



Oral Microflora in Patients with Salivary Gland Hypofunction

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Summary: Saliva plays a significant role in the maintenance of oral hard and soft tissue integrity as well as for the oral microflora by providing mechanical cleansing, buffering effect and antimicrobial actions. Saliva not only enhances the clearance of micro-organisms and dietary carbohydrates from the oral cavity, but also regulates the composition and growth conditions of the oral microflora. It is well documented that the susceptibility to dental caries and oral mucosal infections is increased in patients suffering from low saliva flow rates. Nonetheless, only a limited number of studies have dealt with the impact of salivary gland hypofunction on the composition of oral microflora. Most of these studies have not included additional variables regarding environmental and behavioural factors that may contribute to changes in the oral microflora such as dental and general health status and sugar intake. This review has its main focus on the oral microflora in patients suffering from salivary gland hypofunction, be it temporary or permanent, due to different aetiologies like Sjögren's syndrome, radiation therapy of tumours in the head and neck region, cancer chemotherapy and intake of other medications. It also outlines the methods used for assessment of oral micro-organisms, and the numerous underlying factors affecting the interpretation of salivary and oral microbial findings.

Conclusions: Despite the different causes of salivary gland hypofunction, these patient groups show some similarities with regard to their oral microbial composition and increased counts of oral pathogens associated with caries activity (mutans streptococci and lactobacilli) and mucosal infections (in particular, *Candida albicans*).

Key words: Sjögren's syndrome, cancer therapy, medication, *Candida*, lactobacilli, mutans streptococci

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INTRODUCTION

In healthy individuals, the saliva fluid and its solutes constantly covers the oral hard and soft tissues. Moreover, micro-organisms as well as dietary sugars are removed from the oral cavity by a cleansing process referred to as oral clearance (Dawes, 1983; Lagerlöf and Oliveby, 1994; Lenander-Lumikari and Loimaranta, 2000), which is dependent on the whole saliva flow rates and the swallowing frequency by the individual. The oral microbial composition and growth conditions are also influenced by numerous salivary antimicrobial factors that are part of the oral defence mechanisms (for review, see Lenander-Lumikari and Loimaranta, 2000).

The saliva composition is dependent on the flow rate, the type of gland from which the saliva is secreted, and the nature and duration of the stimuli applied to activate the secretion reflexes (for review, see Pedersen et al, 2002a). The composition of salivary antimicrobial proteins may therefore vary from one oral site to another in an individual. Subsequently, oral sites can harbour specific microfloras depending on the site's morphology and the specific saliva composition (Rudney, 2000). Other local factors such as oral hygiene, dental caries, periodontitis, dental restorations and life-style factors can also affect the oral microflora (for review, see Almståhl, 2001a). This furthermore accounts for a number of systemic factors like diseases and their medications.

Table 1 Definitions of xerostomia and hyposalivation as well as 'cut-off' values of normal unstimulated and stimulated whole saliva flow rates and hyposalivation (Sreebny et al, 1991)

Xerostomia: the subjective feeling of oral dryness.

Hyposalivation: decreased whole saliva flow rates measured by sialometry.

Whole saliva flow rates (ml/min)	Normal	Hyposalivation
Unstimulated whole saliva	0.3-0.5	≤0.1
Stimulated whole saliva	1.0-2.0	≤0.5*

* In the diagnosis of Sjögren's syndrome the value is ≤0.7 ml/min (Workshop on diagnostic criteria for Sjögren's syndrome, 1989).

The significant role of saliva in the maintenance of a natural balance between oral host tissues and the oral microflora becomes evident when the saliva flow is reduced. In general, about 25% of the adult population is assumed to suffer from oral dryness (Sreebny and Valdini, 1988; see Table 1 for definitions). The most common causes of salivary gland hypofunction include intake of certain medications and systemic diseases. However, regardless of the aetiology of salivary gland hypofunction, changes in the oral ecology occur already at unstimulated whole saliva flow rates below 0.20 ml/min. At such flow rates, the oral microbial profile includes increased candidal scores (Navazesh et al, 1995) and increased numbers of lactobacilli (Bardow et al, 2001) leading to an increased risk of candidiasis and a high caries activity.

Although several clinical studies indicate that salivary gland hypofunction of various aetiologies leads to a seriously compromised oral health, only a few studies have addressed the impact on the oral microflora (for review, see Almståhl, 2001a). Most of these studies, however, suffer from lack of information concerning the dental and general health status and nutritional behaviour like sugar intake, and often it is not stated whether use of the term 'xerostomia' covers the patient's feeling of dry mouth, or if it is based on the objective measurement of reduced salivary flow rate. Oral microbiological findings and their interpretation are dependent on the cultivation techniques and sampling methods applied. The growth of oral microbial cultures under *in vitro* conditions (growth on a plain agar surface with controlled nutritional and environmental factors such as constant temperature and oxygen/carbon dioxide tension), however, does not resemble those found under *in vivo* conditions.

Furthermore, the use of different sampling methods makes comparisons of microbiological findings between studies very complicated (Soto-Rojas et al, 1998; Almståhl, 2001a). Even oral biofilm models have their limitations when extrapolating findings to the *in vivo* conditions of the oral cavity. Thus, in the oral cavity the micro-organisms are exposed to continuously varying nutritional and environmental conditions including saliva quantity and quality as well as dynamic changes in gas tension and pH (Schonfeld, 1992).

Although a limited number of studies have dealt with the impact of salivary gland hypofunction on the composition of oral microflora, this review attempts to present the current status of the field. The review focuses on data obtained from patients suffering from chronically or temporary impaired saliva secretion due to Sjögren's syndrome, cancer therapy (radiation therapy or chemotherapy) and intake of certain medications. These patient groups are selected because they are characterised by having an increased risk of developing oral diseases like dental caries and oral candidiasis. The methods used for assessment of oral micro-organisms, and the numerous underlying factors and effect modifiers affecting the interpretation of salivary and oral microbial findings in these patient groups, are outlined.

