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INVITED MEDICAL REVIEW

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Salivary functions in mastication, taste and textural perception, swallowing and initial digestion

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Saliva exerts multiple functions in relation to the initial digestive processes taking place in the upper parts of the gastrointestinal tract. Ingestion of food and beverages, in turn, is a strong stimulus for secretion of saliva with a differential composition depending on the neuronal stimulation pattern. This review paper provides insight into the mechanisms by which saliva acts in relation to taste, mastication, bolus formation, enzymatic digestion and swallowing. Also, the protective functions of saliva including maintenance of dental and mucosal integrity will be discussed as they indirectly influence the digestive process. The final part of this study focuses on the implications of xerostomia and salivary gland dysfunction on gastrointestinal functions.

KEYWORDS
digestion, human salivary glands, mastication, saliva, swallowing, taste

1 | INTRODUCTION

Saliva plays an important role in the digestive processes of taste, initial breakdown of foods, chewing, bolus formation and swallowing (Nauntofte & Jensen, 1999; Pedersen, Bardow, Jensen, & Nauntofte, 2002; Valdez & Fox, 1991). Ingestion of food and beverages is a substantial stimulus for the secretion of saliva. Thus, the presence of food in the oral cavity induces both mechanical and olfactory and chemical stimuli via neural reflexes resulting in an increased output of saliva, sufficient to process the food. This study reviews the role of human saliva in the oral phase of digestion, and in the transfer of food from the oral cavity to the oesophagus, and transport of the food bolus from pharynx to the stomach. The protective functions of saliva important for the maintenance of dental and mucosal integrity are also addressed as they indirectly influence the digestive functions. Finally, the impact of xerostomia and salivary gland dysfunction on gastrointestinal functions is discussed.

1.1 | Saliva and salivary glands

The mixed fluid that covers the teeth and oral mucosa is designated whole mouth saliva (WMS) as it consists of saliva produced by three paired major salivary glands, the parotid, submandibular and sublingual glands, which together account for about 90% of the fluid production, and by about 600 to 1,000 minor salivary glands, particularly located in the labial, buccal, palatal, lingual, retromolar regions of the oral submucosa (Edgar, 1992; Hand, 2008). WMS also contains gingival crevicular fluid, microorganisms, discarded oral epithelial cells and food debris. The normal daily production and swallowing of saliva is on average 0.6 ml (Watanabe & Dawes, 1988).

In the unstimulated state, that is the salivary secretion taking place during rest and in the absence of exogenous stimuli, the contribution to the WMS volume is approximately 60% from the submandibular glands, 25% from the parotid glands, 7%–8% from the sublingual glands and 8% from the minor salivary glands (Edgar, 1992). However, the minor salivary glands secrete a relative large fraction of the mucins that provide lubrication to the oral surfaces (Dawes & Wood, 1973). Upon stimulation, and particularly mechanical stimulation (chewing), the parotid glands account for at least 50% of the whole saliva volume, whereas the percentage contribution from the submandibular, sublingual and minor glands is reduced compared to unstimulated conditions. Upon chemical stimulation (taste), secretion of saliva from both the parotid and submandibular glands is considerable.

The salivary gland parenchyma consists of secretory end pieces (acini), which produce primary fluid/saliva, connected to a system of ducts (intercalated, striated and excretory) which modify the saliva. 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 parotid glands and the minor lingual (von Ebner's) glands are purely serous glands. Upon stimulation, they produce a watery, protein-rich fluid with a high content of enzymes such as amylase and lipase. Others are purely mucous like the minor palatal glands, which make more viscous, mucin-rich saliva. The submandibular glands, the sublingual and most of the minor salivary glands are composed of mixed serous and mucous acini, but mainly serous acini in the submandibular glands, and predominantly mucous acini in the sublingual and minor glands (Young & Cook, 1996).

1.2 | Neural control of salivary secretion and formation of saliva

Salivary secretion is under autonomic nervous control and hence regulated by both the parasympathetic and sympathetic nervous system (Figure 1). Salivary secretion is based on reflex pathways comprising an afferent sensory part, a central connection (salivatory nuclei) and an efferent secretory part consisting of parasympathetic and sympathetic nerve fibres, which separately innervate the salivary glands (Figure 1). The afferent impulses mainly arise from

