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Review article

Saliva: An all-rounder of our body

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ABSTRACT

Saliva is a multifaceted bodily fluid that is often taken for granted but is indispensable for oral health and overall well-being in humans. Although mainly comprised of water (99.5%), proteins, ions and enzymes turn saliva into a viscoelastic solution that performs a variety of vital tasks. This review article gives a brief overview of the salivary gland system, as well as the composition, output and functions of saliva. It also addresses the current applications of saliva for diagnostic purposes, the clinical relevance of saliva in oral diseases as well as current treatment options.

1. Introduction

Saliva is an all-rounder in our body that manages a variety of tasks. Although it is not one of the more often discussed bodily fluids, it is indispensable for maintaining oral health and essential for overall health in humans. Salivary disorders that are most often seen in the clinic include xerostomia or dry mouth, sialadenitis or salivary gland inflammation, and salivary stones. For example, in the general population the estimated prevalence of dry mouth is around 20%. In the elderly it increases to up to 50% [1]. Dry mouth caused by anxiety, acute infection or dehydration may be reversible. However, causes of permanent xerostomia include radiation therapy in head neck cancer patients, autoimmune inflammatory diseases (e.g., Sjögren syndrome) or the use of xerogenic drugs. In this review, we summarize current knowledge in the literature about the salivary glands, as well as the secretion, composition associated with diagnostics, properties, and functions of saliva. We then discuss the clinical relevance of saliva to oral diseases and current treatment options.

2. The salivary glands and the secretion of saliva

Saliva consists of water (99.5%), inorganic salts and enzymes (0.2%), and proteins (0.3%). It is synthesized and secreted by the salivary glands (SG), which are innervated by the autonomic nervous system, specifically by sympathetic and parasympathetic nerves [2]. SG can be classified into major (parotid, submandibular, sublingual) and minor glands (labial, buccal, lingual and palatal) or according to the histochemical nature of the secreted saliva, i.e., serous, mucous or mixed (Fig. 1). Thereby, serous saliva is a watery fluid, while mucous saliva is more viscous. Human major glands produce about 90%, minor glands consist of up to 1000 glands and secrete less than 10% of the total saliva [3–5].

All SG consist of two cell types; the acini (mucous and/or serous), which produce the salivary fluid and the salivary proteins, and the ductal network (Fig. 2). The ductal system is formed by the intercalated ducts and striated ducts that modify the salivary fluid, and by the excretory ducts that collect saliva and transport it to the mouth, assisted by the myoepithelial cells [8].

Salivary fluid production is a well-studied two-stage process [9,10]. In the first stage, active secretion of salt (sodium (Na^+) and chloride (Cl^-)) in the acinar cells takes place due to the interaction of four ion transporters [9]. Water is transported from the blood system to the lumen through tight junctions and aquaporin channels, so that a primary isotonic liquid is formed [11]. The ducts, which are impermeable to water, modify the liquid by removing Na^+ and Cl^- and adding potassium (K^+) and bicarbonate (HCO_3^-). Hence, the primary isotonic fluid changes into hypotonic saliva and enters the oral cavity through the excretory ducts (for a more detailed review of the salivary fluid secretion see Turner and Sugiya 2002 [10]).

The parotid glands, which are the largest SG, are present on each side of the head in front of the ears. They secrete serous saliva, which is rich in amylase, sulphomucins and sialomucins, via Stenseńs duct into

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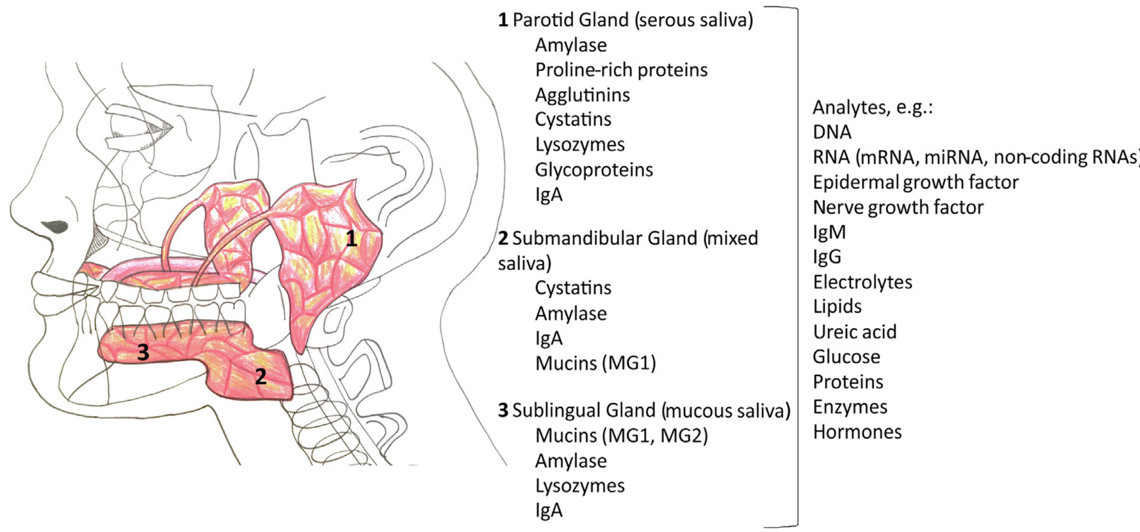

Fig. 1. Schematic illustration of the major salivary glands and their contributions to the components of saliva. Adapted from [6,7].