SALIVA AND ORAL MICROFLORA IN SJÖGREN'S SYNDROME

Sjögren's syndrome (SS) is a common chronic inflammatory systemic autoimmune disease of unknown aetiology, which predominantly affects women. It is characterised by impaired function of the exocrine glands, especially the salivary and lacrimal glands, which presumably is caused by lymphocyte-mediated destruction of the glandular tissue (for review, see Pedersen and Nauntofte, 2001). SS is classified into two forms: primary SS (pSS) is the simultaneous presence of keratoconjunctivitis sicca and hyposalivation in patients not fulfilling internationally accepted criteria for another chronic inflammatory connective tissue disease; secondary SS (sSS) defines the disease entity in the presence of another chronic inflammatory connective tissue disease such as rheumatoid arthritis (Manthorpe et al, 1986). The syndrome may develop into a disabling disease that impairs the patient's general well-being and health-related quality of life (Pedersen et al, 1999a; Strömbeck et al, 2000).

Not only the quantity, but also the quality of saliva is affected in SS (Thorn et al, 1989; Kalk et al, 2001).

Table 2 Frequency (%) of *Candida* species determined semi-quantitatively, and the numbers of colony-forming units per ml (CFU/ml) in patients with primary Sjögren's syndrome (pSS) compared to patients with secondary Sjögren's syndrome (sSS)

Microbiological tests	pSS	sSS	References
Tongue smear	33%	76%	Sota-Rojas et al (1998)
Tongue swab culture	52%	76%	Sota-Rojas et al (1998)
Saliva culture/oral rinsing technique	76%	79%	Sota-Rojas et al (1998)
	81%	67%	Kindelan et al (1998)
	65%	60%	Almståhl et al (1999a)
Numbers of CFU/ml			
Tongue/palate swab culture	3.1×10 ⁶ (mean)	1.2×10 ⁵	Rhodus et al (1997)
Saliva culture	419/μl (mean)	739/μl	Sota-Rojas et al (1998)
Oral rinse	2100 (median)	1710	Kindelan et al (1998)*
Oral rinse	380 (median)	500	Almståhl et al (1999a)**

* The study included denture-wearers (44% pSS/25% sSS).

** The study only included dentate subjects.

Two studies state flow rates of the two groups: in Rhodus et al (1997) and Almståhl et al (1999a) pSS patients had lower unstimulated whole saliva flow rates and lower stimulated whole saliva flow rates as compared to patients with sSS.

The salivary gland hypofunction results in reduced buffering capacity, saliva pH and reduced oral clearance (Pedersen et al, 2004). These salivary changes, in combination with an inadequate oral hygiene (Najera et al, 1997) and an increased intake of fermentable carbohydrates (Cermak et al, 2003), may favour an aciduric and acidophilic oral microflora, which may promote development of oral diseases commonly seen in SS, i.e. dental caries and oral candidiasis (Sota-Rojas et al, 1998; Pedersen et al, 1999b, 2004). However, only few studies, of which all are cross-sectional, have investigated alteration of the oral microflora in patients with SS in relation to the development of oral diseases in the hard and soft tissues. Furthermore, most of the studies have compared the oral microflora between SS patients and healthy controls, whereas only a few studies have related microbial findings of SS to patients with hyposalivation of other aetiologies (Kindelan et al, 1998; Almståhl et al, 2001b).

Candidiasis-related Yeasts in the Saliva and on the Oral Mucosa

Recurrent oral candidiasis is prevalent among patients with SS and the most common clinical presentation of *Candida albicans* (*C. albicans*) colonisation is erythematous candidiasis and angular cheilitis (MacFarlane and Mason, 1974; Tapper-Jones et al, 1980; Hernandez and Daniels, 1989; Lundström and Lindström, 1995; Soto-Rojas et al, 1998; Pedersen et al, 1999b). Further, papillary tongue atrophy, dorsal tongue fissuring and erythema of the oral mucosa including a burning sensation may be signs of fungal infection (Pedersen and Nauntofte, 2001).

Only a few studies have examined the frequency and number of *C. albicans* in saliva of SS patients (Abraham et al, 1998; Kindelan et al, 1998; Soto-Rojas et al, 1998; Almståhl et al, 1999a). *C. albicans* is the most frequently isolated (66–72%) species in saliva of patients with SS. It may occur as the only *Candida* species or mixed with other *Candida* species such as *C. tropicalis*, *C. pseudotropicalis*, *C. parasilosis*, *C. kefyr* and *C. glabrata* (Soto-Rojas et al, 1998; Kindelan et al, 1998). The prevalence of *Candida* as well as the numbers of colony-forming units per ml (CFU/ml) not only varies between studies, but also between the pSS and sSS patients (Table 2). The diversity of results may reflect differences in the patient groups regarding dental status, oral hygiene habits, concomitant diseases, medication and/or immunological status. On the other hand, the severity of salivary gland hypofunction does not appear to differ between the two disease entities (Dawson et al, 2001). Generally, the results of saliva cultures and oral rinses correspond well to the clinical signs and symptoms of oral candidiasis (Abraham et al, 1998; Kindelan et al, 1998; Soto-Rojas et al, 1998). Although patients with sSS appear to have a higher prevalence of clinical oral candidiasis as well as colonisation of *Candida* than patients with pSS (Soto-Rojas et al, 1998), Kindelan et al (1998) found no significant differences in the incidence of *Candida* carriage and the total CFU/ml between pSS, sSS and 'xerostomic' controls. On the other hand, Almståhl et al (2001b) showed that patients with pSS had significantly higher levels of *C. albicans* in rinsing samples than subjects with hyposalivation of unknown cause. There appears to be a trend toward an inverse correlation between

stimulated parotid flow rate and *Candida* count in oral rinses among patients with SS (Abraham et al, 1998). Additionally, it has been shown that SS patients with immeasurable unstimulated whole saliva flow rates have the highest levels of *C. albicans* in oral rinses (Almståhl et al, 1999a). Overall, results of the studies performed on *Candida* in saliva indicate that both pSS and sSS patients have a higher frequency of *Candida* present in saliva cultures and higher numbers of CFU/ml obtained from oral rinses than the healthy controls (Abraham et al, 1998; Soto-Rojas et al, 1998; Almståhl et al, 1999a).

