salivary pH below 5, the main contribution to the buffer capacity derives from the proteins. Salivary pH and salivary concentrations of calcium and phosphate are significant factors for the maintenance of saturation with regard to hydroxyapatite in the saliva. Saliva also contains proline-rich proteins and statherins, which prevent precipitation of calcium phosphate salts from saliva and keep the environment around the teeth supersaturated with regard to calcium phosphate salts.

Salivary proteins and the tooth pellicle

In addition to the oral clearance, the saliva buffer capacity and maintenance of saturation with regard to mineral, the salivary proteins also play a role in relation to protection of the teeth against caries and dental erosion. Several saliva proteins such as proline-rich proteins, cystatins, MG1, lactoferrin, lysozyme and amylase take part in the formation of the acquired pellicle that covers the teeth. The protein composition of the pellicle seems to determine the initial colonisation of bacteria to the tooth surface and thereby the risk of developing caries. Similarly, the salivary protein composition of the pellicle as well as the thickness of the pellicle seems to be important in relation to the risk of developing dental erosion. Thus a thick pellicle seems to be more protective against acid challenge on the hard dental tissue than a thin one.

Salivary mucins

Mucins (glycoproteins) are essential components in human saliva. They lubricate the oral mucosa and give

saliva its characteristic viscosity. There are two types of mucins in human saliva, namely MG1 which has a high molecular weight and MG2 having a low molecular weight. MG1 is a part of the pellicle on the tooth surface and plays an important role in the bacterial adhesion to the tooth surface. It is produced in the mucous acini in the submandibular and sublingual glands and also in the palatal and labial salivary glands. MG2 is produced in the serous cells in the submandibular and sublingual glands, but not in the parotid glands. Mucins are hydrophilic and capable of absorbing and retain large amount of water due to their significant content of carbohydrates, and therefore offer protection of the oral surfaces against dehydration.

Antimicrobial factors in saliva

Saliva also contains a large number of organic substances with antimicrobial effects including lysozyme, lactoferrin, peroxidase, histatins and immunoglobulins, in particular secretory IgA. Lysozyme is an enzyme that can break down peptidoglycan, an essential

component in the cells walls of gram-positive bacteria. Lysozyme can also inhibit bacterial agglutination due to its strong positive charge. Lactoferrin binds to iron, whereby the concentration of iron available as co-factor for the bacterial enzymes is reduced. Lactoferrin also has bactericidal, fungicidal as well as antiviral properties besides its iron-binding properties. Lysozyme and lactoferrin are both secreted by the duct cells. Peroxidase is an enzyme which catalyses the oxygenation of thiocyanate to hypothiocyanate. The latter has bacteriostatic effects due to its blocking of central bacterial metabolic processes. Additionally, saliva contains histidin-rich proteins like histatins that besides having bactericidal and fungicidal (especially against *Candida albicans*) properties also prevent precipitation of calcium phosphate salts on the teeth from saliva which is supersaturated with regard to calcium phosphate salts. Cystatins are inhibitors of cystein proteases and protect the oral mucosa from break down by these enzymes.

Secretory IgA

Secretory IgA is the predominant immunoglobulin

in saliva. Formation of IgA takes place in the plasma cells in the salivary gland tissue, and then transported to the salivary gland cells which synthesise the secretory component that binds to plasma-IgA. The immunoglobulin is subsequently designated secretory IgA and secreted to the saliva. Secretory IgA inhibits among others the colonisation of bacteria and acts synergistically with mucins to inhibit bacterial growth by agglutination.

Growth factors in saliva

The duct cells produce and secrete certain growth factors like epidermal growth factor (EGF) and fibroblast growth factor, which enhance healing of ulcers in the mouth and play a role in the protection of oesophageal mucosa. Salivary EGF interacts with the innate salivary protein defence mechanisms to form a mucosal defence barrier. Nerve growth factor is important for among others the development of sympathetic nerves. Chewing- and acid (pepsin) exposure to the oesophageal mucosa lead to increased secretion of epidermal growth factor from the salivary glands.

