Microb Health Dis 2019; 1: e209

European Helicobacter & Microbiota Study Group

The oral microbiota in oral and systemic diseases

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Abstract: While it is increasingly outlined the link between gut microbiota and several systemic and gastrointestinal diseases, to date the role of the oral microbiota is not well clarified.

Different factors like diet, smoke, alcohol, and use of probiotics have an active role in the development and modification of the oral microbiota. The relation between oral microbiota and oral diseases was better studied in the past, but during the last years, a deeper link between systemic disease and oral microbiota was discovered. This review aims to summarize the results of the most relevant studies published on this topic between April 2018 and March 2019.

Keywords: Oral microbiota, Diet, Nutrition, Probiotics, Personalized medicine, Systemic diseases, Oral diseases, Caries, Tooth decay, Periodontitis.

INTRODUCTION

Human Oral Microbiota (OM) is defined as the genome of the entire microorganism population findable in the oral cavity[1]. It is the second-largest microbial community of human organism and the preferred targets of bacterial colonization are oral soft tissues (i.e., gingival surfaces, soft palate, lips, cheeks, etc.) and teeth[2].

Both systemic and oral pathologies can affect the composition of the OM through a decrease in the abundance of its bacterial taxa and/or an increase of inflammation[3].

This review aims to summarize the most relevant studies published on this topic between April 2018 and March 2019.

We divided the entire review into three main chapters:

- The impact of Lifestyle and Dietary Habits on Oral Microbiota;
- The impact of Systemic Diseases on Oral Microbiota;
- The impact of Oral Microbiota on Oral Diseases.

THE IMPACT OF LIFESTYLE AND DIETARY HABITS ON ORAL MICROBIOTA

The physiological Oral Microbiota

Human OM can be categorized into six different phyla that are: *Firmicutes, Actinobacteria, Bacteroides, Proteobacteria, Spirochaetes,* and *Fusobacteria*, with over than 600 different taxa[4].

It is possible to divide these bacteria into three categories, according to their location[5]:

1. *Salivary bacteria*. The human saliva is like a fluid culture and permits the growth of a large different species of bacteria, most of them are aerobes;
2. *Mucosal bacteria*. They are aerobes, except for the stable population of *tongue bacteria* that are mostly anaerobes;
3. *Non-mucosal bacteria*. This group is represented by bacteria that live on teeth or over artificial hard surfaces like implants, tooth filling, orthodontic appliances, etc; they can be aerobes or facultative anaerobes[6].

Geographical differences between human OM are not well understood; in fact, some papers reported differences between OM from different regions of the world, while some other works reported no differences[7].

Diet

Several papers highlighted the role of diet on gut microbiota[8,9], while its impact on OM has not already been completely defined.

It is well known that diet has a fundamental role in the development of tooth decay (Figure 1), which is considered a multifactorial process due to the interaction between ingestion of simple sugars and the activity of oral bacteria, able to ferment this substrate producing acids inside the oral biofilm[10]. In particular, *Streptococcus mutans* and *Streptococcus sobrinus* possess the enzymatic array to better metabolize simple sugars than more complex carbohydrates and to promote the formation of cariogenic biofilms[11]. Although many theories exist on tooth decay pathogenesis, a diet high in simple sugars overrides bacterial biofilm composition; in fact, the bacterial acidogenesis remains the critical factor for tooth decay development[12].

Starches are common carbohydrates of the human diet, possessing an important cariogenic activity. Neverthless, they seem to determine tooth decay development only when salivary alpha-amylase digests them into simple sugars, stimulating the acidogenic potential of bacterial biofilm[11].

