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REVIEW ARTICLE

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# Salivary secretion in health and disease

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**Summary**

Saliva is a complex fluid produced by 3 pairs of major salivary glands and by hundreds of minor salivary glands. It comprises a large variety of constituents and physicochemical properties, which are important for the maintenance of oral health. Saliva not only protects the teeth and the oropharyngeal mucosa, it also facilitates articulation of speech, and is imperative for mastication and swallowing. Furthermore, saliva plays an important role in maintaining a balanced microbiota. Thus, the multiple functions provided by saliva are essential for proper protection and functioning of the body as a whole and for the general health. A large number of diseases and medications can affect salivary secretion through different mechanisms, leading to salivary gland dysfunction and associated oral problems, including xerostomia, dental caries and fungal infections. The first part of this review article provides an updated insight into our understanding of salivary gland structure, the neural regulation of salivary gland secretion, the mechanisms underlying the formation of saliva, the various functions of saliva and factors that influence salivary secretion under normal physiological conditions. The second part focuses on how various diseases and medical treatment including commonly prescribed medications and cancer therapies can affect salivary gland structure and function. We also provide a brief insight into how to diagnose salivary gland dysfunction.

**KEYWORDS**

autonomic nervous system, saliva, salivary dysfunction, salivary glands, xerostomia

## 1 | INTRODUCTION

The saliva present in the oral cavity constantly covering the teeth and oral mucosa is termed whole or mixed saliva. It is a complex mixture of fluids secreted by 3 pairs of major salivary glands, the parotid, submandibular and sublingual glands, and by numerous minor salivary glands, but it also contains various amounts of gingival crevicular fluid, microorganisms, desquamated epithelial cells and food debris.[1] Salivary glands are mostly regulated by neural reflexes as part of the autonomic nervous system, but are also under the influence of various centres in the brain and gastrointestinal hormones as well.[1-15] Salivary output differs with regard to volume and composition depending on differential activation of glands by different types of stimuli.[7,10,12-14,16-19] Saliva has multiple functions, which are linked to its fluid characteristics and to specific components. Saliva protects the teeth and oropharyngeal mucosa, it facilitates articulation of speech, it is imperative for mastication and swallowing, it exerts digestive actions, and plays an important role in maintaining a balanced microbiota.[10,13,14,20-32] Several diseases, medical conditions and medications can affect salivary gland function leading to a sensation of dry mouth (xerostomia), usually caused by reduced salivary flow and altered salivary composition.[33-37] Salivary hypofunction increases the risk of oral disease (dental caries, dental erosion and fungal infections) but may also lead to changes in dietary intake resulting in malnutrition and/or weight loss as well as impaired quality of life.[1,10,14,28-34,38,39] This review article focuses on the salivary gland structure, the neural mechanisms of salivary secretion, the

  

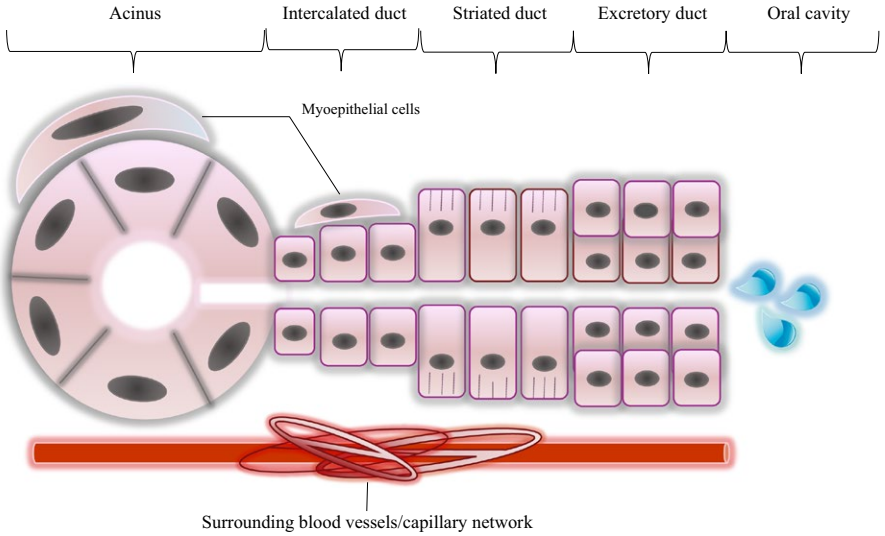


**FIGURE 1** Secretory end piece (acinus) terminating into a duct system. An acinus consists of either serous or mucous acinar cells or mucous cells capped with a serous demilune. The intercalated duct, consisting of a monolayered cuboidal epithelium, leads into the striated duct, which consists of a monolayered columnar epithelium with several folds of the plasma membrane basally, and mitochondria between the folds. The final segment of the duct system is the excretory duct (multilayered columnar epithelium), which leads the final saliva into the main excretory duct into the oral cavity. Acini and intercalated ducts are surrounded by myoepithelial cells

process of saliva formation, functions of saliva and the factors that influence salivary secretion and composition under normal physiological and pathophysiological conditions. The latter includes various diseases, medical conditions, commonly prescribed medications and cancer therapy. The search for biomedical literature on normal salivary gland structure and function and dysfunction (years 1954 to 2017) was conducted in PubMed, Embase and Web of Science databases. Articles from the primary, secondary and tertiary literature were selected for inclusion on the basis of their significance and relevance to the clinician.

## 2 | SALIVARY GLAND STRUCTURE

Salivary glands are categorised into the 3 pairs of major glands, including the parotid, submandibular and sublingual glands and about 600 to 1000 minor salivary glands particularly located in the labial, buccal, palatal, lingual and retromolar regions of the oral mucosa.[40] The salivary glands consist of parenchymal and stromal components. The parenchyma is composed of secretory end pieces (acini), which make a primary fluid/saliva, connected to a system of ducts (intercalated, striated and excretory) which modify the saliva (Figure 1). Each acinus consists of either serous or mucous cells, or mucous cells capped by serous demilunes (only found in the submandibular gland), arranged about a central lumen. The salivary glands are classified histologically according to their structural composition and their secretions[1,5,6,9,10,12-14,22-28] (Table 1). The length and the diameter of the duct system vary depending on the gland type. The major salivary glands have long, branched ducts, the parotid and submandibular glands contain all ductal segments (intercalated, striated and excretory), whereas the sublingual and minor glands lack striated ducts.[40]

Myoepithelial cells are contractile cells with a stellate shape that surround the acini and intercalated ducts variably in the different glands. They are located between the basal lamina and the cytoplasmic membrane of acinar or ductal cells (Figure 1). The myoepithelial cells are controlled by the autonomic nervous system and upon contraction they are believed to assist the flow of saliva by compressing the acini and the ducts and also to provide structural resilience to the parenchyma during secretion.[41] Although they are contractile there is no evidence to suggest they force saliva out of acini by increasing intra-acinar pressure and indeed their presence is not required for secretion to occur.