Saliva and the initial digestive processes

Both α -amylase, which are being secreted from the serous acinar cells of the parotid gland and lipase, being secreted from the lingual (von Ebner's) glands, take part in the initial digestion of starch and triglycerides, respectively, in the oral cavity. However, the salivary α -amylase and lipase are considered to be of minor significance in the polysaccharide digestion and lipolysis of healthy individuals, but may be of particular importance to patients suffering from chronic pancreatic insufficiency and patients with cystic fibrosis due to the lack of pancreatic amylase and lipase activity. The concentration of salivary α -amylase increases with increasing salivary flow rate. Salivary α -amylase also appears to have antimicrobial properties like inhibitory effects on the bacterial adhesion on the teeth and oral mucosa.

Oral dryness and reduced salivary secretion

Subjective oral dryness is a common problem to many people. It is assumed that at least 10% of an adult population suffers from oral dryness. The prevalence of oral dryness increases with age which is primarily ascribed to a higher incidence of systemic diseases and intake of medications among the elderly. Approximately 30% of persons aged 65 years and above is assumed to suffer from oral dryness. The sensation of oral dryness (xerostomia) is often related to a severely reduced salivary unstimulated flow rate. However, xerostomia may also occur without objective evidence of reduced salivary flow (hyposalivation). Accordingly, the sensation of oral dryness is apparently closely related to the composition of saliva, in particular to the content of glycoproteins (mucins). The moistening and lubricating properties of glycoproteins are believed to minimize the sensation of mucosal dryness. In addition, it has been shown

that the symptoms of oral dryness first occur when the unstimulated salivary flow rate falls to about 50% of its normal value.

Consequently, the detection of salivary gland hypofunction requires, in addition to a thorough medical and oral history taking and a clinical examination, measurement of the salivary flow rate (sialometry). The most commonly used method for measuring the whole saliva flow rate is the so-called "draining method". This method is highly reproducible and simple to use in the dental office. The term hyposalivation is based on objective measures of the salivary flow rate and describes the condition where the unstimulated whole saliva flow rate is ≤ 0.1 ml/min and the chewing stimulated whole saliva flow rate is ≤ 0.7 ml/min. Selective collection of saliva from the parotid glands and the submandibular/sublingual glands give valuable information concerning the function of each individual gland and the specific salivary composition of each gland (sialochemistry), but is also

Table 2.
Consequences of permanently reduced salivary secretion

Dryness of the lips, oral mucosa and pharynx
Soreness, itching and burning sensation of the oral mucosa
Problems with eating spicy and acidic foods
Angular cheilitis
Altered/impaired taste perception
Difficulties in chewing, swallowing and speech
Very viscous and foaming saliva
Gastrointestinal reflux, heartburn
Halitosis
Increased frequency of mucosal ulcerations
Difficulty in wearing removable dentures
Increased caries activity and atypical caries pattern (cariou lesions on cervical and incisal tooth surfaces)
Atrophy of the filiform papillae, red or fissured appearance of the tongue
Pale and atrophic oral mucosa
Increased frequency of oral candidosis
Soreness and enlargement of the major salivary glands
Altered and impaired diet due to the reduced salivary secretion, causing malnutrition or weight loss

Table 3.
The most common causes to oral dryness, salivary gland hypofunction and altered salivary composition.

Intake of medications	Such as antihypertensives, antidepressants, antipsychotics and antihistamines
Systemic diseases	Sjögren's syndrome, rheumatoid arthritis, dysregulated diabetes mellitus, HIV-infection and conditions causing dehydration
Irradiation	Radiation therapy of tumours in head- and neck region
Psychogenic disorders	Such as depression, anxiety and stress
Neurological conditions and factors affecting the autonomic outflow pathway	Such as cerebral-vascular diseases, brain tumours and neurosurgical traumas affecting the peripheral nerves and the central nervous system (e.g. the trigeminal, facial or glossopharyngeal nerves and salivation centre, respectively)
Local factors	Salivary gland infection and obstruction

technically more challenging than the measurement of whole saliva secretion.

Several systemic diseases

and their treatment can result in reduced salivary flow and altered salivary composition. Some of the most evident salivary gland dysfunctions are seen in patients with

Sjögren's syndrome, a chronic, inflammatory autoimmune connective tissue disease, in patients who have received radiation therapy in the head and neck region and patients who take

medications affecting the salivary gland functions, in particular antidepressants and anxiolytics. These patients often experience the most severe complications associated with salivary gland hypofunction. Other frequent causes of oral dryness and salivary gland hypofunction are shown in Table 3.