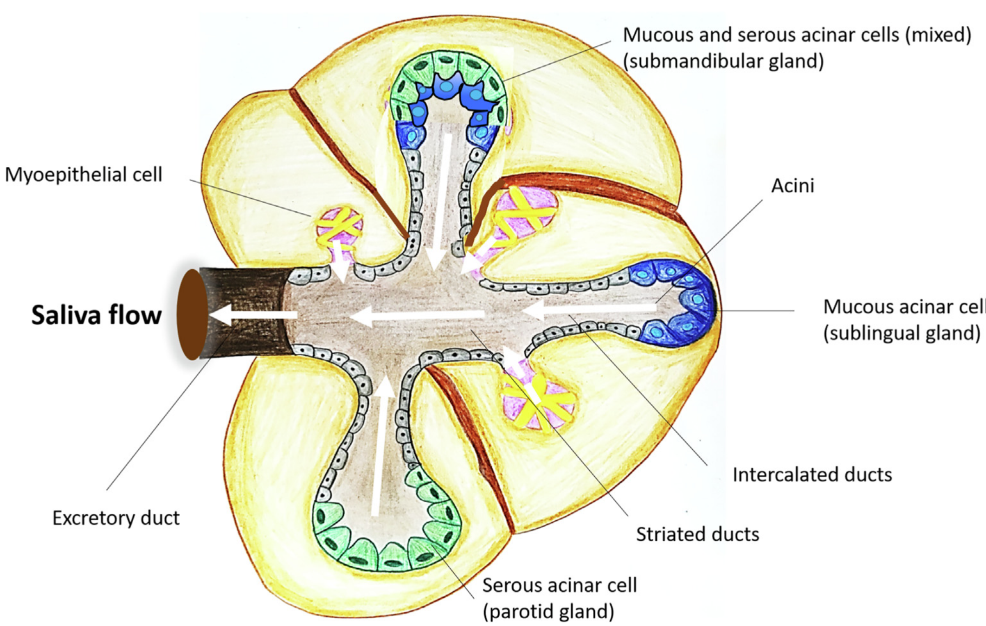

Fig. 2. Schematic figure of a salivary gland, structured into acini (serous, mucous and mixed) and the duct network (intercalated, striated and excretory). The parotid gland consists of serous acini, the sublingual gland mainly comprises mucous acini and the submandibular gland contains both cell types. Stellate-shaped myoepithelial cells, which have structural features of epithelial as well as smooth muscle cells, wrap around the ducts and constrict when the gland is stimulated to secrete.

the mouth [8]. At rest, they contribute 20–25% to whole saliva flow, while production increases to about 60% upon stimulation [12–14]. The submandibular glands represent the second largest glands and can be found beneath the floor of the mouth [15]. They produce mucous saliva, which consists mainly of glycoproteins, sulfated cystatins, and epidermal and neural growth factors, and reaches the oral cavity via Whartońs ducts. At rest, the submandibular glands contribute 60–65% to the total flow of saliva. The sublingual glands are present in the connective tissue of the floor of the mouth. They produce mucous saliva that reaches the oral cavity via Whartońs and Bartholińs ducts. It is mainly comprised of mucins and high levels of lysozymes, and contributes 7–8% to the total flow. The minor glands secrete less than 10% at rest as well as during stimulation [13]. A smaller subset of the minor glands are von Ebneŕs glands, which are located at the base of crypts together with the taste buds [16]. They produce a very small volume of saliva that contains lipocalin and lingual lipase. It has been speculated that these proteins support the maintenance of the environment of the taste buds rather than playing a major role in digestion [2].

3. The composition and output of saliva

The composition of saliva strongly depends on the flow rate. It must be noted that the flow rate is a very individualized measurement, thus, values reported in literature vary [13,17]. In unstimulated whole mouth saliva (UWMS), the average range of flow rate is 0.3–0.4 mL/min with an osmolality ranging from 50 to 70 mosmol/kg [13,18]. The normal pH is 6.0–7.0, showing a buffer capacity from 3.1 to 6.0 mmol H^+/L. Factors affecting the flow rate of UWMS include for example the degree of hydration, the body position (standing or lying), or the circadian and circannual rhythm [19,20]. Once the flow rate increases because of masticatory, gustatory or pharmacological stimulation, the average maximum level of whole saliva is up to 7 mL/min. Thereby, the salivary electrolyte levels of Na^+, Cl^-, Ca^{++} and HCO_3^- increase, whereas K^+ levels decrease [9]. The higher HCO_3^- concentration in stimulated whole mouth saliva (SWMS) increases the buffer capacity to 3.3–8.5 mmol H^+/L [21,22] and the associated pH value (7.4) [21]. However, due to the large number of influencing factors, it is easier to measure whole saliva flow volume [13].