The connective tissue capsule that surrounds the major salivary glands forms septa, which divide the gland into lobes and lobules. These septa contain large blood vessels, nerves and ducts, whereas the acini, intercalated and striated ducts, small blood vessels and nerves are located within the lobules. In the minor salivary glands, the connective tissue merges imperceptibly with the surrounding connective tissue.[41] The parenchyma has a rich supply of blood vessels, which form a capillary plexus, particularly adjacent to the ducts. Sympathetic stimulation makes the blood vessels constrict, whereas parasympathetic stimulation lead to vasodilation and increased blood flow to the salivary glands.[42] Virtually all protein in "pure glandular saliva" is derived from the salivary glandular cells and not the blood stream. Most of the about 2.500 different proteins in whole/mixed saliva probably originate from exfoliating epithelial cells and oral microorganisms, and only one-tenth is thought to be of gland origin.[26]

The final saliva that enters the oral cavity is composed of more than 99% water and less than 1% solids, including proteins and salts. The normal daily production of saliva is approximately 0.6 L.[37,43] The major salivary glands produce about 90% of the fluid secretion and

**TABLE 1** Salivary gland structural features, parasympathetic innervation and contribution to whole saliva volume under unstimulated (in the absence of exogenous stimuli) and under chewing-stimulated conditions[1,10,12-14,40]

| | Acinar cell type | Secretory product | Contribution (%) to whole saliva volume | Parasympathetic nerve supply | Ducts to the oral cavity |
|---|---|---|---|---|---|
| Major salivary glands | | | | | |
| Parotid glands | Serous | Watery, amylase-rich | Resting: 25%<br>Stimulated: 50% | Glossopharyngeal nerve | Stensen's duct |
| Submandibular glands | Mixed, mainly serous | Viscous, mucin-rich | Resting: 60%<br>Stimulated: 35% | Facial nerve | Wharton's duct |
| Sublingual glands | Mixed, mainly mucous | Viscous, mucin-rich | Resting: 7%-8%<br>Stimulated: 7%-8% | Facial nerve | Ducts of Rivinus<br>Bartholin's duct |
| Minor salivary glands | | | | | |
| Palatinal glands | Mucous | Mucin-rich | Resting: 8%<br>Stimulated: 8% | Facial nerve | Individual small ducts |
| Buccal glands | Mixed, mainly mucous | Mucin-rich | | Facial nerve | |
| Labial glands | Mixed, mainly mucous | Mucin-rich | | Facial nerve | |
| Lingual glands | Serous | Watery, lipase-rich | | Glossopharyngeal | |
| Retromolar glands | Mucous | Viscous, mucin-rich | | Facial nerve/ Glossopharyngeal | |

The sympathetic nerve supply is obtained from the superior cervical ganglion. Mixed means that the glands contain both serous and mucous acini, also mucous acini capped with serous demilunes may be seen in these glands.

the minor glands less than 10%. However, the minor salivary glands secrete a relative large fraction of the salivary mucins, providing lubrication to the oral surfaces.[44] Table 1 details the contribution of the various glands to the whole saliva volume under unstimulated and stimulated conditions.

## 3 | NEURAL REGULATION OF SALIVARY SECRETION AND THE SECRETORY ELEMENTS

Salivary secretion is controlled by the autonomic nervous system and regulated by reflexes. The reflex pathways consist of an afferent component, the salivation centre and an efferent component, which leads to activation of salivary gland cells (Figure 2).

The gustatory-salivary reflex involves sensory signals from taste-activated chemoreceptors in the taste buds in the lingual papillae, in pharynx and larynx, transmitted along sensory fibres of the facial, glossopharyngeal and vagal nerves to the nucleus of the solitary tract.[45] The masticatory-salivary reflex conducts somatosensory impulses, which are primarily induced by activation of mechanoreceptors in the periodontal ligament during mastication, but also by activation of proprioceptors and/or nociceptors in the oral cavity, along with sensory trigeminal and glossopharyngeal nerves to the mesencephalic and spinal trigeminal nuclei.[7,46] The sensory nuclei convey these inputs to the salivation centre and to higher brain structures. Thus, salivary reflex pathways situated in the lower brainstem can in theory activate salivary secretion without involvement of higher brain centres.[47] Concomitantly, afferent signals transmitted from the sensory nuclei along second and third order ascending neurons activate higher brain centres, which then via efferent inputs can modulate the reflexes. Accordingly, not only masticatory and gustatory afferent impulses, but also olfactory, nociceptive, thermoreceptive and psychic stimuli influence salivation.[8,48-50]

Afferent sensory impulses are transmitted to the salivation centre (comprising the parasympathetic superior and inferior salivatory nuclei in the brainstem and the sympathetic salivation centre in the upper thoracic segments of the spinal cord) and to higher brain structures, which may send both excitatory and inhibitory efferent projections to the salivatory nuclei. The inputs are integrated in the salivation centres, which induce generation of nerve impulses in the parasympathetic and sympathetic neurons innervating the salivary glands. In the human brain, the exact neuroanatomical pathways for connections between the salivation centre and forebrain structures have not yet been fully explored, and most of the knowledge about projections from higher brain centres to the brain stem derives from animal studies.[51-53]

The efferent part of the reflex consists of parasympathetic and sympathetic secretomotor neurons, which innervate the salivary glands. Overall, the parasympathetic innervation of the salivary gland cells is more abundant than the sympathetic innervation. Upon stimulation, both parasympathetic and sympathetic nerves cause secretion of fluid and protein, as well as contraction of myoepithelial cells, and the 2 divisions of the autonomic nervous system interact synergistically. Since parasympathetic activity results in large volumes of saliva and sympathetic activity results in small