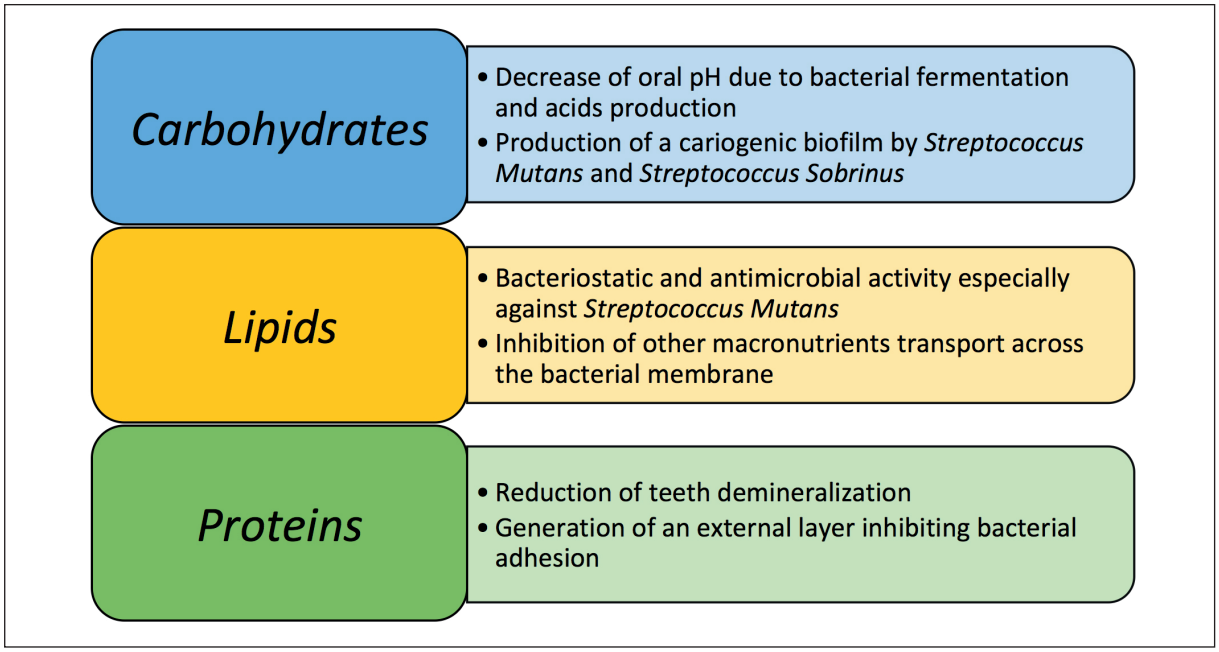

Figure 1. Dietary macronutrients and oral microbiota.

Artificial sweeteners can be classified into caloric carbohydrate sweeteners (i.e., polyols like xylitol, sorbitol, maltitol, mannitol, etc.) and non-caloric non-carbohydrate sweeteners (i.e., stevia, aspartame, saccharin, sucralose, etc.)[13]. Xylitol, the most studied polyol, shows the capability to prevent caries formation through the direct inhibition of several metabolic pathways of *Streptococcus mutans*, through the reduction of oral acid formation and of cariogenic biofilm accumulation[11].

Lipids, in particular fatty acids, appear to show anticaries property having both a bacteriostatic and a direct antimicrobial activity, especially against *Streptococcus mutans*. Moreover, they show the capability to inhibit other cariogenic nutrients transport across the bacterial membrane[11].

Proteins seem to possess anticaries activity too, especially milk proteins, which are reported to reduce demineralization by forming an external layer, which inhibit bacterial adhesion[14,15].

Giacaman RA[11] reported that higher protein consumption could be a protective factor against caries in children.

There is a high interest among polyphenol antioxidants and their impact on various diseases[16-18]. These compounds have been studied for their potential role against the development of caries[19], for their capability to inhibit bacterial-growth[20], and to reduce the formation of cariogenic biofilm[21].

Smoke

It's well known that smoke habit can impact the development of several oral diseases, through the increase of some proinflammatory cytokines (i.e., IL-4, IL-8, TNF-α, etc.) and of periodontal pathogens growth (i.e., *Porphyromonas gingivalis*, *Tannerella forsythia, Treponema denticola*, etc.)[22].

The cross-sectional study presented by Pimentel et al[22], showed that smoking habits alter the peri-implant microbiome. The authors found a statistically significant difference between smokers and non-smokers in terms of clustering of main microbial profiles. In particular, the study showed an increased number of phyla *Bacteroidetes, Fusobacteria, Tenericutes, Spirochates*, and *TM7* in smokers while *Firmicutes, Synergistetes,* and *Proteobacteria* are less represented. Regarding genera analysis, they found a higher number of *Streptococcus* and *Veillonella* in non-smokers, while smokers showed more abundance of *Fusobacterium*.

On the other hand, Joaquim et al[23] demonstrated that smokers with chronic periodontitis did not find any difference in OM compared to non-smokers.

Alcohol

Some studies hypothesized that alcohol habits could change the microbial community thought direct cytotoxic effects on bacteria and providing ethanol as a substrate for their metabolism[24].

A large cross-sectional study, involving 1044 patients from USA, was published last year by Fan et al[25]. The authors divided the study population into three groups by the alcohol drinking level (non-drinkers, moderate drinkers, or heavy drinkers) and by the alcohol content (liquor, beer, or wine). They found that the alcohol amount is related to overall microbiome community composition. In particular, they found in heavy drinkers a decrease of the class *Bacilli* and its major order *Lactobacillales* and an increase of *Streptococcus* and *Lachnoanaerobaculum*, which are usually less represented in OM. Regarding beverages types, the authors showed that beer and liquor drinkers did not differ from non-drinker in richness, while wine drinkers had increased richness of OM[25].