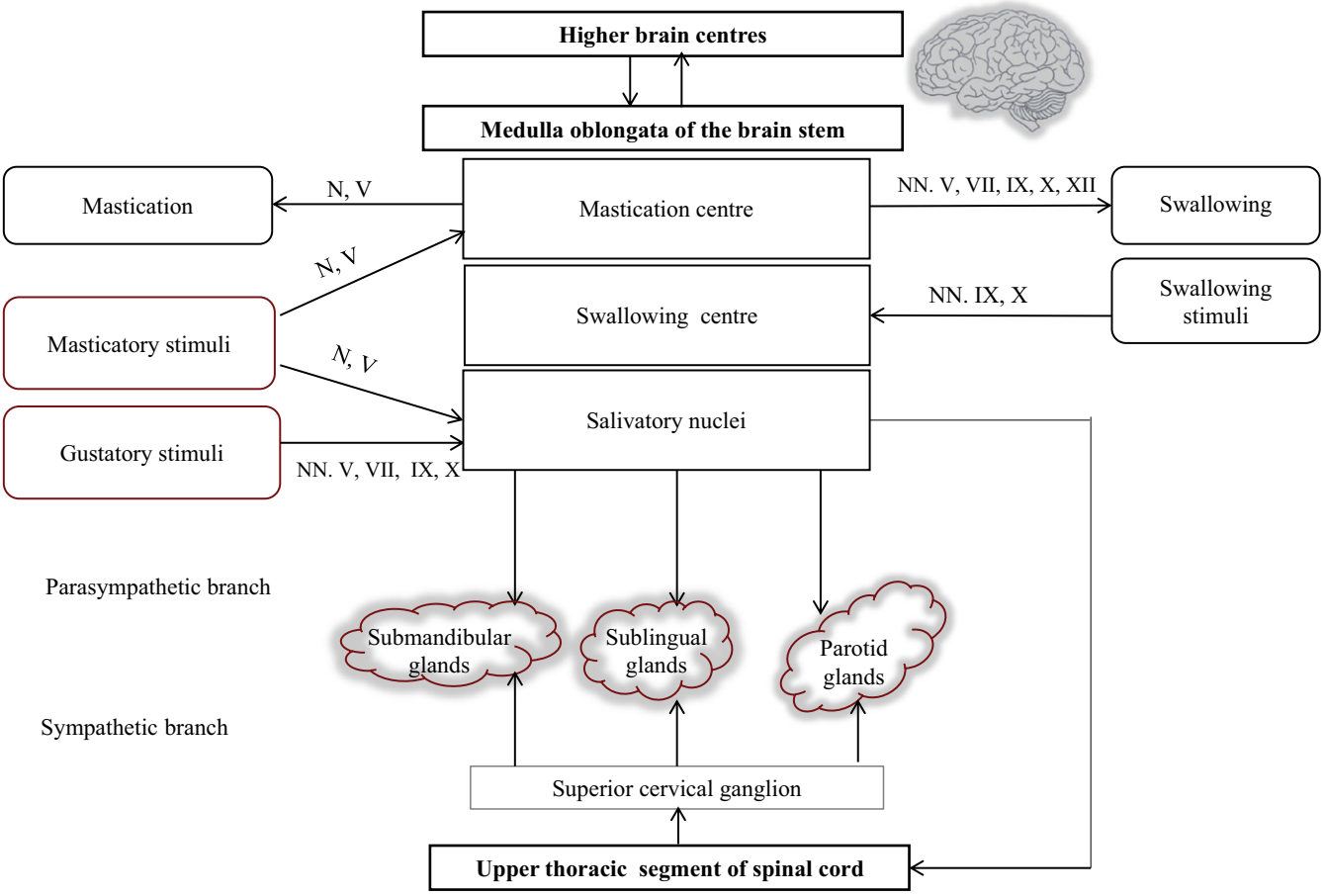

FIGURE 1 Salivary secretion is under autonomic nervous control and thus regulated by the parasympathetic and sympathetic nervous system. Impulses that arise from activation of chemoreceptors in the taste buds are carried to the salivatory nuclei in the medulla oblongata through the trigeminal (V), facial (VII), glossopharyngeal (IX) and vagal (X) nerves (NN.), whereas impulses from activation of mechanoreceptors in the periodontal ligament and gingival tissue (mastication) are carried through the trigeminal nerve. Other sensory impulses transferred to the brain stem, which can evoke salivary may arise from activation of nociceptors in the oral mucosa, stretch receptors in the oesophagus and stomach and through olfaction. Afferent impulses are also transmitted to higher brain centres, which in turn conduct impulses to the salivatory nuclei, which either facilitate or inhibit salivary secretion. Efferent impulses from the sensory nuclei or higher brain centres are conveyed to the sympathetic and parasympathetic salivary centres in the upper thoracic segment of the spinal cord and the medulla oblongata of the brainstem, respectively. The superior salivatory nucleus transmits parasympathetic secretory impulses via the facial nerve to the submandibular and the sublingual glands, whereas the inferior salivatory nucleus transmits impulses via the glossopharyngeal nerve to the parotid glands. Sympathetic impulses are transmitted along sympathetic nerves, which run from the sympathetic trunk, synapse in the superior cervical ganglion and then follow the blood vessels to the salivary glands. The role of mastication and swallowing is detailed in the text

activation of sensory receptors, particularly in response to ingestion of food and beverages (Hector & Linden, 1999). Accordingly, activation of chemoreceptors in the taste buds (the gustatory-salivary reflex) elicits increased secretion of protein-rich saliva, especially from the submandibular glands. Stimulation of mechanoreceptors in the periodontal ligament and gingival tissue (the masticatory-salivary reflex) leads to activation of parasympathetic nerves, resulting in an increased secretion of watery saliva, particularly from the parotid glands (Jensen Kjeilen, Brodin, Aars, & Berg, 1987). Unilateral stimulation of mechanoreceptors primarily elicits ipsilateral salivary secretion. In addition, activation of stretch receptors in the stomach due to nausea and/or vomiting as well as oesophageal distension induces increased salivary secretion via impulses from the vagal nerve (Sarosiek et al., 1994). Activation of the "oesophageal-salivary reflex" not only increases salivary secretion in relation to gastro-oesophageal reflux of acid, but also under normal physiological conditions with increased need of oropharyngeal and oesophageal cleansing (Helm, Dodds, & Hogan, 1987; Shafik, El-Sibai, Shafik, & Mostafa, 2005). Olfactory receptors, located at the cribriform plate in the roof of the nasal cavity, are activated by volatile molecules of the nasal airflow as well as the airflow ascending from the oral cavity or the pharynx. The submandibular glands are also regulated by an "olfactory-salivary reflex," whereas secretion from both the parotid and submandibular glands can be induced by "irritating odours" via stimulation of epithelial trigeminal receptors. Activation of nociceptors may also elicit salivary secretion, for example in response to mucosal pain or intake of spicy food like chilli pepper (Dunér-Engström, Fredholm, Larsson, Lundberg, & Saria, 1986). Interestingly, functional transient receptor potential vanilloid subtype 1 (TRPV1), which is activated by capsaicin, heat and low pH, has been found in myoepithelial cells of human submandibular glands (Ding et al., 2012). Moreover, the temperature of ingested food and beverages affects salivary secretion; for example, ice-cold drinks lead to a higher salivary secretion than hot drinks (Dawes, O'Connor, & Aspen, 2000). The existence of conditioned reflexes to sight, sound and the thought of food is challenging to investigate and document in humans (Holland & Matthews, 1970). The sensation of "drooling "at the sight of appetising food is considered related to increased activity of the tongue and lips, which stimulates the release of pre-made saliva, but may also increase the awareness of saliva in the mouth (Hector & Linden, 1999).

The sensory signals from taste-activated chemoreceptors, chewing-activated mechanoreceptors and/or activated nociceptors are conducted to the sensory nuclei in the brainstem, from which impulses are relayed to the salivatory nuclei and to higher brain centres. It is likely that the salivary reflex can be initiated locally in the brainstem without processing of the afferent stimuli by higher brain centres (Matsuo, 1999). Efferent impulses from the sensory nuclei or higher brain centres are then transmitted to the sympathetic and parasympathetic salivary centres in the upper thoracic segment of the spinal cord and the medulla oblongata of the brainstem, respectively (Figure 1). The efferent secretory part of the reflex consists of parasympathetic and sympathetic nerves that run along separate pathways to the salivary glands and initiate neural activation of the salivary secretion. The superior salivatory nucleus transmits parasympathetic secretory impulses via the facial nerve to the submandibular and the sublingual glands, whereas the inferior salivatory nucleus transmits impulses via the glossopharyngeal nerve to the parotid glands (Ekström, Khosravani, Castagnola, & Messana, 2012; Matsuo, 1999). Sympathetic impulses are transmitted along sympathetic nerves, which run from the sympathetic trunk, synapse in the superior cervical ganglion and then follow the blood vessels to the salivary glands (Figure 1).

The higher centres in the brain can exert both excitatory and inhibitory actions on the salivary nuclei (Garrett & Proctor, 1998; Proctor, 2016). Accordingly, depression, anxiety, emotional stress and sleep are conditions associated with decreased salivary secretion and sensation of dry mouth (xerostomia) as they can inhibit cholinergic pathways that are responsible for the secretion of fluid (Bosch, Ring, de Geus, Veerman, & Amerongen, 2002; Garrett & Proctor, 1998). Moreover, medications which act on the central nervous system like morphine and anxiolytics have inhibitory effect on salivary secretion (Wolff et al., 2017).

Salivary secretion is induced by the binding of neurotransmitters to specific receptors on the plasma membranes of the acinar cells. Stimulation of the parasympathetic nervous system leads to release of acetylcholine from the peripheral postganglionic nerve endings, which binds to cholinergic muscarinic M1- and M3-receptors and elicits secretion of copious, protein and glycoprotein-containing saliva. Sympathetic stimulation leads to release of noradrenaline, which binds to adrenergic receptors of the $\alpha 1$ and $\beta 1$ subtypes, and secretion of viscous saliva with high concentration of proteins and glycoproteins as the content of water is low (Baum & Wellner, 1999; Proctor, 2016; Proctor & Carpenter, 2007). Salivary secretion is also modulated by neuropeptides; for example, vasoactive intestinal polypeptide (VIP) is co-released from parasympathetic nerves supplying the salivary glands. Following sympathetic stimulation protein, secretion is particularly induced by activation of $\beta 1$-receptors, whereas fluid secretion, serving as carrier for the proteins, is induced by activation of $\alpha 1$-adrenergic receptors. In relation to parasympathetic stimulation, acetylcholine is mainly responsible for fluid secretion and VIP for protein secretion (Ekström et al., 2012).