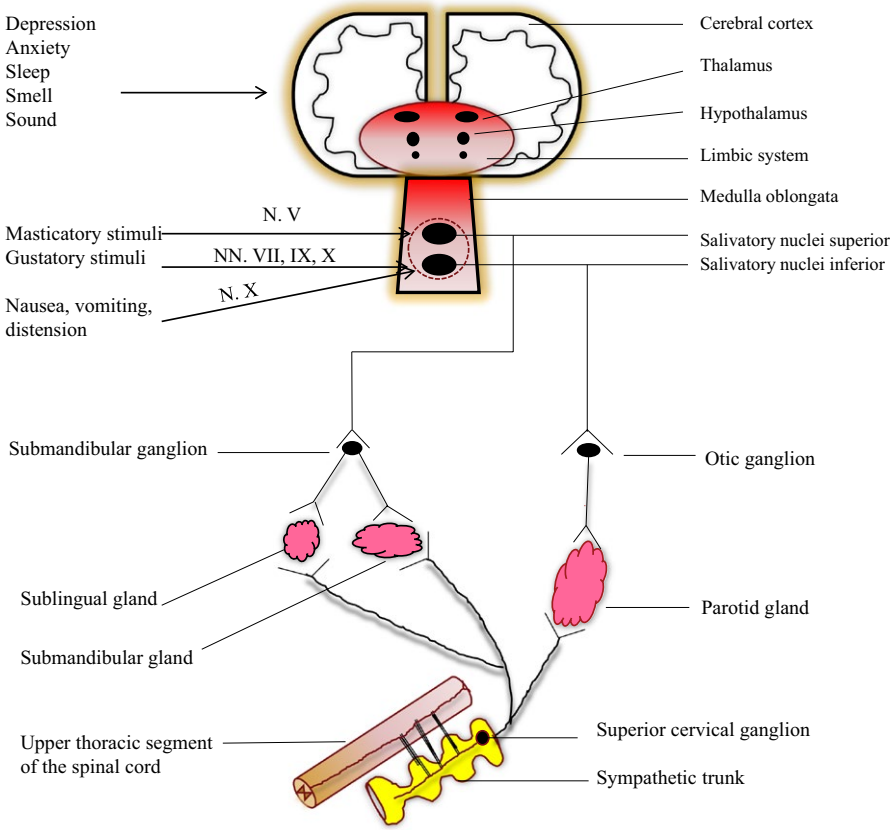


**FIGURE 2** Regulation of salivary secretion illustration of the reflexes involved in salivary secretion. Afferent nerves carry sensory inputs that arise from taste activation of chemoreceptors (via the facial [VII], glossopharyngeal [IX] and vagus [X] nerves) or from activation of mechanoreceptors or nociceptors (via the trigeminal [V] nerve) to the salivatory nuclei in the medulla oblongata. The salivatory nuclei also receive impulses from higher brain structures, which thereby influence salivary secretion. Afferent inputs are integrated in the salivatory centre, which then activate the efferent part of the reflex, comprising parasympathetic and sympathetic nerves. The parotid glands receive parasympathetic signals from the glossopharyngeal nerve that synapse in the otic ganglion. The submandibular and sublingual glands receive parasympathetic signals from the facial nerve that synapse in the submandibular ganglion. The sympathetic nerves run from to the sympathetic trunk and synapse in the superior cervical ganglion. Postganglionic sympathetic nerves then follow the blood vessels to the salivary glands which they innervate. Acetylcholine and noradrenaline are released from the postganglionic the parasympathetic and the sympathetic nerve endings, respectively, and elicit salivary secretion. Other co-transmitters are released to which have a modulatory effect on the formation of saliva

volumes, the parasympathetic saliva is characterised as protein-poor (in terms of concentration) and the sympathetic saliva as protein-rich.[13] Under reflex secretion, the sympathetic nerve is thought to act in a background of a parasympathetically induced flow of saliva. Hormones, apart from adrenaline, do not seem to evoke fluid secretion. However, recent findings indicate a possible secretory role of gastrointestinal hormones.[13,15] Gastrin, cholecystokinin and melatonin (the latter found in large amounts in the intestines apart from its traditional pineal localisation) induce protein secretion, but not fluid secretion, in the rat parotid gland.[11,15,54] Moreover, the 3 hormones stimulate protein synthesis in the experimental gland. In addition, in vitro studies on human parotid tissue demonstrate acinar exocytosis of protein storing granules upon stimulation with pentagastrin and melatonin.[11,54] Thus, salivary glands and the secretion may, like other digestive glands, be under the control of a cephalic phase (nerves), a gastric phase (gastrin) and an intestinal phase (cholecystokinin and melatonin).[13]

### 3.1 | Blood supply to the salivary glands

The blood vessels of the glands are supplied with parasympathetic vasodilator fibres that upon stimulation cause the blood flow to increase up to 20-folds, thus providing water for secretion.[26,42] The sympathetic innervation supplies the vessels with vasoconstrictor fibres. Importantly, these vasoconstrictor fibres are separate from those sympathetic secretomotor fibres for the gland cells and further, they are activated in connection with a fall in blood pressure such as in a situation of blood loss and not under normal conditions such as during a meal.[26,42]

### 3.2 | Activation of salivary gland receptors

Beside the traditional transmitters of the parasympathetic and sympathetic postganglionic nerves, acetylcholine and noradrenaline, respectively, a number of co-transmitters may occur in cholinergic

and adrenergic axons, of which some induce secretion themselves or potentiate the effects of the classical transmitters.[18,55-59] Particular attention has been paid to the parasympathetic innervation and a number of neuropeptides as potential co-transmitters, one of which is vasoactive intestinal peptide (VIP), causing secretion of proteins but only a small fluid secretion, if any, and moreover, vasodilatation.[18,57,59]

Nitric oxide of parasympathetic origin is also involved in the vasodilator response, and in the acinar cells, nitric oxide may be mobilised upon stimulation, contributing to cAMP-mediated protein secretion.[13,26,60] Substance P, another neuropeptide, causes a profuse salivation but only in some species and *not* in humans.[18,59] In contrast to the acinar cells of the human parotid and submandibular glands