The microbial sampling demonstrating the presence of *Candida* species on the oral mucosa have usually been conducted by smears or culture swabs taken from the dorsum of the tongue, the buccal or palatal mucosa, the right tonsillar area, and/or from the fitting surface of the denture (MacFarlane and Mason, 1974; Tapper-Jones et al, 1980; MacFarlane, 1984; Rhodus et al, 1997; Soto-Rojas et al, 1998; Almståhl et al, 2001c; Pedersen et al, 2002b). Results revealed a significantly higher mucosal colonisation of *C. albicans* in both pSS and sSS patients as compared to healthy controls (Tapper-Jones et al, 1980; MacFarlane, 1984; Rhodus et al, 1997; Soto-Rojas et al, 1998) and in pSS as compared to patients with oral lichen planus (Pedersen et al, 2002b). Furthermore, patients with sSS harboured higher numbers of *C. albicans* than the patients with pSS, which was attributed to the presence of an additional inflammatory disease in sSS (Rhodus et al, 1997). Results also suggest an approximate inverse relationship between the presence and the density of *C. albicans* and salivary flow rates (Tapper-Jones et al, 1980; Hernandez and Daniels, 1989; Rhodus et al, 1997). Clinical atrophic changes on the dorsum of the tongue have been observed in 9 out of 10 SS patients of whom 90% had immeasurable stimulated parotid secretion (MacFarlane, 1984). In addition, Hernandez and Daniels (1989) found that SS patients with clinical chronic atrophic candidiasis were older, had oral symptoms for a longer period, more extensively inflamed labial salivary gland tissue and lower stimulated parotid flow rates than the SS patients without clinical atrophic candidiasis. In contradiction to oral rinses, not all mucosal cultures correspond to the clinical signs and symptoms. Thus, MacFarlane (1984) found that 73% of the patients with pSS had clinical signs of oral candidiasis, although cultures obtained from the dorsum of the tongue were only positive in 52% of the cases. This discrepancy between clinical signs and results of *Candida* cultures may reflect difficulties in obtaining representative material from a dry mucosa (Lundström

and Lindström, 1995; Soto-Rojas et al, 1998). It also emphasizes the importance of using a standardised method regarding sampling site and sampling area. On the other hand, subjects infected with *Candida* species do not necessarily exhibit oral lesions. This could be due to an asymptomatic carrier status or early candidiasis without clinically apparent lesions or a less virulent strain of *Candida*. Regarding site specificity, it is noteworthy that *C. albicans* were found twice as frequently in the supragingival plaque than on the tongue in the pSS patients, but could not be detected in the gingival crevicular region using the paper point technique (Almståhl et al, 2001c). Finally, saliva culture has been suggested as the most proper method for identification of *Candida* in SS patients corresponding better to clinical oral candidiasis than tongue smear and tongue smear culture (Soto-Rojas et al, 1998).

Caries-related Micro-organisms

Only few studies have examined bacteria cultures from saliva of patients with SS (Lundström and Lindström, 1995; Kolavic et al, 1997; Almståhl et al, 2001c). Kolavic et al (1997) found higher counts of *Streptococcus mutans* (*S. mutans*) and lactobacilli (by means of Dentocult SM strip and LB assay) in caries-inactive SS patients, having stimulated parotid flow rates 0.25 ml/min, than in healthy controls with significantly higher parotid flow rates. Almståhl et al (1999a) showed that the pSS patients harboured higher numbers of both *S. mutans* and *Lactobacillus* species, whereas the sSS patients only harboured higher numbers of *Lactobacillus* species as compared to the healthy controls. Despite good oral hygiene, the pSS group had the highest proportions of subjects harbouring the highest levels of *S. mutans* compared to other patients with hyposalivation due to radiotherapy in the head and neck region and patients on neuroleptic treatment (Almståhl et al, 1999a). The counts and numbers of *S. mutans* and lactobacilli have been found positively correlated (Kolavic et al, 1997) as well as inversely correlated to stimulated whole saliva flow rates (Lundström and Lindström, 1995). The low salivary flow rates, low pH, reduced buffering capacity, impaired salivary antibacterial activity, high number of retention sites as well as high caries activity have been suggested as contributing factors to the high number of *S. mutans* and *Lactobacillus* species found in pSS patients (Almståhl et al, 1999a). In this context, the activity of salivary amylase, which also has antibacterial properties (Scannapieco, 1994), has been found inversely correlated to the number of lactobacilli, whereas the salivary concentration of MUC5B (high

molecular weight mucin, MG1) did not correlate to any of the numbers of micro-organisms studied (Almståhl et al, 2001b). Surprisingly, the concentration of the salivary antibacterial component lactoferrin was positively correlated to the number of *Lactobacillus* species as well as *C. albicans* (Almståhl et al, 2001b). However, with decreasing flow rates, the output of salivary antibacterial components decreases and the concentration increases. This means that the overall available amount of salivary antibacterial components in the oral cavity is in fact diminished.

Conclusions

Both pSS and sSS patients harbour an oral microflora which is associated with caries activity and fungal infections. Furthermore, recent studies indicate site specificity regarding oral micro-organisms in SS. These findings may have an impact on the planning of preventive dental care strategies. In SS, changes in the oral microflora are related to permanently reduced salivary flow rates, low saliva pH, decreased clearance of micro-organisms in the oral cavity and reduced oral sugar clearance, which lead to an increase in acidophilic micro-organisms such as *S. mutans*, lactobacilli and *C. albicans*. Furthermore, the autoimmune disease itself resulting in an altered immune response may in addition to intake of immune-modulating medications and intake of a more cariogenic diet affect the oral microflora. Some studies have revealed slight differences in certain oral micro-organisms between the pSS and sSS groups that may be attributed to diversity in salivary changes. Despite good oral hygiene, the majority of pSS patients harbour significant high levels of *S. mutans* compared to patients with hyposalivation of other aetiologies.