The estimated daily production measures between 0.5 and 1.5 L. During sleep, low flow occurs, and during stimulation, for example by taste or chewing, the salivary flow increases and contributes 50–90% of this total [19,23]. For taste stimulation, citric acid generates the largest flow compared to other stimulants that taste sweet, salty, and bitter or umami [24]. Hence, the nature, duration and intensity of the stimulus together with circadian variations affect not only the volume of salivary flow but also the concentrations of its components [25]. In addition to the electrolytes mentioned above, these components also include phosphate, SCN^-, Mg^{++}, F^-, urea, ureic acid or maltase, enzymes, minerals and gases (CO_2, O_2 and N_2), and proteins.

Most of the salivary proteins are synthesized in the endoplasmic reticulum and packed into vesicles and secretory granules in the Golgi complex. They fuse with the apical cell membrane and release their contents by exocytosis into the acinar lumen [26]. Secreted proteins include α-amylase, mucoglycoproteins (mucins), and other proteins such as proline-rich proteins, agglutinins, histatins, cystatins, lysozymes, and glycoproteins [12–14,27]. Amylase is the most abundant protein in saliva, secreted by all glands and converts non-soluble polysaccharides into soluble units. Secretory immunoglobulin A (IgA) is the most important immunologic component. IgA is produced by plasma cells of the connective tissues and actively transported via the polymeric immunoglobulin receptor (pIgR) across the acinar and ductal cells of the parotid, sublingual, submandibular and minor glands [28]. Briefly, IgA binds to pIgR on the basolateral surface. After endocytosis, the vesicle is transported to the apical membrane and released as secretory IgA. The salivary mucins are a family of large glycoprotein polymers that prevent the inner lining from dehydration. Mucins can be divided into secreted soluble mucins (MUC5B, MUC7) and cell-associated mucins including MUC1, MUC4, and MUC16. MUC1 is synthesized in the SG and is also expressed by the epithelial cells of the superficial and intermediate layer. The main secreted components are the high molecular-weight mucin (MG1) MUC5B, which is produced by the goblet cells in the submandibular and sublingual glands and the lower molecular weight mucin (MG2) MUC7, which is excreted by the submandibular, sublingual and minor glands [29]. Both mucins show a protein backbone rich in serine, proline and threonine amino acids (SPT-rich regions), which allow for O-glycosylation. The SPT-rich regions are mostly glycosylated with O-linked glycan chains [30]. Small cysteine-rich domains that are less glycosylated interrupt the O-glycosylated portion. These cysteine-rich domains consist of N- and C-terminal regions, which are essential for mucin polymerization by disulfide bridges. The sialylated and sulfated residues equip mucins with a negative charge [31,32]. Thomsson et al. showed that MUC5B consists of 19% protein and 81% carbohydrate. The latter group includes N-acetylneuraminic acid, fucose, galactose, N-acetylglucosamine and N-acetylgalactosamine in molar ratios 1:5:4:3:1 [33]. MUC5B forms an entangled network because of calcium-mediated crosslinking and interactions between carbohydrates and hydrophobic interactions, and is responsible for the viscoelastic properties of saliva [34]. MUC5B together with MUC7, MUC1, sIgA and cystatine, creates the so-called mucosal pellicle, a thin layer of residual saliva that coats oral soft tissues. Thereby, MUC1 and other surface proteins act as an anchor by adhering to epithelial cells with an intracellular and extracellular domain and cross-linking with mucins [35,36]. The mucosal pellicle is different from the enamel pellicle, which consists of salivary biomolecules that bind to the surface of the teeth (for a review see Hannig et al. [37]).

In addition to the salivary components described, blood-based molecules enter the highly vascularized salivary glands through transcellular and para-cellular routes. Thus, alterations in the composition of blood also may lead to modifications in the biochemical composition of saliva. This fact makes saliva a preferred diagnostic medium for the detection of biomarkers, including antibodies, microbes, DNA, RNA, lipids, metabolites and proteins for both oral and systemic diseases [38]. The advantage of using saliva for diagnostic purposes compared to other bodily fluids is that the collection is fast, non-invasive, and inexpensive [39]. Moreover, procurement is painless for the patient, sample storage and shipping are easy and sample preparation is simple. Currently, salivary diagnostics are applied in medicine, dentistry, pharmacotherapy, epidemiology, and bioterrorism [38].