Salivary gland function and aging

It is still controversial whether xerostomia and reduced salivary flow are natural consequences of age-related degeneration of the salivary gland tissue or rather results of an increased incidence of systemic diseases and a more extensive intake of medication among the elderly. It has been shown that in healthy, non-medicated elderly persons the parotid flow rate is similar to that of the younger, healthy persons. Regarding the unstimulated and stimulated submandibular/sublingual (mixed serous/mucous glands) flow rates results are contradictory. It is possible that the various salivary gland cell types are differently affected by age. Some studies have found that the unstimulated whole saliva secretion (where the

largest contribution originates from the submandibular and sublingual glands) and the concentration of mucins in saliva decline with age. These observations are consistent with histomorphological findings revealing age-related degenerative changes of the submandibular/sublingual glands and the minor (mucous) salivary glands. Overall, these findings may in part explain the increased prevalence of xerostomia among elderly, since a decline in the submandibular/sublingual functions has an extensive influence on the sensation of oral dryness due to the content of mucins in these secretions.

Medications and salivary gland function

Intake of medications is the most common cause of xerostomia and salivary gland hypofunction. There is also a relationship between the number of medications taken on a regular daily basis and xerostomia and salivary gland hypofunction in such a way that when the number of medications taken on daily basis is increased, the complaints of oral dryness become more pronounced and the salivary flow rate decreases. The medication-

induced side effects are often reversible meaning that salivary gland function will recover after withdrawal of the pharmacotherapy. Medications can affect the salivary glands and their secretions in several ways. Benzodiazepines, for example, affect the central neural regulation of salivary secretion. Others exert actions on the peripheral neural regulation via interaction with the binding of neurotransmitters and -peptides to receptors on the plasma membranes of the salivary gland cells. These medications include among others atropine, which binds to muscarinic cholinergic receptors, and α - and β -blockers which bind to adrenergic receptors on the plasma membranes of the salivary gland cells. In addition, medications like diuretics can indirectly affect the salivary secretion mainly via their diuretic effect.

Management of oral dryness and salivary gland hypofunction

It is important to identify the etiological factor, if possible, to the oral dryness and salivary gland hypofunction in order to make appropriate decisions regarding

therapeutic interventions for the patient. It is also important to inform the patient about the relationship between hyposalivation and the increased risk of developing oral diseases. In case of medication-induced xerostomia and salivary gland hypofunction, change in dose or alteration of dose schedules of the causative (xerogenic) medications may occasionally prove to be effective. Thus many patients complain of oral dryness at night and change in dose schedules can result in reduced maximal blood levels of the drug during the night and thereby minimize the symptoms of oral dryness. Substitution of the causative drug for another with fewer side effects on the salivary secretion, but with similar clinical effect, if possible, may also prove to be useful. It must be stressed that changes in the patient's medication should always be carried out in collaboration with the patient's physician. In cases where change in dose, alteration of dose schedules and substitution of a drug is

not possible, the therapeutic approaches are aimed at alleviating the symptoms of oral dryness and limiting the consequences of salivary gland hypofunction. Patients with salivary gland hypofunction should reduce their consumption of fermentable carbohydrate (sucrose) due to the increased risk of caries. They should also be advised to sip water when eating and swallowing, and they should rinse their mouths thoroughly with water after eating. One of the key elements in maintaining a functional dentition often includes a strict individual oral hygiene regimen with regular follow-up at a dental clinic at least every 3 months. Topical application of fluoride may be useful in periods.

In patients with residual functioning salivary gland tissue, stimulation of the salivary reflex is highly recommended. Patients with natural dentition are recommended to use sugar-free chewing gum (including chewing gum containing fluoride), while patients with full dentures are recommended use of

sugarless sour sweets. Pharmacological sialogogues such as pilocarpine, a muscarinic cholinergic agonist, may also provide an increase in salivary secretion. Pilocarpine is given as tablets and systemic side effects like headache, sweating, frequent urination, increased production of gastric acid and diarrhoea may occur. If gustatory and masticatory stimulation do not provide increased salivary secretion, symptoms of oral dryness may be alleviated by commercially available saliva substitutes with lubricating and moistening properties (spray, gel and mouth rinse). Finally, acupuncture therapy and electrostimulation of the salivary glands have shown to increase salivary secretion and reduce symptoms of oral dryness. Patients with salivary gland hypofunction are predisposed for oral candidosis. This predisposition is further enhanced if the patients wear removable dentures. If present, oral candidosis should be treated with a topical antimycotic drug.

Selected references

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