The binding of transmitter substance to receptors elicits a cascade of intracellular signalling and transport mechanisms, resulting in secretion of isotonic primary saliva from the acinar cells, with an ionic composition similar to that of plasma. During its passage through the duct system, the primary saliva is modified by selective reabsorption of sodium and chloride (but not water) and some secretion of potassium and bicarbonate. Thus, the final saliva secreted into the oral cavity is hypotonic (Thaysen, Thorn, & Schwartz, 1954; Turner, 1993). The secretion rate, the volume and the composition of the final saliva secreted into the oral cavity are determined directly by the formation rate of primary saliva by the acinar cells and the metabolic activity in the duct system. The concentrations of sodium, chloride, total protein, total calcium and bicarbonate increase, whilst the concentration of total phosphate decreases, with increasing

salivary flow rates (Bardow, Madsen, & Nauntofte, 2000; Bardow, Moe, Nyvad, & Nauntofte, 2000; Dawes, 1974a; Kreusser, Heidland, Hennemann, Wigand, & Knauf, 1972; Thaysen et al., 1954).

Various factors influence the salivary flow rate and composition including the type and size of gland from which saliva is secreted (different types of glands produce different types of secretion) (Ericson, 1971; Inoue et al., 2006), gender (Heintze, Birkhed, & Bjørn, 1983; Inoue et al., 2006), the level of hydration of the body (Dawes, 1987; Fortes, Diment, Di Felice, & Walsh, 2012; Ship & Fischer, 1997; Walsh, Montague, Callow, & Rowlands, 2004), nutritional state (Johansson, Saellstrom, Rajan, & Parameswaran, 1992), the chemical and mechanical nature and duration of stimulus (Dawes, 1969), emotional state (Bergdahl & Bergdahl, 2000; Bolwig & Rafaelsen, 1972) and the time of collection (Dawes, 1975; Löfgren, Wickström, Sonesson, Lagunas, & Christersson, 2012). It is well known that salivary secretion follows a circadian rhythm. Thus, the salivary flow rate typically rises during the day to an afternoon peak and decreases to very low levels during sleep (Dawes, 1974b, 1975; Ferguson & Botchway, 1980). Certain salivary proteins also follow a diurnal pattern that is independent of the variation in salivary flow rate (Atwood, James, Keil, Roberts, & Hartmann, 1991; Dawes, 1972; Dawes & Ong, 1973). Furthermore, it also appears that the unstimulated salivary secretion has a circannual rhythm as the flow rate is higher during winter than during summer (Elishoov, Wolff, Kravel, Shiperman, & Gorsky, 2008). In addition, changes in the ambient temperature by only 2°C in a warm climate have been shown to inversely influence the unstimulated whole saliva flow rate (Kariyawasam & Dawes, 2005). Both major and minor salivary glands undergo age-related degenerative changes including loss of acini and stromal alterations (Scott, 1977; Scott, Flower, & Burns, 1987; Vered, Buchner, Boldon, & Dayan, 2000). However, reports concerning functions of the salivary glands during ageing are conflicting. Thus, some studies show stable (Baum, 1981; Fischer & Ship, 1999; Heft & Baum, 1984; Ship & Baum, 1990; Smidt, Torpet, Nauntofte, Heegaard, & Pedersen, 2010) and others decline in salivary gland function with age (Heintze et al., 1983; Percival, Challacombe, & Marsh, 1994; Smith et al., 2013; Yeh, Johnson, & Dodds, 1998). Overall, the parotid function appears unaffected by ageing.

1.3 | Functions of saliva

Saliva serves multiple functions that are important for the maintenance of oral and systemic health. The fluid characteristics and viscoelastic properties of saliva are essential for the mechanical cleansing of the oral cavity, clearance of food debris and microorganisms, dissolution of tastants and dilution of hot, cold or spicy food, as well as for the lubrication and moistening of teeth and oropharyngeal mucosa, which facilitate the processes of chewing, bolus formation, swallowing and articulation of speech. Salivary mucins play a crucial role as lubricants as they form a slimy coating of all oral surfaces, thereby providing both mechanical and chemical protection (Park, Chung, Kim, Chung, & Kho, 2007; Veerman, Valentijn-Benz, & Nieuw Amerongen, 1989). Mucins are also prominent constituents of the acquired enamel pellicle and the mucosal pellicle and thus play an essential role in the initial bacterial colonisation of oral surfaces (Carpenter, 2013; Dawes et al., 2015; Lendenmann, Grogan, & Oppenheim, 2000; Ligtenberg & Veerman, 2014; Slomiany, Murty, Piotrowski, & Slomiany, 1996). Specific salivary components exert buffering capacity and maintain salivary pH around 7.0, thereby protecting the teeth and oropharyngeal mucosa from dietary acids or acids from bacterial fermentation of carbohydrates. Saliva is also kept supersaturated with respect to hydroxyapatite, protecting against dissolution of tooth mineral. In addition, numerous substances in saliva have antibacterial, antiviral and/or antifungal properties which modulate the oral microbiota in various ways (Amerongen & Veerman, 2002; Dawes et al., 2015; Kilian et al., 2016). Certain salivary components also facilitate the healing of oral wounds (Brand & Veerman, 2013). The digestive functions or functions that indirectly influence digestion are reviewed in details in the following sections.

1.4 | Saliva and protection of teeth

Saliva and its various constituents play an essential role in the protection of the teeth and in the maintenance of an intact dentition, which is important for the ability to chew. The teeth are frequently exposed to acids that originate from food and beverages or bacterial metabolism. For instance, exposure of bacteria in dental plaque to high levels of sucrose leads to the production of acids from carbohydrate fermentation, resulting in plaque pH drops which can promote development or progression of dental caries. Thus, a very important function of saliva is the dilution and elimination of dietary sugars and acids, oral bacteria and potentially noxious agents from the oral cavity, also referred to as salivary or oral clearance (Lagerlöf & Oliveby, 1994; Lenander-Lumikari & Loimaranta, 2000). The salivary flow rate, the volume of saliva in the oral cavity before and after swallowing and the swallowing frequency determine the rate of oral clearance. In a theoretical clearance model, it has been shown that high unstimulated and stimulated salivary flow rates enhance the rate of clearance, whereas unstimulated flow rates below 0.32 ml/min markedly reduce it (Dawes, 1983). Before swallowing, the volume of saliva present in the oral cavity is on average 1.1 ml, and after a swallow, the residual volume of saliva was shown to be about 0.8 ml (Lagerlöf & Dawes, 1984). The volume of this residual saliva is dependent on the maximum volume of saliva before swallowing and the unstimulated whole saliva flow rate. The residual saliva is spread out in a thin, mobile film on the oral surfaces (Collins & Dawes, 1987), and it contains mucins, enzymes, antibacterial proteins and immunoglobulins that protect the oral cavity.

The thickness of this film is estimated to be approximately 0.1 mm (Collins & Dawes, 1987). However, the film thickness, and velocity with which it moves, varies considerably between the different oral sites and therefore the rate of clearance of microorganisms and dietary carbohydrates (Dawes, 1989; DiSabato-Mordarski & Kleinberg, 1996).