In medicine it serves as a tool in the early detection of infectious viral and bacterial diseases, autoimmune diseases, anxiety disorders, renal diseases, cardiac disease, metabolic diseases, Alzheimeŕs disease, caries, periodontal diseases and cancer. The latter group includes oral squamous cell carcinoma (e.g. [40]), pancreatic cancer (e.g., [41]), breast cancer (e.g., [42]), lung cancer (e.g., [43]) and gastric cancer (e.g., [44]). Thereby, one transport option and mechanism by which cancer-derived biomarkers/tumor-circulating DNA can be shuttled into the mouth are extracellular microvesicles also referred to as exosomes. They function as cargo carriers and information messengers, transferring substances and forming communications. Exosomes are associated with a variety of physiological processes such as apoptosis, coagulation, inflammation, secretion of oncogenes, and immune function [45]. They enter saliva via blood circulation or directly through saliva components. Currently, the gold standard for exosome isolation and analysis is by density gradient or sucrose cushion ultracentrifugation and PCR based systems. Recently, a liquid biopsy technology termed EFIRM (electric field-induced release and measurement) has been introduced as signal amplification platform, which is fast, affordable, requires small sample volumes, sensitive, and easy to use [46,47]. It has been proven to be able to detect and quantify circulating tumor DNA in patients suffering from e.g., non-small cell lung cancer in plasma as well as in saliva [46].

4. The properties of saliva

Freeze-edging combined with transmission electron microscopy showed that the salivary mucin fibers form a coherent network [18]. This network shows a broad pore size distribution ranging from the microscale to the nanoscale. The mode diameter of the pores is 0.7 µm, with a peak width of 1.9 µm. Microrheological investigations using optical tweezers showed that the pores are filled with a low-viscosity fluid similar to water. The morphological observations correlate with the rheological properties, i.e., viscosity, elasticity, stickiness, and Spinnbarkeit (i.e., stringy or stretchy property) of saliva [48]. Macrorheological measurements showed that considering the high shear rates that occur during eating and speaking (i.e., from 60 to 160 s^{-1}), the dynamic viscosity of whole-mouth saliva decreases with increasing shear, indicating a non-Newtonian fluid [49]. For UWMS, G′, the elastic modulus, is slightly larger than G″, the viscous modulus, confirming the viscoelastic behavior of a strongly structured fluid with a loss factor close to 1 [18]. The viscosity of SWMS is 1.3-fold lower than that of UWMS. This decrease in viscosity has been attributed to the parotid glands, which contribute to about 60% of serous saliva flow [15,21]. Vijay and co-workers showed that sensory stimuli, specifically chewing, also stimulate the submandibular and sublingual glands, resulting in saliva with lower Spinnbarkeit than unstimulated saliva [50]. Interestingly, no changes in mucin, protein, and Ca^{++} concentration compared to unstimulated saliva were observed, although HCO_3^- concentration and pH correlated with the drop in Spinnbarkeit.

5. The functions of saliva

Both the salivary components and the viscoelastic properties are responsible for the functions of saliva, which can be organized into: (1) lubrication and moistening, (2) microbial homeostasis and protection, (3) digestion, bolus formation and clearance, (4) taste and smell, (5) buffering, (6) mineralization, and (7) wound healing. The physiological salivary functions are summarized in Table 1 [2,13].

The viscoelastic properties allow saliva to be spread and retained on the (vertical) surface of the oral mucosa. Statherins act as a boundary

Table 1
The salivary functions adapted from Dawes et al. [68].

Function	Description	Components
Lubrication and moistening	Protection against mechanical, chemical and thermal irritation, to remove microorganisms, microbial homeostasis	MUC 7, MUC 5B
Microbial homeostasis	Anti-bacterial, anti-viral, anti-fungal effects, agglutination	Salivary proteins
Tooth protection	Formation of an enamel pellicle to protect teeth against abrasion, attrition, erosion and dental caries	Salivary proteins
Digestion and bolus formation	Splitting of starch into maltose, maltotriose, maltotetrose and oligosaccharides Facilitation of the swallowing process	α-amylase
Clearance	Residual saliva volume after swallowing removes materials (food, cells, microorganisms) from the mouth	
Taste and smell	Dissolution and distribution of tastants Taste stimulates salivary flow Saliva triggers odor release of food Saliva maintains the environment of the taste buds	Taste receptors present on taste buds Hypotonicity of saliva facilitates taste Lipocalin and lingual lipases
Buffering	Protection against damaging effects No accumulation of the acidic form of buffer after reaction with acid Prevention of dental caries pH modulation	Electrolyte level and HCO_3^-, phosphates, urea
Mineralization	Prevention of dissolution of teeth	Ionic components (calcium and phosphate) and salivary proteins
Wound healing	Saliva accelerated wound healing	Mucus pellicle Growth factors Salivary proteins