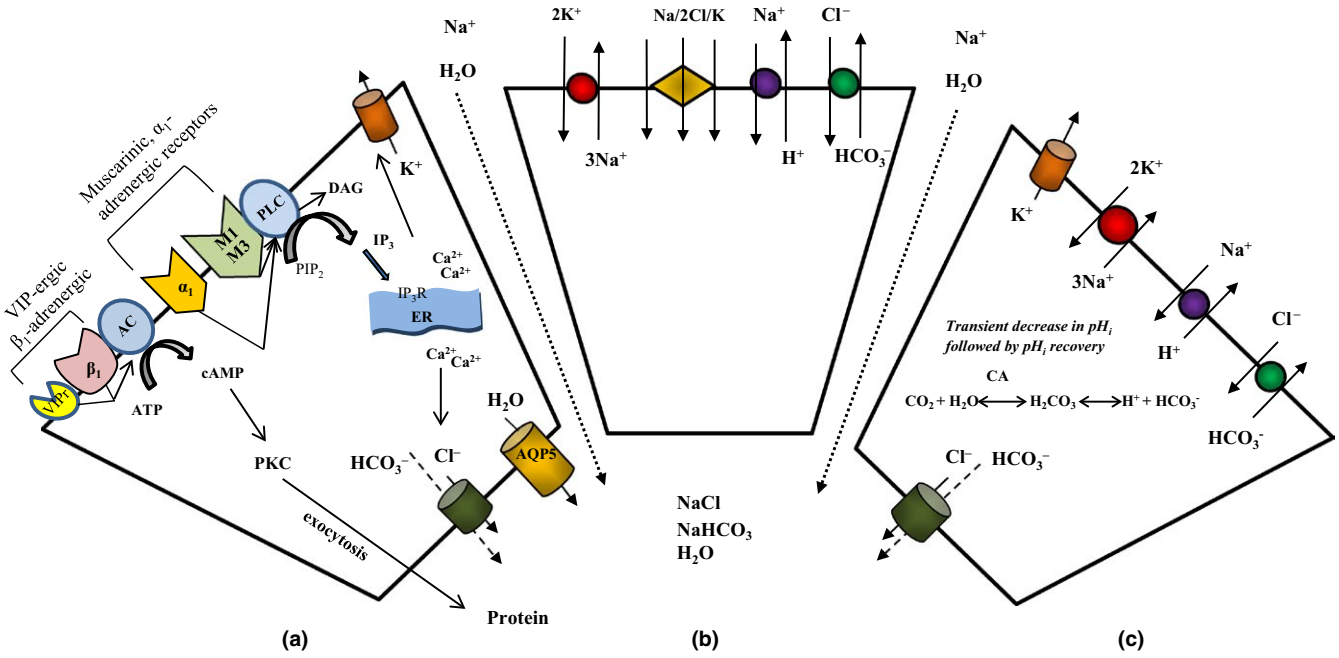


**FIGURE 3** Model for acinar ion transport mechanisms involved in salivary fluid formation. A, Salivary secretion depends on increase in the free intracellular calcium concentration $[Ca^{2+}]_i$ in response to receptor stimulation to initiate key ion transport pathways necessary for primary fluid formation. Stimulation of $G_{q/11}$-protein coupled, primarily the muscarinic M3 and M1 receptors by acetylcholine, leads to phospholipase C (PLC)-mediated inositol 1,4,5-triphosphate ($IP_3$) production, subsequent $IP_3$ receptor activation on the endoplasmatic reticulum (ER) and rapid $Ca^{2+}$ release from the ER. Acinar cells further express α1- and β-adrenergic receptors, which bind noradrenaline released from the glandular sympathetic innervation. Stimulation of $\beta_1$-adrenergic receptors, coupled to $G_s$-protein, induces activation of adenylyl cyclase (AC), followed by cyclic adenosine monophosphate (cAMP) production. cAMP activates protein kinase A (PKA), which via phosphorylation events mediates exocytosis of proteins from acinar cells. $\beta_1$-adrenergic receptor activation may also elicit fluid secretion. $\alpha_1$-adrenergic receptor stimulation evokes similar to M3 and M1 activation PLC/IP3-mediated $[Ca^{2+}]_i$ increase, however, parasympathetic muscarinic receptor activation by acetylcholine is the primary stimulus for production of the bulk of salivary fluid. Transepithelial movement of anions is regarded the main driving force for acinar electrolyte and fluid secretion. Both chloride and bicarbonate can drive salivary secretion, and details primarily the chloride-dependent model. Increase in $[Ca^{2+}]_i$ upon receptor stimulation immediately opens luminal, calcium-activated chloride channels, consistent with TMEM/ANO-1. In parallel, basolateral calcium-activated potassium channels are opened, the molecular identities of which are the intermediate conductance KCa3.1 (IK1) and the large-conductance KCa1.1 (maxi-K) channels. Basolateral potassium efflux leads to hyperpolarisation, which provides electrical driving force for the luminal chloride efflux. The accumulation of chloride ions intraluminally creates a transepithelial lumen negative potential difference, which drives sodium paracellularly into the lumen. The resulting high intraluminal sodium chloride concentration causes osmotic water movement to the lumen, both transcellularly via aquaporin water channels as well as paracellularly. The final result is formation of isotonic primary saliva with plasma-like sodium chloride concentrations. To obtain sustained secretion from acinar cells, $[Ca^{2+}]_i$ is maintained high due to extracellular calcium influx induced by the mechanism of store-operated calcium entry, in which initial calcium release from intracellular stores leads to gating of plasma membrane calcium channels. Resting conditions in acinar cells are rapidly reestablished after stimulation is terminated. Intracellular calcium concentrations are reduced to the pre-stimulatory level by plasma membrane calcium ATPases, the Sarco/Endoplasmic Reticulum Calcium ATPase-pump and by calcium binding proteins. B, Chloride secretion from acinar cells depends on basolateral ion transporters, which in cooperation accumulate intracellular chloride above equilibrium. The $Na^+/K^+$ -ATPase creates an inwardly directed sodium gradient across the basolateral membrane, and provides energy for this activity. The gradient is utilised for chloride uptake by the loop-diuretic sensitive $Na^+/K^+/2Cl^-$ cotransporter NKCC1 and a coupled parallel pathway consisting of a basolateral $Cl^-/HCO_3^-$ exchanger (AE2) and a $Na^+/H^+$ exchanger (NHE1). C, The secretory response from acinar cells is paralleled by transient intracellular acidification caused by the efflux of $HCO_3^-$. $HCO_3^-$ and $H^+$ are produced by the carbonic anhydrase catalyzed conversion of $CO_2$ and $H_2O$. $HCO_3^-$ efflux can significantly contribute to primary saliva formation, likely via a similar luminal conductance as $Cl^-$, however, in many salivary glands $Cl^-$ secretion is sufficient to drive fluid formation. Following $HCO_3^-$ efflux, the intracellular pH recovery is achieved by up-regulated activity of the basolateral $Na^+/H^+$ exchanger, which can use the $Na^+$ gradient established by the $Na^+/K^+$ ATPase to export protons

which lack a substance P innervation,[59] substance P-immunoreactive fibres are present in the human labial salivary glands, where stimulation with substance P also induced a raise in intracellular calcium suggesting that it is involved in fluid secretion in these glands.[58]

The receptors upon which the transmitters act are located on the basolateral part of the cell membrane. The cholinergic receptors are of muscarinic M1- and M3-subtypes, whereas the adrenergic receptors are of $\alpha_1$-and $\beta_1$- subtypes.[18,26,55] VIP acts on so called VIP-ergic receptors. Interestingly, with respect to the sympathetic response noradrenaline evokes protein secretion particularly by $\beta_1$-receptors, while fluid secretion, serving as carrier for the proteins, is caused by $\alpha_1$-adrenergic receptors. With respect to the parasympathetic response, VIP is particularly responsible for protein secretion and acetylcholine for fluid secretion, serving as carrier.[18,26,55,61,62] Cross-talk of these transmitter substances, via the intracellular messengers cAMP (preferentially protein secretion) and $Ca^{2+}$ (preferentially fluid secretion), amplifies the neurotransmitter effects and is responsible for augmented fluid and protein secretion under normal reflex conditions. Several purinergic receptor subtypes have also been found in salivary gland cells from various species, including human labial salivary glands, which indicates additional modulation of salivary gland function by extracellular nucleotides.[18,58,63,64] Figure 3 illustrates the events occurring upon stimulation of the muscarinic, $\alpha_1$-adrenergic (both Gq/11-protein-coupled receptors) and $\beta_1$-drenergic and VIP-ergic receptors.[18,19,65-69]

### 3.3 | Trophic effects of nerves on salivary gland size

The parasympathetic innervation is of particular importance for the gland size and secretory capacity. A parasympathetic denervation is followed by a marked fall in weight, which is gradually restored as re-innervation progresses.[57] However, denervation procedures are not necessary to produce changes in gland size. Animal studies show gland size, secretory capacity and neuronal synthesis of acetylcholine to decrease in response to decreased demands on reflex secretion induced by liquid diet and to increase in response to increased demands on reflex secretion induced by a chewing-demanding diet.[70] Acetylcholine is not the likely transmitter responsible for changes in gland weight, but rather a phenomenon involving neuropeptides.[57]

### 3.4 | Sensory gland innervation

Patients experience pain in the salivary gland region upon gland swelling in response to gland inflammation or sialolithiasis. The pain is often referred to stretching of the gland fascia and, as a consequence, activation of afferent nerves of the fascia.[71,72] However, sensory nerves, containing the neuropeptides substance P and calcitonin gene-related peptide occur along the small ducts and close to the vessels.[73] Local release of these sensory peptides occurring as a protective response may result in contraction of the myoepithelial cells and release of ductal located antimicrobial agents as well as vasodilation, protein extravasation and formation of oedema.[74] Experimentally, increase in ductal pressure and, in particular, exposing the ductal cells to noxious substances, activate impulse activity in the glandular sensory nerves travelling in the parasympathetic and sympathetic nerves of the glands.[75]