Saliva also forms the acquired enamel pellicle which covers the tooth surfaces and consequently assists in modulating the initial adhesion and colonisation of microorganisms and shapes the composition of the resident oral microbiota (Biyikoglu, Ricker, & Diaz, 2012; Hannig, Hannig, & Attin, 2005; Hannig, Hannig, Kensche, & Carpenter, 2017; Lee et al., 2013). The acquired enamel pellicle is formed by the sequential adhesion of salivary proteins to the enamel, where a layer with larger molecule aggregates is formed with time (Hannig & Joiner, 2006), providing an environment that may be protective to the enamel mineral. The acquired enamel pellicle also provides colonising bacteria with nutrients through breakdown of dietary starch, lipids and proteins and bacterial metabolism of salivary components, for example glycoproteins (van't Hof, Veerman, Nieuw Amerongen, & Ligtenberg, 2014; Marsh, Do, Beighton, & Devine, 2016).

Saliva buffers acids and its buffer capacity originates from the content of bicarbonate, phosphate and proteins (Bardow, Moe, et al., 2000; Cheaib & Lussi, 2013; Izutsu & Madden, 1978; Lilienthal, 1955). Salivary pH is maintained at a relatively constant physiological level, that is 6.5–7.4, by buffering dietary acids and acids derived from bacterial fermentation of carbohydrates and thereby diminishing the rate of tooth demineralisation (Bardow, Moe, et al., 2000; Ericsson, 1959). The concentration of bicarbonate in saliva, the salivary pH and the buffer capacity are highly dependent on the salivary flow rate, and they increase when the salivary flow rate increases and *vice versa* (Bardow, Nyvad, & Nauntofte, 2001; Bardow, Moe, et al., 2000; Dawes, 1969; Grøn & Messer, 1965). The concentration of bicarbonate is highest in parotid saliva and lowest in the minor salivary glands (Bardow, Madsen, et al., 2000; Edgar, 1992). Salivary pH and the levels of calcium and phosphate are important factors for maintaining saliva supersaturated with respect to hydroxyapatite (Dawes, 2003). In the stimulated state, the bicarbonate buffer system is responsible for about 90% of the buffer capacity, whereas in the unstimulated condition, the phosphate concentration is nearly equal to the bicarbonate concentration and they contribute almost equally to the buffering capacity. At lower flow rates and salivary pH below 5, proteins constitute the major buffering capacity (Bardow, Moe, et al., 2000; Lilienthal, 1955). Saliva also contains certain proteins including acidic proline-rich proteins, histatins, cystatins and statherins, which are among the first proteins that adhere to a clean enamel surface to initiate enamel pellicle formation. They display high affinity for hydroxyapatite as they bind calcium ions, and inhibit precipitation of calcium phosphate salts from saliva supersaturated with respect to hydroxyapatite, thus protecting the teeth from demineralisation and calculus formation (Hay, Carlson, Schluckebier, Moreno, & Schlesinger, 1987; Lamkin & Oppenheim, 1993; Moreno, Varughese, & Hay, 1979; Schupbach et al., 2001). The ions in saliva, including calcium, are also important to the function of salivary α-amylase (Ramasubbu, Paloth, Luo, Brayer, & Levine, 1996). In addition, oral bacteria help to buffer saliva by breaking down urea to ammonia and carbon dioxide resulting in an increase in pH (Dibdin & Dawes, 1998).

Salivary mucins have the capacity to bind and aggregate microorganisms which prevents their adherence and colonisation. Saliva also provides antimicrobial activity through numerous proteins and peptides including mucins, lactoferrin, lysozyme, lactoperoxidase, statherin, histatins and secretory immunoglobulin A (SIgA) (Amerongen & Veerman, 2002; van't Hof et al., 2014; Kilian et al., 2016; Lenander-Lumikari & Loimaranta, 2000; Marsh et al., 2016; Scannapieco, 1994). Mucins, for example MUC5B, also interact with the enamel and may mediate specific bacterial adhesion to the tooth surface (Amerongen & Veerman, 2002; Lenander-Lumikari & Loimaranta, 2000; Scannapieco, 1994).

1.5 | Saliva and protection of oro-oesophageal mucosa

Saliva contributes to the maintenance of oro-oesophageal mucosal integrity by lubrication, clearance, buffering and tissue repair (Helm et al., 1983; Sarosiek & McCallum, 2000). Lubrication of the oral, pharyngeal and oesophageal mucosal membranes is provided by the high molecular weight glycoproteins, MUC5B, and the lower molecular weight, MUC7, secreted from the submandibular, sublingual and minor salivary glands. The mucosal pellicle is formed by adherence of salivary mucins and proteins to the oral mucosal epithelial cells. MUC5B and MUC7 can bind membrane-associated epithelial mucins, MUC1, and can form complex of carbonic anhydrase IV, SIgA and cystatins (Gibbins, Proctor, Yakubov, Wilson, & Carpenter, 2014). The formed mucosal pellicle is like a hydrogel, with a lower tenacity than the enamel pellicle (Gibbins et al., 2014). Maturation and turnover are influenced by the various salivary proteins, by the whole saliva flow rate and the desquamating rate of oral epithelium. The mucosal pellicle provides lubrication and a protective barrier against exogenous potential damaging substances and microorganisms, thereby limiting the microbial colonisation of the oral cavity and preventing primary infection of the oral mucosa (Bradway et al., 1992; Lenander-Lumikari & Loimaranta, 2000; Pramanik, Osailan, Challacombe, Urquhart, & Proctor, 2010; Tabak, 1995). MUC7 is less efficient as lubricant, but notably more efficient in bacterial agglutination and clearance than MUC5B (Loomis, Prakobphol, Levine, Reddy, & Jones, 1987; Reddy, Bobek, Haraszthy, Biesbrock, & Levine, 1992; Tabak, 1995). Given their extensive glycosylation, mucins are able to cross-link and therefore to aggregate bacteria, which subsequently are eliminated from the oral cavity by the act of swallowing and eventually by the gastric juice. MUC7 also binds to acidic and basic proline-rich proteins, statherins and histatin 1, and through the formation of protein complexes, it protects them from proteolysis, modulates their function and activity, also serving as a delivery system for distribution of secretory salivary proteins throughout the oral cavity (Loomis et al., 1987). In addition, both histatins and mucins prevent colonisation of *Candida albicans* in the oropharyngeal mucosa (Hoffman & Haidaris, 1993; Oppenheim et al., 1988; Pollock, Denepitiya, MacKay, & Iacono, 1984).

Saliva clears oesophageal acid from normal reflux activity (Helm et al., 1983, 1984). The first stage of oesophageal clearance is

initiated by swallowing, whereby one or two peristaltic waves clear most of the refluxed acid (95%) from the oesophagus (Helm et al., 1984). In the second stage, the residual acid is diluted and buffered by subsequent swallows of stimulated whole saliva and then cleared from the oesophagus by secondary peristaltic waves (Helm et al., 1984). The consequence of this two-stage process of oesophageal emptying and acid neutralisation is reduction of the time where the oesophageal mucosa is in contact with gastric acid. The neutralisation of acids increases with increasing salivary flow rates due to increased bicarbonate concentration (Helm et al., 1984). It has been shown that stimulation of salivary secretion by the muscarinic cholinergic agonist, bethanechol, and by chewing gum augments clearance of the oesophageal acid (von Schonfeld, Hector, Evans, & Wingate, 1997).