lubricant, for example, to prevent teeth from wearing and chipping during chewing [51,52]. The most important lubricating components are the aforementioned mucins that form the mucous network that acts as a physical barrier. The network architecture may allow the entrance of viruses or bacteria smaller than 700 nm but prevents the passage of irritants, larger bacteria and viruses, deleterious molecules and foreign particulate matter into the underlying epithelia [53–55]. This is important because the moist environment suits the growth of characteristic microorganisms. To date, over 700 bacteria species have been identified, which colonize the hard surfaces of teeth and the soft tissues [56]. Notably, up to 10^8 microorganisms have been detected per mL of saliva, mostly derived from oral mucosal surfaces [57] (for a detailed review of the oral microbiome see Kilian et al. [58]). The salivary components are not only the nutritional source for these microorganisms, but also help to maintain a balanced microbiota. For example, different mucins modulate adhesion of microorganisms and control bacterial and fungal colonization. Thereby, MG1 adsorbs to the tooth by forming the enamel pellicle that protects the tooth from acids. MG2 also binds to the enamel, but controls aggregation and clearance of bacteria [59]. Histidine-rich proteins, known as histatins, control fungal growth and neutralize the lipopoly-saccharides of bacterial membranes. Cysteine-rich proteins inhibit proteases and lysozymes produced in the basal cells of striated ducts, hydrolyze bacterial cell walls and trigger aggregation of bacteria [13]. Secretory IgA, the most important immunologic component, is able to aggregate bacteria, and prevent them from adhering and colonizing the oral lining during inflammation [60]. Moreover, it neutralizes toxins released by bacteria or viruses by blocking their binding to cell receptors.

Saliva also facilitates mastication, speech, and swallowing, and is crucial for processing food. Amylase does not directly support the initial digestion process of starch in the mouth, but provides assistance in the post-mastication process due to dissolution of residual food stuck on teeth [2]. The presence of saliva is essential to wet hydrophilic and hydrophobic food surfaces to enable bolus formation and help swallow and clearance. It also stimulates taste receptors in the taste buds, which are mostly located on the tongue [61]. Interestingly, the hypotonicity of saliva reinforces salty taste because the taste receptors are adapted to the background salt concentrations in UWMS. Taste is one of the main stimulants for saliva production, and as stated earlier, the highest saliva stimulation is obtained with sour taste, followed by salt, sweet and bitter [62].

Buffering is another important property of saliva that protects against dental caries. HCO_3^- shows the highest buffering capacity, followed by histidine-rich peptides, urea and phosphate. HCO_3^- is able to diffuse into plaque and to neutralize acids. Simultaneously, urea is metabolized in the plaque and releases ammonia that in turn increases plaque pH to 6–7. Importantly, buffer activity and consequent effects on plaque pH depend on the flow rate; these effects are low at low flow of unstimulated saliva, and high during stimulation. However, a saliva or plaque pH above 5.5 is required to achieve supersaturation so that Ca^{++} and phosphate ions can start to repair the enamel - a process also referred to as remineralization [63]. The salivary Ca^{++} concentration is controlled by proline-rich proteins and statherins in saliva that inhibit precipitation of calcium phosphate salts onto the teeth due to binding of Ca^{++} [64,65]. Finally, saliva accelerates wound healing in the mouth. Tissue factors and growth factors in saliva promote this process by e.g., re-epithelialization and regulation of the extracellular matrix [66]. Other components such as histatin 1 enhance epithelial migration [67].

6. Clinical relevance of saliva and treatment options

The inability to produce adequate volumes of saliva leads to perpetual dry and sticky mucosa and stringy saliva and results in a loss of essential stomatological functions. A variety of causes can lead to these conditions. Salivary disorders that are most often seen in the clinic include xerostomia or dry mouth, sialadenitis or salivary gland inflammation, and salivary stones.

Salivary disorders and potential treatment options are summarized in Fig. 3 and further described below.

6.1. Xerostomia

Xerostomia is clinically defined as the subjective sensation of dry mouth. It does not always correlate with objective measurements of salivary flow rates and hyposalivation or salivary gland hypofunction, and might be related to the altered composition of saliva [17,70]. Symptoms of xerostomia include oral discomfort and pain related to reduced protection against trauma to the mucosa, difficulty speaking, changes to taste sensation, and difficulty swallowing [71]. Patients are also at increased risk of malnutrition and dental caries and the saliva consistency is thicker [72]. Sometimes oral infections or inflammation can be seen in the unprotected mucosa of the oral cavity. The incidence of xerostomia in relation to the general population is quite high, about 20–30%, and the rate of xerostomia is much higher in elderly patients,