SALIVA AND ORAL MICROFLORA IN PATIENTS RECEIVING CHEMOTHERAPY

During chemotherapy, cancer patients have a significantly increased risk of oral infections due to the direct effects of the cytotoxic drugs on oral epithelial barrier function and the indirect effects of the systemic immunosuppression. In some patients such opportunistic infections may even have a fatal outcome. Most studies on changes in the oral microflora caused by chemotherapy have been conducted during and shortly after initiation of the treatment. Only few studies deal with the long-term effects of chemotherapy on salivary flow rates and composition and the impact of

these changes on the oral microflora. It is therefore still an open question if chemotherapy results in temporary or permanent salivary gland hypofunction.

Chemotherapeutics target cells characterised by a high mitotic turnover, like cancer cells, but effects on more slowly dividing cells like in healthy tissues also occur. Studies have shown that saliva flow rates decrease during chemotherapy, although there is some controversy whether it is caused by the chemotherapy *per se* or by other factors, e.g. concomitant intake of anticholinergic antiemetic drugs (Main et al, 1984; Harrison et al, 1998; Wahlin, 1991). Nevertheless, specific and non-specific salivary antimicrobial components are influenced by chemotherapy. Accordingly, the concentration of salivary immunoglobulin secretory-IgA (s-IgA) has been found to decrease both during and following chemotherapy (Main et al, 1984; Laine et al, 1992; Meurman et al, 1997a; Harrison et al, 1998) and the concentration of lysozyme to decrease after chemotherapy (Meurman et al, 1997a). The salivary peroxidase system in stimulated whole saliva is impaired during chemotherapy due to a lower concentration of thiocyanate and its oxidised form hypothiocyanate with antibacterial properties (Mansson-Rahemtulla et al, 1992). It has also been reported that unstimulated whole saliva pH and stimulated whole saliva buffer capacity decrease during chemotherapy (Schum et al, 1979; Pajari et al, 1989). Thus, salivary gland hypofunction and reduced output of antibacterial factors may impair the oral defence against micro-organisms and thereby disturb the balance of the patient's normal oral microflora.

Candidiasis-related Yeasts – During Chemotherapy

The oral yeast counts and especially the prevalence of *Candida* species may increase significantly from a prevalence of about 50% in the normal population to 75–80% in cancer patients during combination chemotherapy (Main et al, 1984; Samaranyake et al, 1984; Wahlin and Holm, 1988; Sixou et al, 1996; Meurman et al, 1997b; Sonis, 1997). This could partly be explained by a simultaneous decrease in unstimulated and stimulated whole saliva flow rates and a reduced output of salivary antimicrobial factors (Main et al, 1984; Wahlin, 1991; Umazume et al, 1995; Epstein et al, 2002) (Table 3). Other studies have not revealed any changes in the composition of the oral microflora (Bergmann, 1991; O'Sullivan et al, 1993), but an initial doubling of the concentration of micro-organisms concomitant with a transient decrease of stimulated whole saliva flow during chemotherapy (Bergmann, 1991). C.

Table 3 Effect of cancer chemotherapy (CT) and CT induced decrease of saliva flow rates on the number of candidiasis-related yeasts and caries-related bacteria (mutans streptococci (MS) and lactobacilli (LB)) during and after CT

Authors	During CT			After CT		
	Yeast	Caries-related bacteria	Saliva flow rates	Yeast	Caries-related bacteria	Saliva flow rates
Meurman et al (1997)	↑	MS↓, LB↑	SWS→	↑	MS+LB↓	SWS→
Bergmann (1991)	*↑		SWS↓			
Wahlin (1991)	↑		SWS↓ initially			
Main et al (1984)	*↑		SWS↓			

SWS: Stimulated whole saliva

↑:High; →: Unchanged; ↓: Low

*: *Candida* species

albicans is the predominant yeast in the oral flora during chemotherapy and accounts for up to 88% of the salivary yeasts (Samaranayake et al, 1984). Clinical candidiasis and angular cheilitis have been found to correlate to higher oral yeast counts and low salivary flow rates (Wahlin and Holm, 1988; Wahlin, 1991). Yeasts have also been detected in both dental plaque and the crevicular fluid of chronic leukaemia patients, but not in the acute leukaemia patients (Pompei et al, 1993). A clinical study found that 68.9% of all oral infections during chemotherapy were caused by yeasts such as *C. albicans*, *Histoplasma capsulatum* and *Cryptococcus neoformans* (Dreizen et al, 1983).

Candidiasis-related Yeasts – After Chemotherapy

A follow-up study found that salivary yeast counts remained high in spite of normal saliva flow rates 5 years after chemotherapy for lymphoma (Meurman et al, 1997b) (Table 3). The salivary concentrations of the immunoglobulins s-IgA, IgG, IgM and lysozyme in stimulated whole saliva were concomitantly found to be significantly decreased as compared to baseline values (Meurman et al, 1997a). These findings suggest that the disease itself or the chemotherapy may affect the body defences against *Candida* in the long term. Furthermore, a significantly decreased amylase concentration and an increased albumin concentration were found in stimulated whole saliva 5 years after chemotherapy (Meurman et al, 1997a), which indicate long-lasting impaired salivary gland function. Amylase is synthesised in the serous acini of the salivary glands and the concentration is positively correlated to saliva flow rates (Froehlich et al, 1987). A lower stimulated whole saliva concentration of amylase suggests acinar degeneration, and increased albumin concentration in

whole saliva indicates leakage of plasma components into the oral cavity, as saliva normally contains low concentrations of this protein. In whole saliva the leakage can result from a direct damage of the salivary gland tissue or from the breakdown of other oral epithelial barrier functions, e.g. inflamed periodontal pockets (Cimasoni, 1974).