Saliva also plays important roles in wound healing and consequently in the maintenance of the mucosal integrity (Brand & Veerman, 2013; Dawes et al., 2015). Apart from the protective salivary mucous layer, tissue factor deriving from salivary exosomes promotes haemostasis, salivary growth factors including epidermal (also called epithelial) growth factor (EGF), transforming growth factor alpha, trefoil factor 3 and vascular endothelial growth factor (VEGF) as well as salivary antimicrobial factors contribute to rapid healing of oral mucosal wounds (Brand & Veerman, 2013; Keswani et al., 2013; Storesund, Hayashi, Kolltveit, Bryne, & Schenck, 2008). VEGF is angiogenic, promotes reepithelialisation and regulates formation of extracellular matrix (Keswani et al., 2013). Leptin, an anti-obesity hormone found in saliva, also stimulates angiogenesis (Umeki et al., 2014). Salivary histatin 1 stimulates the migration of epithelial cells and fibroblasts *in vitro* and thereby wound healing (Oudhoff et al., 2008). Salivary EGF also appears to play a role in the maintenance of the oesophageal mucosal integrity (Barnard, Beauchamp, Russell, Dubois, & Coffey, 1995; Eckley, Sardinha, & Rizzo, 2013; Jankowski, Coghill, Tregaskis, Hopwood, & Wormsley, 1992; Kongara & Soffer, 1999; Marcinkiewicz, Grabowska, & Czyzewska, 1998). EGF is a single-chain polypeptide secreted by the submandibular salivary glands and parotid glands (Thesleff, Viinikka, Saxen, Lehtonen, & Perheentupa, 1988), but also duodenal Brunner's glands, small intestinal Paneth cells and other exocrine glands including the pancreas (Jankowski et al., 1992). Salivary EGF contributes to maintain an appropriate pre-epithelial oesophageal defence barrier by its interaction with other salivary components such as mucins, transforming growth factor alpha and salivary prostaglandin E2 (Marcinkiewicz et al., 1998; Rourk, Namiot, Sarosiek, Yu, & McCallum, 1994; Sarosiek & McCallum, 2000; Sarosiek et al., 1994). Both mastication and oesophageal exposure to acid/pepsin elicit increased secretion of salivary EGF (Konturek, Bielanski, Konturek, Bogdal, & Oleksy, 1989; Marcinkiewicz et al., 1998).

1.6 | Saliva and taste

Taste is a strong stimulant for secretion of saliva which plays an essential role in tastants perception and sensitivity (Matsuo, 2000). The sensation of taste is activated during the initial phase of food ingestion, which is important for the differentiation of essential nutrients from harmful and potentially toxic substances. Saliva acts as a solvent of tastants as food particles need to be in solution in order to stimulate taste receptor cells in the taste buds within the lingual papillae (fungiform, foliate and vallate papillae) (Dulac, 2000). The water in saliva dissolves some tastants, which then diffuse to the taste receptor sites. The proteins in saliva, particularly mucins, help to emulsify fats and tastants dissolved within fats which permits their delivery to taste buds. In addition, taste sensitivity is related to the composition of saliva as the upper surface of receptor cells are bathed by saliva. Thus, some salivary constituents chemically interact with tastants. For example, salivary bicarbonate ions can reduce the concentration of free hydrogen ions and thereby affect sour taste, and proline-rich proteins can affect bitter taste. Moreover, salty taste is perceived above the background sodium chloride concentrations in unstimulated whole saliva to which the taste receptors are adapted (Matsuo, 2000).

Upon activation of the taste receptor cells in the taste buds, gustatory impulses are carried to the brain by afferent nerve fibres (Figure 1). The fungiform taste buds are innervated by the chorda tympani (branch of the facial nerve); the anterior receptor cells of the foliate taste buds receive innervation from the chorda tympani and the posterior ones from the glossopharyngeal nerve. Also, the taste buds in the circumvallate papillae are innervated by the glossopharyngeal nerve. Fibres of the vagal nerve innervate taste buds in the tonsillar region, the epiglottis, the pharyngeal wall and oesophagus (Gilbertson, 1998). There are currently five basic taste modalities common to most people (sweet, sour, salty, bitter and umami) (Dulac, 2000; Niki, Yoshida, Takai, & Ninomiya, 2010). Each modality is based on distinct transductional pathways in the single receptor cell leading to depolarisation of the receptor potential and generation of action potentials, leading to the release of neurotransmitters onto the gustatory afferent nerve fibres, followed by signalling to the brain. Each taste receptor cell responds, however, in varying degrees to substances that fall into more than one taste category (Gilbertson, Fontenot, Liu, Zhang, & Monroe, 1997; Spielman, 1998). Flavour of foods is often described as a combination of taste and smell and once again saliva plays a role in the liberation of aromas during the processing of foods. Most smells from foods are transmitted from the mouth to the nose via the retro-nasal route following a swallow. In addition, chemosensory perception is provided by TRP (Transient Receptor Proteins) channels located mostly in the oral mucosa on bare nerves. Agonists for TRPs are often referred to as spices and include capsaicin (from chilli peppers), vanillin and menthol and have different binding characteristics to the basic tastants as they often persist much longer despite requiring lower concentrations. It is unknown if saliva has a role in the perception of TRP agonists. Other cues from eating real foods include mechanoreceptors, proprioceptors for the texture of the food, whilst the temperature of foods is thought to be detected by TRP channels (Houghton et al., 2017).

In addition to the basic tastes and chemoperception, there are other mouthfeel effects, the best-known example is astringency,

which is described as the oral sensation of dryness, tightening and shrinking of the oral mucosa following the imbibition of products rich in tannins, for example, red wine, green tea and berries (Schobel et al., 2014; Soares, Sousa, Mateus, & de Freitas, 2012). Unlike the other tastes, there has been no specific receptor described for astringency. Instead, an interaction between the polyphenols and several salivary proteins including the proline-rich proteins, histatins and mucins has been cited as a possible mechanism for astringency. In particular, interaction with mucins and disruption of the mucosal pellicle is likely to cause the dry feeling, probably detected by stretch receptors within the oral mucosa (Chaudhury, Shirlaw, Pramanik, Carpenter, & Proctor, 2015; Vijay, Inui, Dodds, Proctor, & Carpenter, 2015).

The taste pathway activated by impulses from the facial, glossopharyngeal and vagal nerves has ipsilateral connections to the salivatory centre in the brain stem (Figure 1). The first neurons synapse in the tractus solitarius and its nucleus, where the secondary neurons cross the midline and travel to the thalamus. In this region, the third neurons communicate with the postcentral gyrus-facial area and there are also projections to the olfactory cortex (Rolls, 1998). The highest saliva stimulation is obtained with sour taste, which can easily result in salivary flow rates ranging from 5 to 10 ml/min, followed by salt (NaCl), sweet and bitter (Dawes & Watanabe, 1987; Kerr, 1961). There is no additive effect on salivary flow by giving a mixture of different taste stimuli. In fact, it elicits a lower flow rate than the sum of the separate stimuli (Speirs, 1971). Furthermore, salivary flow increases with increasing concentration and amount of a separate taste stimulus (Bardow, Madsen, & Nauntofte, 2000; Froehlich, Pangborn, & Whitaker, 1987; Watanabe & Dawes, 1988). Continuous taste stimulation usually leads to varying degrees of adaptation, which is highest for sweet taste, but lowest for sour taste (Bornstein, Wiet, & Pombo, 1993; Matsuo, 2000).

Saliva protects the taste receptors from desiccation, mechanical damage, bacterial infection and from atrophy due to lack of taste stimuli to the receptor sites. Gustin (carbonic anhydrase, CA VI) has been shown to be important for the growth and development of taste buds (Henkin, Martin, & Agarwal, 1999), and an experimental study indicates that salivary EGF is essential to the maintenance of normal fungiform taste buds (Morris-Wiman, Sego, Brinkley, & Dolce, 2000).