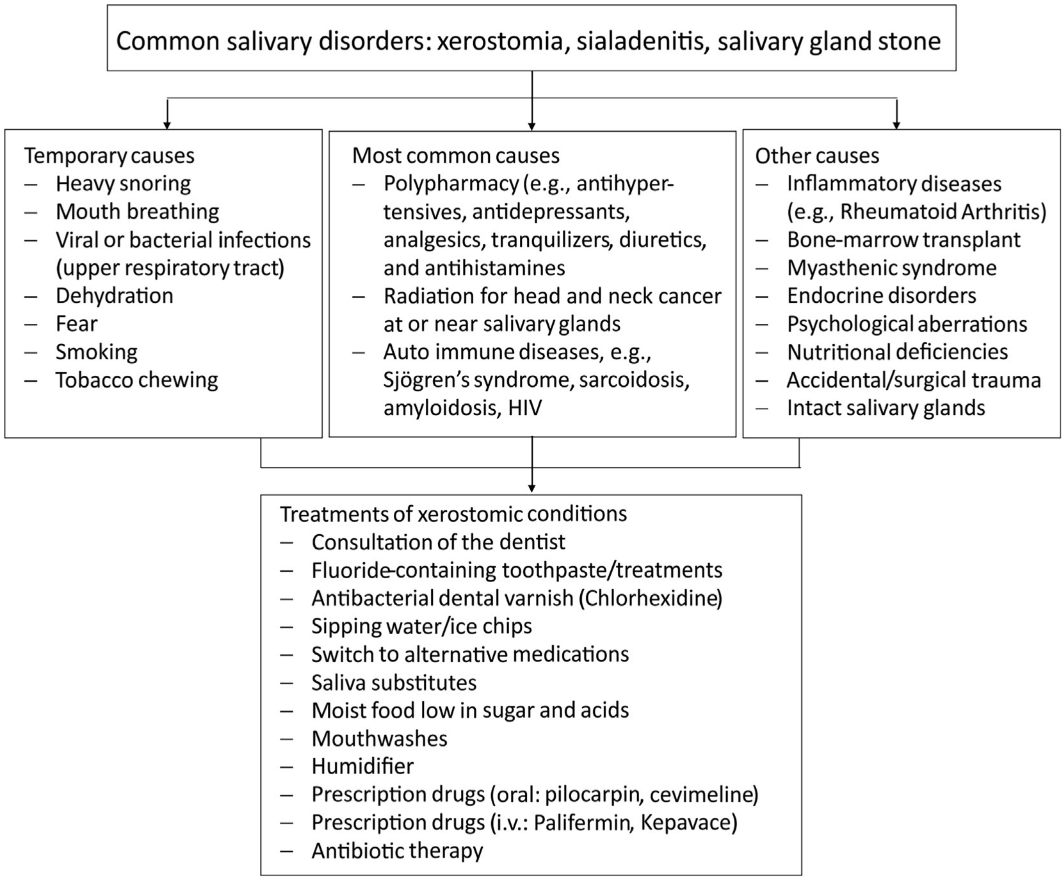

Fig. 3. Causes of salivary disorders and treatment options of xerostomic conditions.
Adapted from [69].

up to 50%, being more frequent among women than men [73–75]. However, xerostomia is not only an age-related consequence; further conditions that reduce the salivary flow rate and alter its composition are polypharmacy, Sjogren's syndrome, radiation-induced xerostomia, and glandular pathologies.

(i) Polypharmacy, or the use of multiple medications by a single patient, is the leading cause of xerostomia. There are more than 500 medications with xerostomia as a known side effect including diuretics, tricyclic antidepressants, hypoglycemics, antihistamines, NSAIDs, and urinary antispasmodics [76,77]. Patients who complain of dry mouth should be screened for polypharmacy. The entire drug history of the patient should be carefully reviewed since the risk of xerostomia increases with the number of medications used even if the individual medications themselves are not xerogenic [78]. Currently, medication-induced xerostomia is highly underrecognized but can be prevented by medication changes towards products with fewer xerogenic side effects and care-oriented approaches that take into account influencing factors to treat oral symptoms [79].

(ii) Sjogren's syndrome is an autoimmune rheumatic disease that attacks both the lacrimal and salivary glands and is the second leading cause of xerostomia. This disease affects predominantly females in their 5th decade of life and is characterized by progressive immune-mediated damage to the salivary glands [80]. Xerostomia is a common complaint related to Sjogren's syndrome, with limited effective treatment for the underlying condition. Over time, the parotids are rendered non-functional with symptomatic chronic sialadenitis in the setting of ongoing xerostomia, leading to a high risk for dental caries, difficulty swallowing, speaking, and a poor quality of life. The gold standard for diagnosis is a minor salivary gland biopsy, typically from the lower lip, and the presence of > 50 lymphocytes surrounding a minor salivary gland biopsy area of 4 mm^2 confirms the diagnosis [81]. It is important to note that for Sjogren's patients, the immune destruction of the gland leads to glandular inflammation (chronic sialadenitis, discussed later) and 10–20× increased risk for developing Non-Hodgkin's Lymphoma that often presents with as a lump or swelling in the parotid [82]. Recommendations for caries prophylaxis include the use of topical fluoride, antimicrobials, remineralizing agents (chlorhexidine) and salivary stimulation [83]. For gland stimulation, pharmaceutical agents are applied as sugar-free lozenges or chewing gum. Pilocarpine and cevimeline are systemic sialogogues approved by the Food and Drug Administration (FDA) for Sjogreńsyndrome. Pilocarpine is a parasympathomimetic drug with muscarin action, cevimeline acts as gland stimulant with strong affinity to muscarinic receptors [84,85]. Both are administered orally for at least 3 months [86]. Side effects associated with their use are excessive sweating, nausea, bronchoconstriction, hypotension, increased urinary frequency and bradycardia. They are contraindicated in patients with asthma, pulmonary diseases, ß-adrenergic blocker users, heart diseases and glaucoma. Other sialogogues are applied topically as spray, rinse, gel or mouthwash to moisten the oral mucosa without altering the salivary flow [85]. However, unpublished data by our group showed that some of these commercially available products do resemble neither the composition of "healthy" UWMS nor the viscoelastic properties. This coincides with a 2011 Cochrane review that found no strong evidence that these agents are effective in relieving dry mouth [70].