Caries-related Salivary Micro-organisms – During Chemotherapy

Studies have shown that the salivary concentration of caries-related micro-organisms may decrease during chemotherapy in spite of any salivary gland hypofunction. To interpret the results, it is necessary to take into consideration that in most studies the patients are concomitantly treated by antibiotics, antifungal drugs and chlorhexidine mouth rinses, and that the prevalence of open caries lesions also influence the oral presence of e.g. *S. mutans* and lactobacilli. Salivary counts of *S. mutans* are found to decrease during chemotherapy (O'Sullivan et al, 1993; Meurman et al, 1997b) (Table 3), which could be attributed to the cytotoxic effect of the chemotherapeutic drugs. Accordingly, *S. mutans* has been found to be sensitive to daunorubicin, a frequently prescribed cytotoxic antibiotic in chemotherapeutic protocols (O'Sullivan et al, 1993). Along this line, a study showed that salivary *S. mutans* counts decreased, whereas lactobacilli counts increased during chemotherapy (Meurman et al, 1997b). Accordingly, examinations of the oral microflora during chemotherapy in leukaemia and lymphoma patients revealed no change in the total number of salivary micro-organisms and lactobacilli (Wahlin and Holm, 1988). A study of the supra- and subgingival dental plaque in adult acute leukaemia patients during chemotherapy found that the percentage of total viable counts of *S. mutans*

in supragingival dental plaque increased and the percentage in subgingival dental plaque decreased (Reynolds et al, 1989). In contradiction, other investigators found the percentage of viridans streptococci (*S. mutans* not specified) to be lower in the supragingival dental plaque of children with acute leukaemia during chemotherapy as compared to a healthy control group (Sixou et al, 1998). As chemotherapy is a time-limited treatment and caries is a process that progresses relatively slowly, it may be debatable whether it is possible to assess an increased progression rate of caries during chemotherapy.

Caries-related Salivary Micro-organisms – After Chemotherapy

Only few studies have examined the oral microflora after chemotherapy and its relation to salivary gland function. One study found that 5 years after chemotherapy, salivary counts of *S. mutans* and lactobacilli were on same low levels as baseline values before chemotherapy (Meurman et al, 1997b) (Table 3). Another study found no significant correlation between salivary immunoglobulin levels in stimulated whole saliva and *S. mutans* or *Lactobacillus* counts in long-term (6 months to 10 years) event-free paediatric patients treated for childhood malignancies by chemotherapy (Dens et al, 1995). The salivary immunoglobulin level was within normal limits, but there was a negative correlation between saliva s-IgA concentration and caries prevalence (DMFT/dmft), although only significant in some age groups. The study is cross-sectional and comparison of intra- and interindividual changes in the immunoglobulin level and caries prevalence before, during, and after the chemotherapy is therefore not possible. In bone marrow transplanted patients, a significant decrease in stimulated whole saliva flow, lower buffer capacity and a change in the oral microflora towards higher salivary counts of *S. mutans* and *Lactobacillus* has been observed during and after the transplantation and chemotherapy (Dens et al, 1996; Dahllof et al, 1997). However, stimulated saliva flow rates reached normal values 1 year after the bone marrow transplantation/chemotherapy and no significant differences in caries prevalence were found between the bone marrow transplanted children receiving chemotherapy and healthy children 4 years after the treatment, but all participants also underwent preventive dental care (Dahllof et al, 1997).

Conclusions

Most studies have demonstrated that salivary flow rates and the output of salivary antimicrobial compo-

nents decrease during chemotherapy. Also a shift in the oral microflora from a predominance of gram-positive micro-organisms to gram-negative pathogens and yeasts has been observed during chemotherapy. However, other studies demonstrated no changes in the composition of the oral microflora. In this context it is important to bear in mind that changes in the oral microflora are not only attributable to the chemotherapy itself, but also to other factors such as concomitant medication, local and systemic antimicrobial treatment, underlying cancer disease and duration of hospitalisation. During chemotherapy, cancer patients have an increased risk of oral infections and especially fungal infections, whereas it is unclear whether the risk of caries is increased. Only few studies have dealt with the long-term effects of chemotherapy on salivary gland function and composition, and thereby the impact on the oral microflora. At present results are contradictory, and further studies are necessary to elucidate whether cancer patients who have completed chemotherapy have an increased risk of oral infection and dental caries in the long term.

SALIVA AND ORAL MICROFLORA IN PATIENTS RECEIVING RADIATION THERAPY

Radiation therapy (RT) of tumours in the head and neck region often includes the major and minor salivary glands in the radiation field depending on the anatomical location and the extension of the tumour. RT can cause severe salivary gland hypofunction (for review, see Jensen et al, 2003). The severity depends on the volume of salivary gland tissue included in the radiation field and on the total radiation dose (Mossman, 1983). RT targets cells with a rapid mitotic turnover like tumour cells and damages the DNA thereby leading to cell death. Acinar salivary gland cells are radiosensitive in spite of their slow mitotic turnover (Berthrong, 1986) and the serous cells appear to be more sensitive to radiation than the mucous ones (Kashima et al, 1965). Radiation damage to the salivary glands may be seen as early as 1 week after initiation of RT (Dreizen et al, 1977) and results in both acute and long-term effects characterised by reduced saliva flow rates, high saliva viscosity and changes of saliva composition. During RT, saliva flow rates decrease and may even reach immeasurable levels (Mira et al, 1981). With decreasing flow rates the salivary pH drops and the buffer capacity decreases both during and after RT (Valdez et al, 1993). RT also affects the salivary antimicrobial components. The salivary concentrations of IgA and IgG, lac-

toferrin, lysozyme and peroxidase have been shown to increase during RT due to acute tissue destruction. But after RT the concentrations of these salivary components decrease due to reduced functioning of the glands (Brown et al, 1976; Makkonen et al, 1986). In the long term, recovery of salivary gland function is dependent on the total radiation dose that the tissue has received. Thus, saliva flow rates may remain severely decreased (Liu et al, 1990) and the compositional changes may persist in response to the decrease in saliva flow rates. The standard therapeutic radiation dose for head and neck carcinoma amounts to a total dose of 60–70 Gy (1 Gy=1 J kg⁻¹) (Vissink, 2003). A mean parotid gland dose of 26 Gy has been suggested as a threshold level for preservation of parotid gland function (Eisbruch, 2003). A compensatory increase in saliva flow from salivary glands not included in the radiation field may be seen (Eisbruch et al, 2001). Irradiation-induced salivary gland hypofunction is associated with a shift of the normal oral microflora increasing the risk for this patient group to develop rampant dental caries and oral infections like candidiasis (Guggenheimer, 2003). Both cross-sectional and longitudinal studies have been conducted on changes in the oral microflora and salivary gland function during and after RT. Regarding evaluation of the salivary gland function many studies characterize the study groups as having radiation-induced hyposalivation or xerostomia and do not specify the saliva flow rates or saliva composition.