1.7 | Saliva and mastication

During mastication, or the act of chewing, food is broken down into smaller fragments and mixed with saliva. The food particles are thereby lubricated and softened and exposed to digestive enzymes, processes which are essential for the formation of a food bolus suitable for swallowing (Jalabert-Malbos, Mishellany, Woda, & Peyron, 2007; Woda, Mishellany, & Peyron, 2006). Mastication, which requires involvement of the teeth, the masticatory muscles, the temporomandibular joint and the tongue (Orchardson & Cadden, 1998), facilitates the subsequent gastrointestinal absorption of food particles. Mastication is under the control of the central pattern generator located in the brain stem (Goldberg & Chandler, 1990; Lund, 1991), which is regulated by the extensive sensory inputs evolving from the oral cavity during ingestion and chewing of food, in order to constantly adjust the act of chewing to the food properties (texture) and facilitate formation of a bolus ready for swallowing (Hiiemae et al., 1996; Peyron et al., 2011; Takahashi, Miyamoto, Terao, & Yokoyama, 2007). The masticatory performance is defined as the capacity to reduce the size of food particles by chewing for a standardised period of time (Mowlana, Heath, Van der Bilt, & Van der Glas, 1994) as well as the number of chews needed to render food ready for swallowing (Chauncey, Muench, Kapur, & Wayler, 1984). The masticatory performance is dependent on the number of teeth in functional occlusion (Akeel, Nilner, & Nilner, 1992) and the maximal biting force (Julien, Buschang, Throckmorton, & Dechow, 1996 Laguna, Sarkar, Artigas, & Chen, 2015). Consequently, masticatory performance is often impaired in relation to loss of teeth (Fontijn-Tekamp et al., 2000; Miyaura, Morita, Matsuka, Yamashita, & Watanabe, 2000), wearing dentures (Miyaura et al., 2000; N'gom & Woda, 2002), inadequate salivary secretion (Dusek, Simmons, Buschang, & Al-Hashimi, 1996; Liedberg & Öwall, 1991), problems with tongue or jaws, and loss of muscle mass and thus most common among elderly people (Ikebe et al., 2011). It has been shown that the number of chew cycles increases gradually with age to compensate for changes in food hardness (Peyron, Blanc, Lund, & Woda, 2004), and to compensate for teeth loss by chewing longer (Woda et al., 2006). In addition, in medication-induced hyposalivation, the number of chewing cycles before initiating a swallow increases (Liedberg & Öwall, 1991). Chewing results in increased salivary secretion due to activation of the masticatory-salivary reflex (Anderson & Hector, 1987) (Figure 1) and is primarily ipsilateral and dependent on the applied stimulus intensity (Bardow, Madsen, et al., 2000; Dong, Puckett, & Dawes, 1995; Mackie & Pangborn, 1990). The variation in the frequency of chewing between 40 and 80 strokes/min does not seem to influence the salivary flow rate (Kerr, 1961). Chewing exerts pressure on the teeth which results in activation of mechanoreceptors in the periodontal membrane and subsequent transmission of impulses through the trigeminal nerve to the salivation centre (Figure 1) (Anderson & Hector, 1987; Hector & Linden, 1987). The threshold for the activation of mechanoreceptors is relatively low (Linden & Millar, 1988), that is below 5% of the comfortable biting force (Anderson, Hector, & Linden, 1996). The response to chewing paraffin is normally a three- or fivefold increase in the salivary flow rate in comparison with the unstimulated flow rate. Salivary secretion increases not only with the size, the hardness and the moisture of ingested food products, but also with the force exerted by the masticatory muscles and the chewing time needed until swallowing (Anderson & Hector, 1987; Engelen, Fontijn-Tekamp, & van der Bilt, 2005; Gavião & Bilt, 2004; Hector & Linden, 1987; Rosenhek, Macpherson, & Dawes, 1993). Moreover, a regular diet that requires considerable masticatory activity or a regular use of chewing gum in addition to a normal diet has been shown to increase parotid salivary flow rate over time (De Muniz, Maresca, Tumilasci, & Perec, 1983; Dodds & Johnson, 1993; Johnson & Sreebny, 1982). If particle size

and concentration of food particles in the ingested food bolus are increased, the number of chews necessary before swallowing increases and the chewing frequency decreases (Prinz & Lucas, 1997).

1.8 | Saliva and bolus formation

During mastication, the food mixes with the saliva to form a bolus, a smooth mass of mechanically broken down food particles (Prinz & Lucas, 1997). During the masticatory process, the hardness and food particle size rapidly decreases, whereas the adhesiveness and cohesiveness increase until the time of swallowing (Peyron et al., 2011; Prinz & Heath, 2000). The water in saliva moistens the ingested food, whereas the salivary mucins bind masticated food into a coherent and slippery bolus that can easily slide through the oesophagus. The enzymatic digestion of carbohydrates and triglycerides is also initiated in the food bolus (Hamosh & Burns, 1977; Salt & Schenker, 1976). After the bolus is formed, it is conveyed to the posterior part of the tongue in preparation for swallowing (Hiiemae & Palmer, 1999; Hiiemae et al., 1996). The optimal moment for swallowing appears to occur when the cohesive forces between the food particles in the bolus are strongest. The cohesiveness and adhesiveness are determined by the food particle size, the liquid in the food and the salivary secretion (Peyron et al., 2011; Prinz & Lucas, 1997).

1.9 | Saliva and swallowing

The essential functions of swallowing are to clear the oral cavity of saliva and act as a transport mechanism of ingested food or beverages. The swallowing process occurs in three continuous phases (Miller, 1982; Thexton, 1992). The first phase, the oral phase, includes voluntary actions involving the tongue, which pushes the saliva, liquid or food bolus up against the palate and sweeps it through the faucial arches. In the second phase, the pharyngeal phase, elicited by a reflex, the saliva or food bolus enters the oesophagus (Ertekin et al., 2001). The third phase is the oesophageal phase, involving a sequential reflexively induced contraction of the oesophagus including a peristaltic movement in a cranial-caudal direction (Logemann, 1988; Thexton, 1992). The receptive regions for reflex swallowing include the soft palate, dorsal surface of the tongue, uvula, pharyngeal surface of the epiglottis, faucial pillars, dorsal pharyngeal wall and the pharyngo-oesophageal junction (Mansson & Sandberg, 1975; Miller, 1982). It is likely that swallowing is initiated by activation of specific fluid or water receptors as well as slowly reacting pressure receptors distributed in the pharyngeal and laryngeal regions (Mathew, Sant'Ambrogio, & Sant'Ambrogio, 1988; Thexton, 1992). Impulses evoked from activation of sensory receptors in the oropharyngeal mucosa are carried in the trigeminal, glossopharyngeal, vagal and hypoglossal nerves to the swallowing central pattern generator in the bilateral reticular formation of the medulla oblongata in the brain stem (Figure 1) (Paton, Li, & Kasparov, 1999). The glossopharyngeal and vagal nerves control the pharyngeal and the oesophageal phase, respectively (Altschuler, 2001; Logemann, 1988). Swallowing also elicits airway-protective reflexes including closure of the glottis, elevation of the larynx and a transient cessation of respiration to protect the airways from aspiration of saliva, liquid or food particles (Broussard & Altschuler, 2000). Under normal physiological conditions, the swallowing frequency is on average 600 times per day, but there are wide interindividual variations. The swallowing frequency decreases to about six times an hour during sleep due to the decrease in salivary secretion (Lear, Flanagan, & Moorrees, 1965).