(iii) Radiation therapy is a common and effective tool used in the treatment of head and neck cancer. Thereby, the most common type of head and neck cancer is the squamous cell carcinoma that originates in the cells that line the inside of the nasal cavity, salivary glands, oral cavity, esophagus, pharynx, and larynx. As a treatment related side effect of radiotherapy, the salivary acinar cells can be irreversibly damaged leading to xerostomia and permanent morbidity from gland hypofunction, which may affect 80% of the patients [87,88]. Thereby, salivary electrolyte levels change, the buffer capacity is decreased due to a reduction of the bicarbonate concentration and consequently, the pH shifts from about 7 to 5. The concentration of immunoproteins increases but because of the reduced flow rate, there is still a significant immunoprotein deficit. Moreover, the number of acidogenic and cariogenic microorganisms increases leading to a decrease of non-cariogenic microorganisms. Radiation induced xerostomia occurs during but also after treatment and produces the most discomfort to patients because both the decreased volume and lack of the protective properties of saliva lead to severe dental caries as well as difficulty with swallowing, speaking, taste, mucositis and chronic infections [89,90]. The incidence of depression from radiation-induced xerostomia is over 40% in some studies [91]. Patients with moderate to severe symptoms wake up at night to moisturize their mouth, which fragments sleep and can be a secondary effect contributing to their depression. Treatment begins with a recommendation to drink sips of water, with preventative measures of improved oral hygiene, including the use of prescription strength fluoride toothpaste for remineralization of teeth. The use of a humidifier at night has shown benefits but is contraindicated in patients with allergies to dust mites. Topical agents include chewing gums and lozenges containing xylitol or sorbitol to stimulate the salivary flow and aid lubrication. Pharmacologic treatments such as muscarinic agonists (e.g., pilocarpine) are fraught with intolerable cholinergic side effects, and therefore, less often used. In a recent phase 0 study, orally applied D-Limonene, a food-flavoring agent has been shown to protect the salivary stem/progenitor cells by activation of aldehyde dehydrogenases to decrease apoptosis and improve gland structure [92]. However, high drug doses are necessary, which makes swallowing more difficult. Yohimbine, an alpha-2 adrenergic antagonist induces an increase in cholinergic activity peripherally. Compared to anethole trithione, a bile secretion-stimulating drug that increases the secretion of acetylcholine and stimulates the parasympathetic nervous system, saliva flow is significantly increased [93]. Amifostine is an oxygen scavenger that may protect salivary glands from free-radical damage during radiation treatment [94]. Amifostine has been approved by the FDA for prevention of xerostomia, in head and neck squamous cell carcinoma patients undergoing radiotherapy and is administered intravenously [95]. It shows additional adverse effects such as nausea, vomiting, hypotension, transient, hypocalcemia, and allergic reactions and thus, not well accepted by patients [96]. Another cytoprotective compound that is applied parenterally is Keratinocyte growth factor-1 (Palifermin, Kepivance). However, according to Riley et al. there is insufficient evidence to suggest that Palifermin performs better than placebo in treatment of xerostomia [97]. Palliative oral care includes sprays, mouthwashes, and gels that mimic natural saliva. They are mainly composed of substances that increase the viscosity of the artificial substitute, such as cellulose derivates, polyethylene glycols, xanthan gum or natural porcine mucins, and minerals. Although some relief is provided, they require frequent application and do not address nighttime xerostomia [98]. Finally, there is anecdotal evidence on the use of acupuncture to treat dry mouth, although there is insufficient evidence regarding its efficacy [99].

(iv) Rheumatoid Arthritis is a chronic inflammatory disease that affects the joints, leading to the destruction of bones and cartilage, most often in the hands and feet. It affects patients after the 3rd decade of life. In North America and Northern Europe, the incidence is estimated at 20 to 50 cases per 100,000 population [100,101]. In addition to having chronic extra-articular symptoms of malaise, fatigue, and weakness, 65% of these patients experience xerostomia, also referred to as secondary Sjogreńs syndrome [70,102]. Interestingly, one study found that the severity of xerostomia was significantly correlated with the number of painful joints and fatigue in rheumatoid arthritis patients [103]. In addition to rheumatoid arthritis, other immune-mediated or granulomatous chronic diseases have been associated with xerostomia, such as systemic lupus erythematosus, scleroderma, primary biliary cirrhosis, sarcoidosis, and inflammatory bowel disease [104–109]. Treatment of xerostomia includes the replacement of saliva by using saliva substitutes and gland stimulants, such as pilocarpine. Moreover, dental management must also be taken into account [110].