Candidiasis-related Yeasts

The number of yeasts increases in the oral cavity of cancer patients with hyposalivation due to RT (Table 4). The increase in the oral yeast colonization is observed during RT and the colonization level remains elevated after RT (Llory et al, 1972; Brown et al, 1975; Silverman et al, 1984; Kuten et al, 1986; Ramirez-Amador et al, 1997; Epstein et al, 1998; Leung et al, 2000). Both number of yeast species and colonization rise to higher levels during and after RT. *C. albicans*, which is the predominant yeast species associated with clinical oral candidiasis in RT patients (Redding et al, 1999), and *C. tropicalis* are the dominant yeasts isolated from the oral cavity in RT (Llory et al, 1972; Martin et al, 1981; Paula et al, 1990). It has been shown that the increase in *C. albicans* in oral rinses is positively related to the radiation dose and the volume of parotid gland tissue included in the radiation field (Rossie et al, 1987). Epstein et al (1998) found a direct correlation between the increase in *C. albicans* in saliva and reduced saliva flow rates during RT. The increased colonization of oral yeasts in RT patients reflect

the importance of good oral hygiene in RT patients due to the risk of developing clinical candidiasis (Rossie et al, 1987; Redding et al, 1999).

Caries-related Salivary Micro-organisms

Higher levels of *S. mutans* and *Lactobacillus* species are often observed in the oral cavity (oral rinses, mucosal swabs, saliva samples, gingival sulcus fluid and dental plaque samples) during and after RT as compared to preradiation levels (Llory et al, 1972; Brown et al, 1975; Brown et al, 1978; Keene and Fleming, 1987; Schwarz et al, 1999; Vuotila et al, 2002) (Table 4). Oral colonization with *S. mutans* is lower and stimulated saliva flow rates are higher at the end of treatment in patients receiving unilateral RT as compared to bilaterally irradiated patients (Beer et al, 2002). In oral rinses, it has been demonstrated that the predominant acid-producing species of the oral microflora may change from *Streptococcus sanguis* (*S. sanguis*), *S. mitis* and *S. salivarius* before RT to *S. mitis*, *S. salivarius* and lactobacilli with a concomitant decrease in saliva flow rates after RT (Tong et al, 2003). The acid-sensitive *S. sanguis* appears to be inhibited by the more acidic oral environment after RT (Tong et al, 2003). The decrease in the presence of *S. sanguis* after RT has been shown in other studies (Brown et al, 1975; Brown et al, 1978). Vuotila et al (2002) found unchanged levels of *S. mutans* after RT as compared to pre-radiation levels. The RT patients suffering from impaired saliva secretion are to be considered a high-risk group regarding dental caries as the oral environment favours acid-producing and acidophilic species of the oral microflora.

Conclusions

RT in the head and neck region can result in a severe and permanent hypofunction of the salivary glands. The severity depends on the volume of salivary gland tissue included in the radiation field and on the total radiation dose. In cancer patients with RT-induced salivary gland hypofunction, the bacterial clearance decreases and the total oral microbial colonization rate therefore increases. It is mainly the colonization of yeasts that increases, but also acidogenic micro-organisms such as *Lactobacillus* species, *S. mutans* and other potentially pathogenic micro-organisms increase dramatically in this patient group. Inconsistency in the reported changes of the oral microflora in relation to salivary gland hypofunction following RT may be due to a wide variation in the underlying cancer diagnosis, concomitant medication, total radiation doses, radiation technique and the irradiated volume of salivary gland tissue in the examined study groups, which renders



Table 4 Effect of radiotherapy (RT) of the head and neck region, and RT-induced decrease of saliva flow rates on the number of candidiasis-related yeasts and caries-related bacteria (mutans streptococci (MS) and lactobacilli (LB)) during and after RT

Authors	During RT			After RT		
	Yeast	Caries-related bacteria	Saliva flow rates	Yeast	Caries-related bacteria	Saliva flow rates
Vuotila et al (2002)	**→	LB↑, MS→	SWS↓	**→	LB↑, MS→	SWS↓
Leung et al (2000)+(2001)				*↑		SWS↓
Schwarz et al (1999)					MS+LB↑	SWS↓
Epstein et al (1998)	**↑	#MS→, LB↑ initially	UWS+SWS↓	**↑	MS+LB→	UWS+SWS↓
Ramirez-Amador et al (1997)	*↑		↓?	*↑		↓?
Keene and Fleming (1987)					MS↓, LB↑ no fluoride MS↑	↓?
Kuten et al (1986)	*↑		UWS↓			
Silverman et al (1984)	*↑		↓?	*↑		↓?
Brown et al (1975)	*↑	MS+LB↑	SWS↓	*↑	MS+LB↑	SWS↓
Llory et al (1972)				↑	MS↑	↓?

UWS: Unstimulated whole saliva; SWS: Stimulated whole saliva

↑: High; →: Unchanged; ↓: Low

↓?: Xerostomia or hyposalivation due to RT are stated in the article, but no measurements are reported.

*: *Candida* species

** : *Candida albicans*

: Daily use of fluoride gel

comparison between studies difficult. The altered oral microflora and chronically impaired salivary gland function following RT imply a marked increased risk of oral infection and dental caries in post-irradiated patients.

SALIVA AND ORAL MICROFLORA IN RELATION TO MEDICATION INTAKE

The most common cause of salivary gland hypofunction is the intake of prescribed medications (Österberg et al, 1984; Handelman et al, 1986; Närhi et al, 1992), which increases with age. More than 75% of adults aged 65 and older take at least one prescription medication (Chrischilles et al, 1992) and the prevalence of xerostomia in this population is about 30% (Ship, 2002). Xerostomia has been associated with 80% of the most commonly prescribed medications (Smith and Burtner, 1994), and many of these have adverse effects directly on the mechanisms responsible for saliva secretion (Sreebny and Schwartz, 1997). Regardless of the type of medication, saliva flow rates have been shown to decrease as the number of medications (polypharmacy) increases (Thorselius et al, 1988; Närhi et al, 1992). Also the duration of medication intake might affect saliva flow rates. Navazesh et al (1996) found

that unstimulated and stimulated whole saliva flow rates were significantly lower in adults who had been taking medication for more than two years as compared to those who had been taking medication for less than two years. Furthermore, the patient compliance in following instructions to take prescribed medication is reflected in salivary gland function.