Swallowing of a food bolus is initiated when the food particle size threshold is obtained by chewing, and when adequate rheological and surface properties of the food bolus have been obtained by the liquid in the ingested food and the saliva. These properties include cohesiveness, adhesiveness and stickiness (Engelen et al., 2005; Hutchings & Lillford, 1988; Jalabert-Malbos et al., 2007; Peyron et al., 2011; Prinz & Lucas, 1997). Swallowing will normally occur after approximately 20–30 chews (Lucas & Luke, 1986).

It has been suggested that delayed swallowing causes excessive salivary secretion, which reduces cohesion between food particles and dissolves the bolus, resulting in reduced swallowing efficiency and decreased oral clearance. However, difficulty in swallowing and risk of choking may also occur if the peak cohesive force between food particles is obtained due to an early swallowing. The latter is also influenced by food texture, salivary flow rate, salivary composition and salivary viscosity (Prinz & Lucas, 1997). Studies on the relationship between swallow frequency and salivary flow rate have revealed a substantial increase in salivary flow and swallowing frequency after stimulation with the muscarinic cholinergic agonist bethanechol, and a significant decrease after stimulation with the antagonist, atropine (Kapila, Dodds, Helm, & Hogan, 1984). The swallowing of saliva can be elicited by an adequate stimulus such as a certain volume of saliva or thickness of the salivary film in the oral cavity, or when the saliva reaches peripheral receptors at the vallecula, the tongue base or in the oropharyngeal region (Mansson & Sandberg, 1975). It has been shown that experimental infusion of 1–3 ml of water into the oral cavity elicits a swallow (Ertekin et al., 2001). Persons who have relatively high salivary flow rates also have the shortest swallowing intervals and *vice versa* (Rudney, Ji, & Larson, 1995).

1.10 | Saliva and digestion of starches and lipids

The most prominent salivary enzyme is α-amylase, which breaks down starches to soluble maltoses and dextrins by cleaving the α-(1-4) glycosidic bonds (Robyt & French, 1970). This breakdown to simple hexoses occurs in two phases. The luminal phase starts in the oral cavity with the initial digestion of starch by salivary α-amylase, and the second phase occurs in the upper small intestine as pancreatic α-amylase reaches the chyme. Salivary α-amylase is considered to be of minor significance in polysaccharide digestion due to its rapid inactivation in gastric acid and its pH optimum at 6.8, but short-chain glucose polymers in the diet may stabilise the enzyme and allow maintenance of activity at acid pH during the first period in the stomach (Rosenblum, Irwin, & Alpers, 1988). Furthermore, a recent study indicates that salivary amylase plays a significant role in

gastric digestion as it hydrolyses up to 80% of bread starch in the first 30 min of gastric digestion (Freitas, Le Feunteun, Panouille, & Souchon, 2018). The activity of salivary α-amylase may be of importance to patients suffering from chronic pancreatic insufficiency and neonates with insufficient development of the pancreas (Alpers, 1987). Salivary α-amylase is secreted upon autonomic nerve stimulation of the serous acinar cells of the parotid glands and to a lesser extent of the submandibular glands. Both glycosylated and non-glycosylated isoenzymes have been identified. Depending on the degree of glycosylation, their molecular weights are 54–57 kDa (Kauffman, Zager, Cohen, & Keller, 1970). In parotid saliva, α-amylase makes up about one-third of the total protein content, whereas the content in secretions from the mixed salivary glands is much lower (Ferguson, 1999). Salivary α-amylase is also considered to play a role in oral health, as it binds to streptococci, and is involved in modulating the adhesion of bacteria on oral surfaces (Scannapieco, Torres, & Levine, 1993).

Lingual lipase is a digestive enzyme which is secreted from acinar cells of the serous minor salivary glands (von Ebner's glands) located on the posterior region of the tongue and beneath the circumvallate papillae (Hamosh & Scow, 1973). Lingual lipase breaks down a small fraction of dietary triglycerides in the oral cavity and stomach (Hamosh & Burns, 1977). Intake of a high-fat diet and the act of suckling stimulate the enzymatic activity of lipase, and it may act synergistically with pancreatic lipase (Harries, 1982). Lingual lipase is, however, considered to be of limited significance in lipolysis of healthy individuals, whereas it may be of particular importance in patients with cystic fibrosis and exocrine pancreatic insufficiency who exhibit varying degrees of steatorrhea because of the lack of pancreatic lipase activity (Abrams, Hamosh, Hubbard, Dutta, & Hamosh, 1984). In addition, preduodenal lingual lipase activity may also compensate for developmental deficiency in pancreatic lipase in neonates (Smith, Kaminsky, & D'Souza, 1986).

1.11 | Interactions between salivary gland dysfunction and gastrointestinal functions

Salivary gland dysfunction is defined as any quantitative and/or qualitative change in the output of saliva. Salivary gland hypofunction results in varying degrees of reduction in the normal salivary flow rate, and it may be temporary or permanent. Unstimulated and stimulated salivary flow rates can be measured for whole saliva and individual gland secretions by means of various techniques (Navazesh & Christensen, 1982; Navazesh & Kumar, 2008). The "draining method" is internationally accepted as a standard for measuring unstimulated whole saliva in relation to the diagnosis of Sjögren's syndrome (Vitali et al., 2002). It is highly reproducible and reliable and can easily be conducted in the dental office (Navazesh & Kumar, 2008). However, as the unstimulated whole mouth salivary flow rates exhibit diurnal variations, measurements must be performed under standardised conditions.

The salivary flow rates display large variations between healthy individuals (Sreebny, 2000; Yeh et al., 1998). However, it is generally accepted that in healthy, non-medicated adults, the unstimulated whole mouth saliva flow rates range between 0.3 and 0.5 ml/min and the chewing-stimulated whole mouth saliva flow rates between 1.0 and 3.0 ml/min (Heintze et al., 1983; Sreebny, 2000). Hyposalivation is a condition characterised by unstimulated whole mouth saliva flow rates is below 0.1 ml/min, and chewing-stimulated whole mouth saliva flow rates below 0.7 ml/min (Heintze et al., 1983; Sreebny, 2000). Salivary gland hypofunction is often associated with a subjective sensation of dry mouth referred to as xerostomia. Xerostomia may occur without objective signs of salivary gland hypofunction, and conversely, hyposalivation may be present without symptoms of dry mouth (Fox, Busch, & Baum, 1987; Ship, Fox, & Baum, 1991). In addition, changes in salivary composition may appear without changes in salivary flow (Nederfors, Dahlöf, & Twetman, 1994). It has been demonstrated that the thickness of the film of residual saliva that covers the oral surfaces is reduced in patients with xerostomia and salivary gland hypofunction (Wolff & Kleinberg, 1998), but an insufficient film of residual saliva has also been found associated with xerostomia in patients with normal salivary secretion (Osailan, Pramanik, Shirodaria, Challacombe, & Proctor, 2011; Pramanik et al., 2010). These findings indicate that the perception of mucosal wetness and coating is closely related to the thickness as well as the quality of this thin film of residual saliva covering the teeth and oral mucosa (Chaudhury, Proctor, Karlsson, Carpenter, & Flowers, 2016; Osailan et al., 2011; Pramanik et al., 2010). Along this line, impairment of the rheological properties of saliva including changes in the sialylation of mucins has been found associated with xerostomia in patients with Sjögren's syndrome (Chaudhury et al., 2016).

Salivary gland dysfunction can also manifest as salivary hyperfunction (sialorrhea), although being much more uncommon in adults than salivary hypofunction. Drooling may occur in relation to genuine salivary hyperfunction (primary sialorrhea), but in most cases, it is 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). Drooling may be associated with oral health problems and compromised orofacial functions that influence the food intake (Bakke, Larsen, Lautrup, & Karlsborg, 2011; Meningaud, Pitak-Arnnop, Chikhani, & Bertrand, 2006; Silvestre-Donat & Silvestre-Rangil, 2014).