## 4 | FORMATION OF PRIMARY SALIVA AND DUCTAL SALT REABSORPTION

Formation of saliva takes place in a 2-stage process.[76] Upon stimulation, the acini produce an isotonic, primary secretion with plasma-like electrolyte composition. This primary saliva is then modified by the striated ducts, where sodium and chloride ions are reabsorbed and bicarbonate and potassium ions are added without further changes in the water content due to the low water permeability of the ductal epithelium. Thus, the final saliva that enters the oral cavity is hypotonic and has low sodium concentration in comparison to plasma. Figure 3 details the cellular mechanisms underlying formation of primary saliva.[19,62,76-88]

Salivary duct epithelial cells express ion transport pathways that enable reabsorption of sodium and chloride across the luminal membrane. Sodium can enter the cells via the amiloride-sensitive, epithelial sodium channel, ENaC[89,90] and chloride via the CFTR (cystic fibrosis transmembrane regulator) chloride channel[91-94] expressed in the luminal membrane. The driving force for sodium reabsorption is provided by the inwardly directed sodium gradient resulting from $Na^+/K^+$ -ATPase activity, which is abundantly expressed in the basolateral membrane foldings of striated ducts.[91] The transporters involved in generation of driving force for luminal chloride uptake are not completely resolved, but may include basolateral $Cl^-$ exit pathways, such as a $K^+/Cl^-$ co-transporter,[95] the AE4 member of the $Cl^-/HCO^-_3$ exchanger family,[96] and the hyperpolarisation-activated Clcn2 chloride channels.[97] An alternative pathway possibly involved in luminal sodium and chloride reabsorption is a luminal $Na^+/H^+$ exchanger (isoforms NHE2 and NHE3,[91] possibly operating in conjunction with a luminal $Cl^-/HCO^-_3$ exchanger (isoforms SLC26A4 and SLC26A6,[98] which promotes $Cl^-$ import in exchange for $HCO^-_3$. Nevertheless, a study on the effect of knockout of the NHE2 or NHE3 isoform in mice did not reveal a significant role of these in sodium reabsorption.[99] Although salivary duct epithelial cells contribute a large amount of bicarbonate to the salivary secretion, neither the proportion contributed or the underlying ion transport mechanisms are fully known. Sodium bicarbonate co-transporters (NBC) may be involved in ductal bicarbonate secretion. For instance, expression of 2 isoforms has been described from the human parotid and submandibular glands, and the cellular localisation differed between these two.[100] Basolateral expression of the NBCn1 isoform is in agreement with a supportive role in ductal bicarbonate secretion, whereas the role of the luminally expressed NBC3 is less clear, but might include absorption of bicarbonate under certain conditions.[100] A further source for bicarbonate release into the salivary secretion is the intracellular, carbonic anhydrase catalysed conversion of $CO_2$ and $H_2O$. In co-operation with the basolateral sodium/proton exchanger (NHE1),

bicarbonate generated from this reaction can leave the cells via the luminal $Cl^-/HCO_3^-$ exchanger. In addition to the ductal bicarbonate contribution, a certain amount of salivary bicarbonate may also originate from acinar cells, as for instance expression of the NBCe1 transporter was observed in human parotid acini.[101] It has been shown that the luminal membranes of ducts in mouse submandibular glands express potassium channels, which may play a role in ductal potassium secretion.[102] Although the bulk protein secretion occurs from the acini, the ductal cells also release various proteins, including growth factors (eg nerve growth factor and epithelial growth factor), immunoglobulin (IgA) and kallikrein.[88]

The final salivary electrolyte composition is dependent on the flow rate, which in turn depends on the stimuli that activate neurotransmitter release from the glandular autonomic neurons. In the human parotid gland, sodium and chloride are largely reabsorbed at low or unstimulated secretion rates.[103,104] Upon stimulation of the submandibular glands, the salivary concentrations of sodium, bicarbonate, chloride, calcium, and protein, the ionic strength, and pH increase with increasing flow rates, whereas potassium concentrations only slightly decline with increasing flow.[16] Testing the effect of the duration of stimulation at different constant flow rates, for instance, on bicarbonate and chloride concentrations, revealed that after an initial increase of both anion concentrations, bicarbonate concentration continued to increase, whereas chloride concentration decreased during prolonged stimulation, resulting in an inverse relationship between these ions with time.[16,103,104] Moreover, parotid salivary pH followed the pattern of bicarbonate and increased with stimulation duration and higher flow rates.[103] Overall, this underlines the importance of the salivary flow rates and duration of stimulation for the final electrolyte concentrations, ionic strength, tonicity and pH of saliva, which are important for the functions of saliva.

## 5 | FACTORS INFLUENCING SALIVARY SECRETION

Salivary gland function is under the influence of various factors and stimuli, which can alter the volume, flow, and composition of saliva. For instance, unstimulated saliva flow rates display circadian variation, with a peak level in the afternoon and a time span of 12 hours between highest and lowest secretory rates.[105-109] Salivary protein displayed a similar pattern, whereas salivary sodium and chloride concentrations followed the reverse rhythm, with highest levels in the early morning.[105,106,108] Labial salivary glands also show some daytime-dependent variation, with highest secretory rates in the evening, and a diurnal pattern different from the rhythm of unstimulated whole saliva.[110] A recent publication has demonstrated expression of certain key clock genes involved in regulation of circadian rhythms and of aquaporin 5 in mouse submandibular gland cells, which both followed a regular rhythmic pattern.[111] Thus, evidence suggests that normal salivary secretion is under influence of a circadian clock mechanism, which may also play a role in different salivary gland pathologies.[112] In addition, it is important to take variations in salivary secretion due to circadian rhythms into consideration, when saliva flow rates are measured and saliva composition is analysed in a clinical context or for research purposes.

The level of hydration of the body also influences salivary secretion.[109] It has been shown that parotid saliva flow rates decreased significantly in both younger and older healthy adults after a 24 h period of fluid and food abstinence,[113] and conditions of acute dehydration are also associated with reduction in salivary flow rates.[114,115] Gland size is another factor related to saliva flow rates.[116-118] With respect to ageing, a number of studies have investigated whether it is associated with decrease in salivary flow rates, since both major and minor salivary glands undergo age-related structural, degenerative changes, such as loss of secretory acini and stromal alterations.[119-125] In this regard, results are contradicting, showing stable[113,126-133] or declining salivary gland function with age.[134-136] This variability may be ascribed to differences in sampling conditions and methods used, and in the health status of study participants, since in older people, reduced salivary flow is often associated with diseases and medication intake.[128] A recent meta-analysis revealed that unstimulated and stimulated whole as well as submandibular/sublingual, but not parotid and minor salivary gland flow rates were lower in older than in younger persons.[137] However, the difference was not significant for stimulated whole saliva flow rates after exclusion of the medicated subgroup in the analysis.[137] Results indicating that unstimulated whole saliva flow may be more prone to decline in older people suggest that the degree of functional glandular impairment with age may vary despite consistently observed age-related loss of secretory tissue in all salivary glands. For instance, the function of the parotid gland, which contributes most to chewing-stimulated secretion, remains stable during ageing in healthy, non-medicated persons.[126]