6.2. Sialadenitis

Sialadenitis is inflammation of the salivary glands. It most commonly occurs due to dehydration, as salivary proteins become more adherent and block outflow through the salivary ducts. For example, exercise with poor hydration, poorly controlled diabetes with polyuria, or iatrogenic use of diuretics can all lead to xerostomia and hyposalivation. This is reversible if hydration is improved [111]. Sialadenitis can also occur as a result of autoimmune destruction of the gland, obstruction of the outflow tract as seen in salivary stones or strictures, or use of radioactive iodine in the treatment of thyroid cancer. In radioactive iodine treatment, iodine is concentrated in the saliva, leading to scarring and stricture of the outflow tracts that in turn causes recurrent sialadenitis [112]. The term "chronic sialadenitis" is used for recurrent episodes of salivary gland inflammation of any etiology that over time can affect salivary gland function (often seen in patients with Sjogren's syndrome). Sialadenitis can also occur secondary to bacterial infection (acute bacterial sialadenitis) ascending from the oral cavity via the salivary ducts. Initial treatment involves antibiotic therapy and rehydration. Botulinum toxin injection of the salivary glands have shown to be beneficial in reducing symptoms from chronic sialadenitis, although regular injections are needed [113,114].

6.3. Acute bacterial sialadenitis (ABS)

ABS presents with sudden onset pain and swelling of the affected gland, usually unilateral and predominantly involving the parotid gland. Purulent discharge may be expressed from Stenson's duct. This condition is often seen in elderly patients in the perioperative period following abdominal surgery leading to systemic dehydration. Poor oral hygiene, dehydration, xerostomia, malnutrition, Sjogren's, smoking and immunosuppression are risk factors [115,116]. Acute bacterial sialadenitis affects the parotid gland at a much higher frequency than the submandibular gland. This is attributed to the weaker bacteriostatic properties of saliva produced from the parotid when compared to the submandibular gland [116]. The main treatment is hydration and antibiotics with evaluation for the underlying etiology following resolution of acute symptoms [111].

6.4. Salivary gland stones

Salivary gland stones are similar to kidney stones in their ability to obstruct the outflow tract and cause pain and increase the risk of infection. The majority of salivary stones are composed primarily of calcium phosphate and hydroxyapatite, as well as cellular debris, glycoproteins, and mucopolysaccharides [117]. The submandibular gland (location of 80–90% of all stones) is the most susceptible salivary gland to stone formation due to its anatomy, flow rate and composition [117,118]. The longer duct of the submandibular gland works against gravity, leading to a slower flow rate and higher stagnation of saliva - conditions conducive to stone formation. Additionally, the unique composition of the submandibular gland saliva provides the ingredients for stones to form. Risk factors for accelerating this process include dehydration, diuretics, anticholinergic medications, trauma, gout, smoking and chronic periodontal disease [117,119]. These patients often present with recurrent sialadenitis with pain (60%) and swelling under the jaw that is worsened with eating [120]. The parotid gland also forms stones, but less commonly, making up only about 6–20% of salivary stones [117,118]. Patients should be counseled on the use of sialogogues, warm compresses, gentle massage of the gland and duct, and improvements to hydration, but many of these stones require surgical removal. This is done through sialendoscopy, in which small endoscopes are inserted through the salivary duct, either by directly cutting into the duct transorally or sometimes by removing the entire gland through the neck.

7. Conclusion

Saliva highly contributes to human wellbeing. Its synthesis and secretion are complex and its properties enable a multitude of important functions to be performed. The variety of molecular and microbial analytes contained in this bodily fluid may serve as effective indicators for local, systemic and infectious disorders, making the application of saliva for diagnostic purposes an increasingly important field. However, salivary disorders that result in inadequate volumes of saliva are often seen in the clinic and lead to oral discomfort and pain related to reduced protection against trauma to the mucosa, difficulty speaking, difficulty swallowing, loss of taste and high risk for dental caries. Despite the significant impact on patients' quality of life, therapeutic options are still limited. Xerostomia induced by polypharmacy requires medication changes towards products with fewer xerogenic side effects and reduction of the number of prescribed medications, which is often a challenge for physicians and pharmacists. Topical agents to treat dry mouth induced by chronic inflammatory diseases, (auto-) immune or granulomatous diseases, and radiation therapy do not take into account nighttime xerostomia and the natural salivary properties and are thus, often ineffective. Although few pharmacological agents can be applied, intravenous injection leads to a variety of side effects and oral application with intestinal absorption requires swallowing of tablets or capsules, which in most cases is very difficult for patients and also associated with side effects. These facts highlight that there is an urgent need for research in this field to improve treatment beyond the current standard of care.

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