Salivary gland dysfunction can be a manifestation of a large variety of systemic diseases or the consequence of local structural or functional pathologies (von Bültzingslöwen et al., 2007; Pedersen, 2015). However, the most common cause of xerostomia and salivary gland hypofunction is intake of medications, especially intake of agents acting on the muscarinic cholinergic receptors of the salivary gland acinar cells; for example, antimuscarinic agents used in the treatment of irritable urinary bladder, or tricyclic antidepressants acting on both peripheral and central components of the salivary reflex, or of agents inducing salivary compositional changes, as well as polypharmacy (Sreebny, 2010; Sreebny & Schwartz, 1997; Wolff et al., 2017). Depression, anxiety and salivary gland infections are prevalent causes of temporary salivary dysfunction. Prominent causes of permanent and severe salivary

gland dysfunction include radiation therapy of head and neck cancer, which induces irreversible damage to the salivary gland tissue involved in the field of radiation (Jensen et al., 2010; Valdez, Atkinson, Ship, & Fox, 1993), and Sjögren's syndrome, a chronic inflammatory systemic autoimmune disease that affects exocrine glands and causes keratoconjunctivitis sicca and hyposalivation due to lymphocytic-mediated destruction of the glandular tissue (Pedersen & Nauntofte, 2001).

Irrespective of the cause, salivary gland hypofunction is usually associated with a large variety of symptoms including sensations of oral mucosal dryness and discomfort, oral burning and thirst. Persistent salivary gland hypofunction often leads to an increased activity of caries with lesions on cervical, incisal and cuspal tooth surfaces, dental erosion, mucosal changes and oral fungal infections (Aliko et al., 2015; Bardow et al., 2001; Fox et al., 2008; Lynge Pedersen, Nauntofte, Smidt, & Torpet, 2015; Pedersen, Bardow, & Nauntofte, 2005; Torres et al., 2002). Also, oropharyngeal functions are gradually impaired leading to difficulties with speaking, chewing and swallowing. Disturbances in the perception of taste, flavour and food texture, impaired lubrication of the oral surfaces, dysphagia and oesophageal acid reflux can lead to loss of appetite and fear of eating. This can lead to behavioural changes including avoidance of certain foods, for example dry, spicy or crunchy food, and/or preference for soft and carbohydrate-rich foodstuff. In turn, changes in food intake can result in nutritional deficiencies, weight loss, malabsorption and atrophy of the masticatory muscles and impaired masticatory performance (Crowder, Douglas, Yanina Pepino, Sarma, & Arthur, 2018; Dusek et al., 1996; Gilbert, Heft, & Duncan, 1993; Jensen et al., 2010; Loesche et al., 1995; Pedersen et al., 2002; Yoshikawa et al., 2012), leading to further aggravation of the oral health (Sheetal, Hiremath, Patil, Sajjansetty, & Kumar, 2013). Consequently, salivary gland hypofunction and its associated symptoms and clinical consequences often have a significant negative impact on the patient's social functioning and well-being and quality of life (Enoki et al., 2014; Fox et al., 1987; Gerdin, Einarson, Jonsson, Aronsson, & Johansson, 2005; Pedersen, Reibel, & Nauntofte, 1999b; Pedersen et al., 1999a; Thomson, Lawrence, Broadbent, & Poulton, 2006).

Another mutual interaction exists between salivary gland dysfunction and gastro-oesophageal reflux disease (GERD). GERD is characterised by retrograde movement of gastric content through the lower oesophageal sphincter due to a sphincter dysfunction, delayed gastric emptying, salivary gland hypofunction and impaired oro-oesophageal clearance (Menezes & Herbella, 2017). The symptoms and signs of GERD include heartburn, nausea, dysphagia, dysgeusia, pharyngitis, laryngitis and fear of eating (Shafik et al., 2005). Impairment of salivary gland function, oro-oesophageal clearance and mucosal protection can lead to an increased risk of oral ulcerations, dental erosion, GERD and gastric ulceration (Biagini et al., 1991; Geterud et al., 1991; Jarvinen, Meurman, Hyvarinen, Rytomaa, & Murtomaa, 1988; Korsten et al., 1991; Rourk et al., 1994). In addition, GERD may aggravate salivary dysfunction through loss of appetite, reduced mastication and malnutrition.

The increased caries activity related to salivary gland hypofunction (Papas et al., 1993; Pedersen et al., 1999a; Rundegren, van Dijken, Mornstad, & von Knorring, 1985; Spak, Johnson, & Ekstrand, 1994; Young et al., 2001) is mainly attributed to the reduced salivary flow rate. This leads to prolonged clearance of fermentable carbohydrates, reduced thickness and velocity of the salivary film, accumulation of food debris and dental plaque, reduced buffering capacity, drop in the salivary pH and an impaired salivary antimicrobial activity resulting in dysbiosis, including colonisation of a more aciduric and acidogenic microbiota that promotes demineralisation of the teeth (Hara & Zero, 2010; Kilian et al., 2016; Marsh et al., 2016). Saliva also protects the teeth against tooth wear by erosion, attrition and abrasion (Young et al., 2001). For example, the risk of developing dental erosion is five times more frequent in patients with unstimulated whole saliva flow rates below 0.1 ml/min (Jarvinen, Rytomaa, & Heinonen, 1991) due to prolonged oral clearance of dietary acids. However, the composition of the acquired pellicle also plays an essential role in the protection against acidic attacks (Vukosavljevic, Custodio, Buzalaf, Hara, & Siqueira, 2014). Caries, erosion and attrition can result in loss of teeth and thus in an impaired masticatory function. Tooth loss, ill-fitting dentures and pain in relation to eating may lead to a significant involuntary weight loss, which in turn has a negative impact on salivary gland function (Sullivan, Martin, Flaxman, & Hagen, 1993). Mucosal inflammation and infections, of which oral candidiasis is the most prevalent, are often caused by salivary gland hypofunction and concomitant reduction in salivary antimicrobial activity (Abraham, Al-Hashimi, & Haghighat, 1998; Almståhl & Wikstrom, 1999; Navazesh, Wood, & Brightman, 1995; Torres et al., 2002). Dysphagia is another common consequence of salivary hypofunction, but may also occur due to congenital or acquired neurological damage including myasthenia gravis, multiple sclerosis, Parkinson's disease or cerebrovascular accident.

2 | CONCLUDING REMARKS

Saliva plays a central role in the complex physiological and biological processes that take place in the upper parts of the gastrointestinal tract in relation to ingestion and processing of food. These processes requires close coordination of teeth, orofacial muscles, oro-oesophageal mucosa and salivary secretion in addition to handling of sensory input and secretory and motor outputs. The preparation of the food for digestion in the oral cavity also prolongs the pleasure of eating. Consequently, salivary dysfunction and its associated symptoms and clinical manifestations are not only detrimental to digestion in the upper gastrointestinal tract, but to social functioning and quality of life. Conversely, gastrointestinal dysfunction may also affect salivary gland function. Evaluation of salivary gland function should therefore be a routine part of any oral examination to manage and prevent serious oral, pharyngeal and oesophageal consequences of salivary gland dysfunction.

CONFLICT OF INTERESTS

The authors declare no potential conflict of interests with respect to the authorship and/or publication of this article.

AUTHOR CONTRIBUTIONS

All authors drafted the paper.

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