## 6 | FUNCTIONS OF SALIVA

Saliva serves multiple functions, which are important for the maintenance of oral and general health. Saliva lubricates and cleanses the teeth and oral mucosa, maintains neutral pH through its buffering capacity, prevents tooth demineralisation, exerts antimicrobial actions, aids in taste and bolus formation, initiates enzymatic digestion of starch and is imperative for mastication and swallowing and articulation of speech (Table 2).[10,13,14,20-29] It also plays an important role in the formation of the acquired enamel pellicle and the mucosal pellicle, which apart from having a protective function also determine the initial adhesion and colonisation of microorganisms and the composition of the resident oral microbiota.[30-32] Saliva contains several proteins and peptides with specific biological functions, a proportion of which are of microbial origin.[26,138] There is a large panel of host salivary proteins and peptides, which range in abundance and a core group of proteins.[139] Table 2 shows the functions of the most abundant salivary proteins. Salivary proteins are involved in a

**TABLE 2** Functions of saliva related to its components and their mode of action (for reviews[1,10,13,14,20-32])

| Function | Component | Mode of action |
|---|---|---|
| Maintenance of oral health | | |
| Lubrication of oral surfaces | Mucins | Mucins are large, highly glycosylated proteins that form a hydrophilic network |
| | Glycosylated proline-rich proteins | MUC5B is the primary gel-forming mucin, MUC7 is less efficient as lubricant |
| | Water | Moisten and lubricate oral surfaces, give saliva its texture and viscosity |
| Oral clearance | Water | Elimination of microorganisms, dietary sugars and acids by dilution and swallowing |
| Buffer capacity | Bicarbonate<br>Phosphate<br>Proteins | Buffer acids from dietary intake and acids produced by bacterial fermentation of sugars, thereby maintaining pH in the neutral range, decreasing the tooth demineralisation rate and promoting/maintaining a balanced oral microbiota |
| Salivary pellicle formation | Salivary proteins | Salivary proteins, eg mucins, proline-rich proteins, α-amylase, cystatins, statherins, lysozyme, lactoferrin, sIgA a.o. interact with dental and mucosal surfaces, each other, and oral microorganisms, thereby altering their properties and ability to modulate the microbial colonisation in the oral cavity. MUC1 and MUC4, which play a role in cell signalling, also interact with other salivary proteins |
| Tooth mineralisation | Proline-rich proteins<br>Cystatins<br>Statherins | High affinity to hydroxyapatite, bind to calcium, inhibit spontaneous precipitation of calcium phosphate salts from the dental surfaces, important for the integrity of the teeth |
| Antimicrobial actions | Mucins | Mucins, promote aggregation of microorganisms, especially MUC7; antibacterial, antifungal and antiviral |
| | Histatins | Antifungal, moderate antibacterial |
| | Cystatins | Antibacterial, antifungal and antiviral |
| | Statherins | Antibacterial, antifungal and antiviral |
| | Proline-rich proteins | Antibacterial (Gram-negative), antiviral |
| | Peroxidases | Catalyse oxidation of thiocyanate to hypothiocyanite by hydrogen peroxide; antibacterial and antifungal |
| | α-amylase | Antibacterial, provide nutrition for certain bacteria via hydrolysis of starch |
| | Lysozyme | Hydrolysis of the polysaccharide layer of the gram-positive bacterial cell wall; antibacterial, antifungal and antiviral |
| | Lactoferrin | Binding and sequestering of iron, depriving microorganisms of iron; antibacterial, antifungal and antiviral |
| | Immunoglobulins, mainly sIgA | Inhibit microbial adhesion, enhance phagocytosis, aggregate microorganisms in interactions with other proteins<br>Antibacterial, antifungal and antiviral |
| | Defensins | Antimicrobial peptides |
| Tissue repair | Growth factors | Epidermal growth factor (EGF) promotes proliferation and migration of oral epithelial cells for wound healing; fibroblast growth factor (FGF) promotes wound healing and tissue repair |
| | Water, mucins | Protects oro-oesopharyngeal mucosa from injury |
| Digestive functions | | |
| Taste | Water, mucins | Dissolution and transport of taste substances to taste buds |
| | Gustin | Growth and development of taste buds, integrity of taste sensitivity |
| | Salivary proteins | Salivary composition influences the perception of fat, saltiness, bitterness, and the perception of texture |
| | Electrolytes | |
| | Proline-rich proteins | Precipitate tannins and thus contribute to the sensation of astringency |

*(Continues)*

**TABLE 2** (Continued)

| Function | Component | Mode of action |
|---|---|---|
| Initial digestion | α-amylase, lipase | α-amylase cleaves the α-1,4-glycosidic linkages of starch into maltose, maltotriose and dextrins |
| Mastication | | Hydrolyses triglycerides into partial glycerides and free fatty acids |
| Food bolus formation, swallowing | Water, mucins | Promotes and facilitates bolus formation and swallowing |
| Articulation of speech | Water, mucins | Facilitates articulation of speech |

range of functions, for example acidic proline-rich proteins, histatins, cystatins and statherins have a high affinity for hydroxyapatite as they bind to calcium. Statherin in particular inhibits precipitation of calcium phosphate salts from saliva and thereby plays a central role in tooth integrity.[140] Some of the more abundant salivary proteins display multifunctionality and act in synergy, for example, histatins are a group of basic proteins which play a role in wound healing, have antimicrobial activity and bind to enamel.[140,141]

Physiological factors, for example reflex stimulation, circadian rhythms and age influence the composition of proteins, and inorganic constituents in whole mouth saliva. As mentioned above, the composition of both glandular and whole mouth saliva is highly dependent on the flow rate, and the concentrations of sodium, chloride and bicarbonate are higher, and the concentrations of potassium and total phosphate are lower in stimulated compared to unstimulated saliva.[16,17,19,76,77] The salivary buffer capacity includes the bicarbonate, phosphate and protein systems and is much higher in stimulated saliva due to the higher concentrations of bicarbonate.[142-145] In the unstimulated state, the bicarbonate and phosphate buffer systems contribute almost to the same extent to the overall buffer capacity, whereas the bicarbonate buffer system is responsible for more than 90% of the total buffer capacity in stimulated whole saliva. At very low saliva flow rates and at pH below 5.0 it is mainly proteins that contribute to the buffer capacity.[144-146] Salivary pH and salivary concentrations of calcium and phosphate are important factors for the maintenance of saturation with regard to hydroxyapatite in the saliva. The salivary buffer capacity, and its ability to keep pH within a neutral range, is also important for the promotion and maintenance of a balanced oral microbiota.[31,32,147] The bicarbonate is an ideal buffer in the oral cavity as it also contributes with a phase buffering effect, due to the carbon dioxide phase conversion from the dissolved state to the volatile gaseous phase, resulting in loss of the acidic end product from the oral cavity. Carbon anhydrase VI, which is secreted into human saliva by the serous acinar cells of the parotid and submandibular glands, catalyses this conversion of carbonic acid to water and the volatile gas carbon dioxide.[148]

Recent studies have revealed several hundred fatty acids, peptides, amino acids and other low molecular weight metabolic derivatives constituting the human salivary metabolome. Components of the human salivary metabolome are derived from and provide biomarkers of both human and microbial metabolic activity and their functional significance is being studied.[149,150]