Medications interacting with the central nervous system (CNS) such as sedatives, anxiolytics (Loesche et al, 1995a), and morphine-based analgesics (Zacny et al, 1994) negatively affect saliva flow rates. There are, however, different types of medication-induced effects leading to salivary gland hypofunction. Some medications affecting the CNS also exert effects on the peripheral nervous system and interact with the target organ receptor complexes. Examples are: tricyclic antidepressants (Clemmesen, 1988; Hunter and Wilson, 1995); the serotonin reuptake inhibitors (Loesche et al, 1995a); some neuroleptics (Hyttel et al, 1985); antihistamines (Monroe et al, 1992); and medications for Parkinson's disease (Suchowersky, 2002) – all of which inhibit the muscarinergic receptors on the salivary glands leading to impaired saliva flow. The salivary gland α_1 -adrenergic receptors are inhibited by: α_1 -receptor blocking antihypertensives (Croog et al, 1994; Gregoire and Sheps, 1995); some neuroleptics (Mueck-Weymann et al, 2002); and

some antidepressants (Dissing et al, 1990), which also induce a decrease in saliva flow rates. β -blockers inhibit the β -adrenergic receptor systems on the salivary glands decreasing the protein secretion into the saliva, while the saliva flow rates remain relatively unaffected (Nederfors et al, 1994). Some medications such as antihypertensives and diuretics may affect the electrolyte transport mechanisms in the salivary glands directly giving rise to changes in saliva composition (Nederfors et al, 1989).

Medication-induced Effects on the Oral Microflora

Several medications have the potential to cause salivary gland hypofunction leading to decreased saliva pH and antimicrobial clearance, which affect the number and composition of oral micro-organisms. Medications used locally may also affect the oral microflora directly. Examples are sugar-containing cough syrups and antimycotics that may increase the growth of oral micro-organisms. Beigthon et al (1991) showed that the salivary level of mutans streptococci, lactobacilli and yeasts in elderly patients treated with sucrose-containing medication was significantly higher than in patients taking non-sucrose-containing medication. The oral microflora can also be directly affected by systemic medications such as antibiotics (Stark et al, 1996) that are released into saliva. Anticonvulsant agents (Yamada et al, 2001), immunosuppressives (Das et al, 2001), and some cardiovascular medications such as calcium channel blockers (Nery et al, 1995) may lead to gingival hyperplasia, thereby affecting the composition of the microflora. In addition, the intake of hormonal contraceptives may be associated with gingival inflammation (Kalkwarf, 1978; Pankhurst et al, 1981). It has been suggested that hormonal contraceptives influence the microbiological parameters in the gingival sulcus leading to an increased risk for periodontal disease (Klinger et al, 1998).

In order to distinguish between the possible effects of medication intake on the oral microflora, attention was paid to the effects on the number of oral micro-organisms caused by medication intake *per se* and the effects caused by medication-induced salivary gland hypofunction (Table 5). Due to the lack of data regarding specific medication-induced changes in the saliva composition in relation to changes in the oral microflora, the following mainly focuses on the changes related to saliva flow rates.

Candidiasis-related Yeasts

Table 5.1 shows the number of studies that have analysed the effect of medication intake on the number of

yeasts. Four studies did not find any significant effect on the number of yeasts, but when groups were separated with regard to gender, Parvinen et al (1984) found significantly higher yeast counts in medicated men as compared to non-medicated men. Interestingly, Kreher et al (1991) showed that *C. glabrata* was the most frequent yeast strain in the oral cavity of medicated patients, when using a test culture that distinguishes *C. glabrata* from *C. albicans*. Regarding the effect of saliva flow rates, 4 out of 8 studies found a significant higher number of yeasts when saliva flow rates were low (Table 5.1). In fact, Navazesh et al (1995) showed significant negative correlations between the flow rates of unstimulated whole saliva, chewing-stimulated whole saliva, sour candy-stimulated parotid saliva, and the level of *C. albicans*. Four studies found a tendency of higher yeast counts. Finally, one study demonstrated a clear negative correlation between unstimulated saliva flow rates and the presence of *Candida* pseudohyphae (Bergdahl and Bergdahl, 2001).

Caries-related Micro-organisms Mutans streptococci

Table 5.2 presents the studies that have analysed the effect of medication intake on the number of mutans streptococci. In all these studies no significant effect on the number of bacteria was found. Nevertheless, some studies reported a tendency for higher counts of mutans streptococci with medication intake. Table 5.2 also shows five studies that tested the effect of saliva flow rates on the mutans streptococci level. Generally, the number of mutans streptococci was significantly higher when saliva flow rates were low. However, one study did not find any significant effect of saliva flow rates on the mutans streptococci counts, but the mutans streptococci level was higher in patients with medication-induced hyposalivation as compared to an age-, gender-, and number of teeth-matched control group with normal saliva flow rates and to a group of healthy young adults. A factor that facilitates the colonization of mutans streptococci is the preference of these bacteria for products containing sugar and for an acidic oral environment. The concomitant presence of *Streptococcus sobrinus* (*S. sobrinus*) may be an indicator of a change to a more carbohydrate-rich diet, since the colonization of *S. sobrinus* seems to be more dependent on a sucrose-containing diet than that of *S. mutans* (Huis in't Veld et al, 1982). A frequent intake of fermentable carbohydrates leads to a dental plaque with low pH, which favours the growth conditions for aciduric bacteria such as *S. mutans* (Marsh, 1994). Also poor oral hygiene and dental caries activity favour the

Table 5 Effect of medication intake (Medication) and medication-induced decrease of saliva flow rates (Saliva flow rates) on the number of yeasts, mutans streptococci and lactobacilli