## 7 | SALIVARY GLAND DYSFUNCTION

Salivary gland dysfunction is defined as any quantitative and/or qualitative change in the output of saliva. It can either be a reduction in salivary secretion ranging from mild to severe hypofunction or an increase in salivary secretion (hyperfunction). The latter, called sialorrhea is relatively uncommon in adults. Drooling may occur as the result of genuine salivary hyperfunction (primary sialorrhea), but most commonly drooling is associated with an overflow of saliva from the mouth due to impaired neuromuscular control with dysfunctional voluntary oral motor activity or disturbances in sensory ability (secondary sialorrhea).[151] In Parkinson's disease drooling is attributed to a swallowing disorder and not to an increase in salivary flow rate.[152] In fact, both unstimulated and stimulated salivary flow rates have been found decreased and the frequency of xerostomia increased in patients with Parkinson's disease.[153-155]

Of note, the side-effects of treatment of schizophrenia with clozapine, the flagship of the second generation of antipsychotics, are often both dry mouth and sialorrhea.[37] Clozapine is a dopamine receptor antagonist but it acts also as a partial agonist on muscarinic M1 receptors and as antagonist on muscarinic M3 receptors and $\alpha_1$ adrenergic receptors explaining mixed actions of the drug.[156] The following section is focused on the most common problem, namely salivary gland hypofunction and the associated changes in saliva composition and oral consequences.

Salivary gland hypofunction is often associated with a persistent sensation of dry mouth (xerostomia). Xerostomia usually occurs when the unstimulated whole saliva flow rate falls by 40-50% of its normal value in any given person, indicating that more than one major salivary gland must be affected.[109] However, xerostomia may also occur without objective evidence of salivary gland hypofunction.[157] Thus, xerostomia may be a result from changes in salivary composition or function, particularly of lubricating mucins.[21] Xerostomia is a common complaint estimated to affect at least 10% of an adult population.[158,159] The prevalence of xerostomia, however, varies from 5.5% to 46% depending on the method of assessment used and the population cohorts studied.[160,161] Generally, women and older people suffer more from xerostomia and have lower salivary flow rates than men and younger people due to a higher number of diseases and a higher intake of medication among women and older people.[159,162-168] Salivary gland hypofunction may develop into

hyposalivation, a term that is based on objective measures of the salivary flow rate (sialometry).

## 8 | CONSEQUENCES OF SALIVARY GLAND HYPOFUNCTION

Patients with salivary gland hypofunction, irrespective of the aetiology, often complain of oral dryness that is present throughout the day, but it can also lead to disturbed sleep at night. Persistent and severe salivary gland hypofunction commonly results in mucosal changes, an increased activity of caries with lesions on cervical, incisal and cuspal tooth surfaces and oral fungal infections.[1,10,14,21-32,38,39,109,168-171] Disturbed taste sensation, impaired lubrication and dysphagia may lead to behavioural changes avoiding certain foods. In turn, changes in dietary intake may result in nutritional deficiencies and atrophy of the masticatory muscles and decreased masticatory ability.[23,172-176] Consequently, salivary gland hypofunction and its related symptoms and clinical consequences often have negative effects on social functioning and quality of life.[34,157,159,177-179] Table 3 shows the various consequences of persistent salivary gland hypofunction. Of note, the feeling of oral mucosal dryness may be associated with dryness in other regions of the body indicating common underlying factors for dryness.[180]

## 9 | CAUSES OF SALIVARY GLAND HYPOFUNCTION

Intake of medications, especially of antidepressants, anxiolytics, opiates, antihypertensives, diuretics and antihistamines, is the most common cause of salivary gland hypofunction and xerostomia. Drugs can affect the salivary secretory mechanisms in various ways. Some drugs, like benzodiazepines and opioids, affect the central neural regulation of salivary secretion, while others act on the peripheral neuro-effector site via interaction with the binding of neurotransmitters to receptors on the plasma membranes of the salivary gland cells, including atropine, which binds to muscarinic cholinergic receptors and α- and β-blockers, which bind to adrenergic receptors. Other drugs like diuretics can indirectly affect the salivary secretion via their action on the salt and water transport and water balance. In addition, polypharmacy, that is a regular daily intake of more than 4 different medications, is associated with xerostomia and salivary hypofunction. The adverse effects of medication on salivary secretion are reversible and salivary gland function will usually recover after withdrawal of the pharmacotherapy.[159,168,181,182]

Numerous diseases and medical conditions can cause salivary gland dysfunction, including hypofunction and altered salivary composition (Table 4).[33,35,36] Some systemic diseases like Sjögren's syndrome and cystic fibrosis permanently affect the salivary gland tissue and function,[177,183] while other conditions, eg salivary gland infections, sialoliths, dehydration, depression and anxiety, have temporary effects.[33,35,36] Other diseases act on the autonomic pathway involving the trigeminal, facial and glossopharyngeal nerves, the central brain structures and/or the salivation centre, eg brain tumours, neurosurgical traumas, diseases of the autonomic nervous system like Holme's-Adie syndrome.[35,36,184] The latter is assumed to be the result of a viral infection that causes inflammation and damage to neurons in the ciliary ganglion, and the dorsal root ganglion, an area of the spinal cord involved in the response of the autonomic nervous system.[184] Finally, diseases can also indirectly affect salivary secretion, which is the case in hormonal disturbances, inflammatory gastrointestinal diseases, and malnutrition.[33,35,36]

Xerostomia and salivary gland hypofunction is extremely common in patients having received radiotherapy to the head and neck region.[34] The development of salivary gland dysfunction depends on the cumulative dose of radiation and the volume of salivary gland tissue included in the field of radiation.[34] Although the turnover rate of the salivary gland tissue is rather slow (approx. 60 days), salivary dysfunction already occurs within the first week of treatment, and the salivary secretion continues to decrease at 1–3 months after radiotherapy. Doses higher than 60 Gray (Gy) usually lead to

**TABLE 3** Symptoms and clinical manifestations related to salivary gland hypofunction

| |
|---|
| Oral mucosal and dental problems |
| Oral mucosal dryness and discomfort, oral burning sensation |
| Dry vermillion border, cracked lips, the tongue sticks to the palate |
| Adherence of food and dental plaque to dental surfaces |
| Sensation of thirst, frequent sipping of liquid |
| Difficulty in wearing removable dentures |
| Atrophic, glazed, dry and red oral mucosa |
| Dorsal part of the tongue lobulated or fissured, atrophy of the filiform papillae |
| Halitosis |
| Mucosal ulcerations, denture stomatitis |
| Increased frequency of oral candidiasis, angular cheilitis |
| Increased number of caries lesions on cervical, incisal and cuspal tooth surfaces |
| Dental erosions |
| Problems related food intake |
| Difficulty in swallowing (dysphagia) |
| Impaired masticatory function |
| Taste disturbances (dysgeusia or hypogeusia) |
| Pharyngitis, laryngitis |
| Oesophagitis, oesophageal dysmotility |
| Acid reflux, heartburn and nausea |
| Malnutrition, constipation, weight loss |
| Change in diet, eg avoiding dry, spicy foods |
| Psychosocial problems |
| Impaired quality of life, depression, social isolation |
| Other problems |
| Difficulty in speech, sleep disturbances |

**TABLE 4** Causes of salivary gland dysfunction[33-37]

| |
|---|
| *Iatrogenic* |
| Intake of certain medications, polypharmacy |
| Radiation therapy for cancer in the head and neck region |
| Graft versus host disease |
| Radioiodide treatment |
| Surgical trauma |
| *Musculoskeletal diseases*, eg chronic inflammatory connective tissue diseases, including Sjögren's syndrome, rheumatoid arthritis, systemic lupus erythematous, scleroderma, mixed connective tissue disease |
| *Neurological diseases*, eg CNS trauma, cerebral palsy, Bell's palsy, Parkinson's disease, Alzheimer's disease, autonomic dysfunctions like Holmes-Adie syndrome |
| *Gastrointestinal diseases*, eg Crohn's disease, ulcerative colitis, coeliac disease, autoimmune liver diseases |
| *Endocrine diseases*, eg type 1 and type 2 diabetes mellitus (especially when dysregulated), hyperthyroidism, hypothyroidism, Cushing's syndrome, Addison's disease |
| *Infectious diseases*, eg parotitis, HIV/AIDS, hepatitis C, Epstein-Barr virus, tuberculosis, bacterial sialadenitis |
| *Genetic disorders*, eg salivary gland aplasia, cystic fibrosis, ectodermal dysplasia, Prader-Willi syndrome |
| *Eating disorders*, eg bulimia nervosa and anorexia nervosa |
| *Additional causes*: depression, anxiety, stress, dehydration, malnutrition, vitamin and mineral deficiencies, mouth breathing |

irreversible salivary gland hypofunction and xerostomia, while doses of 30-50 Gy may be reversible. Radiotherapy causes direct damage to the acinar cells, and initially mainly the serous acini, but also the surrounding blood vessels and nerves. It has been shown that parotid- and submandibular-sparring intensity-modulated radiotherapy (IMRT) can reduce the prevalence and severity of salivary gland hypofunction, which also increase patient's quality of life.[185] However, it may be difficult to spare the minor salivary glands, which contribute significantly to secretion of mucins and thereby lubrication. The prevalence of xerostomia in patients receiving chemotherapy is about 50% and salivary gland function usually restores 6 months to 1 year after treatment. It is unknown whether concomitant radiotherapy and chemotherapy affect the risk of developing salivary gland dysfunction.[34]

## 10 | DIAGNOSIS OF SALIVARY GLAND DYSFUNCTION

The diagnosis of salivary gland dysfunction requires a careful and systematic evaluation of the patient. It includes a detailed history of present symptoms, oropharyngeal functions, systemic and oral diseases, type and number of medications, previous therapies including surgery, radiotherapy in the head and neck region and/or chemotherapy (Tables 3 and 4). Several questionnaires have been developed for the identification of patients with xerostomia and salivary gland hypofunction, and for assessment of their severity[157,158,166,186-189]. The following scientifically validated questions are simple to use in a clinical setting and may be helpful in identifying these patients: (i) Does your mouth feel dry when eating a meal?, (ii) Do you have any difficulty swallowing?, (iii) Do you sip liquids to aid in swallowing dry food?, and (iv) Does the amount of saliva in your mouth seem to be too little, too much or you do not notice it? Positive responds to these questions are highly predictive of salivary gland hypofunction.[157]

The second step is a thorough facial and intraoral examination, including inspection and palpation of the salivary glands, expulsion of saliva from the major salivary duct orifices, and inspection of the oral mucosa, the dentition and gingivae. It is important to stress that there are no specific clinical signs that make it possible to discriminate between the various causes of salivary gland dysfunction, and patients with xerostomia and/or may present with some or none of the symptoms and clinical signs mentioned in Table 3. Apart from being indicative of Sjögren's syndrome, salivary gland enlargement may also be related to medication-induced sialadenosis, sodium retention syndrome, malignancies or parotitis.[190]

The third step is measurement of salivary flow rates. There are various methods for assessment of the unstimulated and stimulated flow rates for whole saliva and for the parotid, submandibular/sublingual and minor salivary glands. Whole saliva flow rates may be measured by means of the draining, spitting, swab (absorbent), and suction methods.[191,192] The most commonly used method is the "draining method," which is internationally accepted as a standard for measuring unstimulated whole saliva in relation to the diagnosis of Sjögren's syndrome. Furthermore, it is simple and can easily be conducted in the dental office.[191,192] As salivary flow and composition are influenced by the time of day and duration of collection, standardisation of the saliva collecting procedure is extremely important. Sialometry should be performed 2 hours after a meal (ideally after breakfast) or after overnight fast and unstimulated saliva should be collected for at least 10 minutes and chewing-stimulated for at least 5 minutes.[193] For measurement of stimulated whole saliva flow, the patient is instructed to chew a standard piece (1-2 g) of paraffin wax or unflavoured gum base at a fixed chewing rate (eg 60-70 chews/minute).[192] Citric acid at a concentration of 2%, applied to the tongue every 30 seconds, can also be used for measuring stimulated flow. However, citric acid may interfere with subsequent sialochemical analysis. Under normal conditions, the average unstimulated whole saliva flow rate is in the range of 0.3-0.4 mL/min, and flow rates below <0.1 mL/min are considered pathologically low and designated hyposalivation.[194,195] The mean chewing-stimulated whole saliva flow rates range from 1.5 to 2.0 mL/min, and flow rates below 0.50-0.70 mL/min are considered abnormal (hyposalivation).[194,195] In cases of medication-induced salivary gland hypofunction, the unstimulated whole saliva flow rate is usually significantly reduced, whereas the chewing-stimulated flow rate is within the normal range.[128,196] However, intake and/or prolonged use of drugs with anticholinergic effect and centrally acting analgesics often cause diminution

of both unstimulated and chewing-stimulated whole saliva flow rates.[128,162] Assessment of the parotid, the submandibular/sublingual saliva flow rates and minor salivary gland secretions requires special equipment and techniques and still primarily used for research purposes.[120,192,193,196]

An additional number of tests may be necessary for adequate diagnosis of salivary gland dysfunction and its underlying cause including sialography, scintigraphy, ultrasound, magnetic resonance imaging (MRI), Cone Beam CT and/or endoscopy of the salivary glands as well as blood tests.

Although analysis of the organic and inorganic constituents in saliva may be promising and valuable tools in the diagnosis of many diseases, it is still not applicable for regular, daily use in a dental practice. However, through recent advances in technology including development of molecular biological methods that can be applied to saliva samples containing human cells, bacteria, DNA, RNA and proteins, novel ways to detect oral and systemic diseases at an early stage are rapidly emerging. Thus the field of saliva proteomics has expanded significantly the last decade, and presently a number of these potential salivary biomarkers are being tested for identification and monitoring diseases including periodontitis, dental caries, oral cancer, but also systemic diseases like Sjögren's syndrome[197-205] Also the emerging fields of transcriptomics and metabolomics open for new possibilities for using saliva in the diagnosis and assessment of various diseases.

## 11 | CONCLUSION

It is important for oral health professionals to have a thorough knowledge and understanding of the normal structure and function of salivary glands including the normal neural control of salivary secretion, normal salivary flow and composition and functions of saliva. Such knowledge facilitates recognition of symptoms or signs related to salivary gland dysfunction at an early stage, and thus provide appropriate diagnosis (or referral). A comprehensive diagnostic evaluation is important in order to determine the cause of xerostomia and salivary gland dysfunction, and consequently initiate proper prevention and treatment.

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## CONFLICT OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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