5.1: Yeasts				
Authors	Medication		Saliva flow rates	
	NS	S	NS	S
Torres et al (2002)			B	
Bergdahl and Bergdahl (2001)			B	
Almståhl and Wikström (1999)			A	
Närhi et al (1998)				B
Loesche et al (1995b)				C
Navazesh et al (1995)				B
Meurman and Rantonen (1994)	A			A
Beighton et al (1991)	A			
Kreher et al (1991)		A	B	
Laine et al (1991)	C			
Parvinen et al (1984)	A	A		
5.2: Mutans streptococci				
Authors	Medication		Saliva flow rates	
	NS	S	NS	S
Almståhl and Wikström (1999)			A	
Närhi et al (1998)				B
Lundgren et al (1997)	B			
Loesche et al (1995b)				C
Närhi et al (1994)	A			A
Beighton et al (1991)	A			
Laine et al (1991)	C			
Ryberg et al (1991)	A			
Fure and Zickert (1990)				B
Arneberg et al (1989)	B			
5.3: Lactobacilli				
Authors	Medication		Saliva flow rates	
	NS	S	NS	S
Bardow et al (2001)				B
Almståhl and Wikström (1999)				A
Anttila et al (1999)		A		A
Närhi et al (1998)				B
Lundgren et al (1997)	B			
Loesche et al (1995b)				C
Närhi et al (1994)	A		A	
Beighton et al (1991)	A			
Laine et al (1991)	C			
Ryberg et al (1991)		A		
Fure and Zickert (1990)				B
Arneberg et al (1989)		B	B	
Parvinen et al (1984)	A	A		

The column **Medication** states if the authors tested the effect of medication intake on the number of micro-organisms and the column **Saliva flow rates** states if the authors tested the effect of saliva flow rates on the number of micro-organisms. NS: Non-significant higher number of micro-organisms, S: Significant higher number of micro-organisms. A: bivariate analysis (medicated to non-medicated or hyposalivating to non-hyposalivating), B: correlation analysis (containing the variables: medication intake versus number of micro-organisms and saliva flow rate versus number of micro-organisms), C: multivariate analysis. Level of significance set at $p < 0.05$.

selection of this species (Loesche et al, 1984; Schüp-
bach et al, 1996).

Lactobacilli

Table 5.3 shows eight studies that have tested the effect of medication intake on the number of lactobacilli. Five of these studies did not find any significant effect on the number of these bacteria, but when groups were separated with regard to gender, Parvinen et al (1984) showed a significant higher number of lactobacilli in medicated men as compared to non-medicated men. The other studies reported a significantly higher number of lactobacilli with medication intake. Eight studies have tested the effect of saliva flow rates on the number of lactobacilli (Table 5.3). Most of these studies found a significant higher number of lactobacilli when saliva flow rates decreased. Two studies did not find significant higher numbers of bacteria, however, one study (Närhi et al, 1994) reported high lactobacilli counts in a higher number of subjects with hyposalivation than in subjects with normal saliva flow rates. A decrease in saliva flow rates leads to a reduced cleansing effect, a low pH, an impaired buffer capacity, and thereby to a more aciduric environment that seem to play an important role for the growth conditions of lactobacilli (Arneberg et al, 1989). A high lactobacilli level in the oral cavity may therefore be an indicator of a low saliva pH and decreased saliva flow rates. However, dental caries activity (Bowden et al, 1990; Bardow et al, 2001) and the presence of dental plaque retention sites (Kidd et al, 1995) can also increase the number of lactobacilli.

Conclusions

Medication intake, which may be temporary or permanent, is likely to have an impact on the oral microflora by direct and indirect medication-induced effects on the salivary glands. Several medications have the potential to cause salivary gland hypofunction and changes in saliva composition. However, in contrast to chronic autoimmune diseases like Sjögren's syndrome, RT in the head and neck region and presumably chemotherapy, medication-induced salivary gland changes are reversible. In patients with medication-induced hyposalivation the number of mutans streptococci, lactobacilli and yeasts increases and results indicate an increased risk of dental caries and fungal infections among these patients. A simultaneous treatment with antibacterial agents as well as frequent intake of easily fermentable carbohydrates, hygiene habits, dental status and the underlying systemic disease also influence the level of cariogenic bacteria.

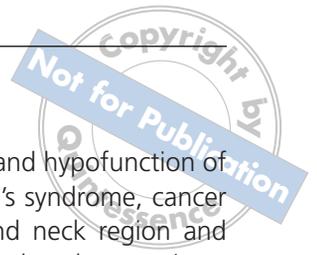
CONCLUDING REMARKS

Studies on patients with salivary gland hypofunction of various aetiologies such as Sjögren's syndrome, cancer chemotherapy, RT to the head and neck region and intake of certain medications show that these patients groups harbour an oral microflora that is associated with common oral diseases like dental caries and oral candidiasis. The decreased clearance of micro-organisms and dietary sugars from the oral cavity, as well as low salivary pH and buffer capacity, simply contributes to an increase in the acidophilic flora comprising *S. mutans*, lactobacilli and *C. albicans*. On the other hand, the studies also reveal differences in the oral microflora between the patient groups. For example, despite having a good oral hygiene, pSS patients may harbour higher levels of *S. mutans* than patients with hyposalivation of other aetiologies such as patients receiving RT and patients receiving certain antidepressants or antipsychotics. Besides the salivary characteristics, the microbial diversity between, and even within patient groups may be attributed to various variables such as the intake of easily fermentable carbohydrates, oral hygiene habits and their dental status. Other variables that come into play when evaluating the impact of salivary gland hypofunction on the oral microflora are the underlying local and systemic diseases as well as their medical treatments (such as irradiation or medication). In contrast to the permanently reduced salivary gland function due to Sjögren's syndrome and RT in the head and neck region, the effect of certain medications on the salivary gland function are reversible, i.e. after cessation of medication the salivary gland function usually recovers.

In conclusion, dental caries and oral candidiasis are both multifactorial diseases occurring as a result of complex interactions between oral micro-organisms and host environment and behaviour. Further improvement of our understanding of the oral microbial ecology in patients suffering from impaired saliva secretion and salivary compositional changes will provide us with new tools and evidence based strategies for prevention, diagnosis and treatment of hyposalivation-related oral diseases.

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