Probiotics

Several papers investigated the impact of probiotics administration on OM last year[26].

Alanzi et al[27] performed a double-blinded, randomized, and placebo-controlled trial, with the aim to compare the Plaque Index (PI), the Gingival Index (GI), and the presence of several salivary and plaque pathogenetic microbes (*Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Prevotella intermedia, Fusobacterium nucleatum*), before and after the probiotic's administration. *Lactobacillus Rhamnosus GG* and *Bifidobacterium Lactis* BB-12 were given to the study group, while the control group received only polyols. The authors found a significant reduction in the PI in both groups, while only the probiotic group showed a reduction in the GI and in the total amount of the four pathogenic species.

Tobita et al[28] made another double-blinded, randomized and placebo-controlled clinical trial, using tablets of *Lactobacillus crispatus* KT-11 strain *vs.* placebo tablets for 4 weeks. They found a decrease in the number of *Treponema denticola* ($p<0.1$) and *Porphyromonas gingivalis* ($p<0.05$) in the intervention group; moreover, the number of *Fusobacterium nucleatum* was significantly increased only in the placebo group ($p<0.05$).

On the other hand, Keller et al[29] performed a double-blind, placebo-controlled, randomized clinical trial using tablets containing *Lactobacillus Rhamnosus* and *Lactobacillus curvatus*. They found substantially no differences between the two groups, reporting that "the natural variation between individuals has a larger effect than the use of probiotics".

Therefore, the use of probiotics to promote oral health is a new exciting area of research that needs to be explored more deeply in the future.

THE IMPACT OF SYSTEMIC DISEASES ON ORAL MICROBIOTA

Diabetes

Due to its high prevalence, type 2 diabetes (DM) represents one of the most common Non-Communicable Diseases among patients. Several studies investigated how this condition can have an impact on OM[30,31].

Saeb et al[32] performed a cross-sectional, case-control, hospital-based study enrolling three cohorts of patients: normoglycemic, pre-diabetes, and DM affected patients. The authors found that the abundance of identified species was highest in normoglycemic group, followed by the pre-diabetes and the diabetes ones; indeed, the biological alpha-diversity of the species decreased across groups, from the controls to the diabetic patients.

The authors proposed three different mechanisms to explain the data obtained from diabetic patients:

1. A selective overgrowth of those bacterial species metabolizing the salivary glucose content;
2. The mouth dehydration, frequent in diabetic patients, leading to a decrease of the total amount of bacterial species;
3. The reduction of oral pH caused by salivary hyperglycemia.

Moreover, the authors found that, among the normoglycemic group, 73.3% of the bacterial species were not oral pathogens, 17.4% were potential pathogens, and 9.3% were potential beneficial bacteria. In the pre-diabetic patients, the percentages changed respectively in 46.7%, 33.3%, and 20%, while in diabetic patients 61.5% were not oral pathogens, 38.5% potential pathogens, and there were not potential beneficial bacteria[32].

Wang et al[33] conducted a community-based, cross-sectional study on the elderly population above 60-years-old. They divided the population into three groups according to the fasting glucose (FG) levels: normal group having a FG <6.1 mmol/L, high group with FG between 6.1 and 7mmol/L, and very high group if FG was above 7 mmol/L. Two orders (*Erysipelotrichales* and *Bacillales*), one class (*Erysipelotrichi*), three families (*Leptotrichiaceae, Erysipelotrichaceae,* and *Staphylococcaceae*), and four genera (*Leptotrichia, Bulleidia, Staphylococcus,* and *Catonella*) were significantly increased in the very high group compared with the normal and high ones[33].

In another study, Latti et al[34] found a statistically significative increase of *Streptococcus mutans, Pseudomonas aeruginosa, Staphylococcus aureus, Klebsiella,* and *Non-Hemolytic Streptococci* between diabetics and non-diabetics.

On the other hand, in the study by Joaquim et al[35], no differences were found in the total amount of bacteria between diabetics and control groups; only in females from DM group the authors described an increased amount of *Fusobacterium nucleatum* spp. compared to the control group.

Chemotherapy and Radiotherapy for Cancer

Chemo and radiotherapy are fundamental in cancer therapy. However, it is well-known that radiation therapy itself can modify the dental structure, altering the morphology of the dental tissue[36]. Nevertheless, only a few studies showed how these therapies influence OM.

Gaetti-Jardim et al[37] published a case-control study analyzing the gingival microbiota from patients affected by head and neck cancer, who underwent radiotherapy. They found a strong association between mucositis and poor oral hygiene. Regarding the different species, the authors found an increase of *Candida* spp., *Actinomyces odontolyticus, Capnocytophaga ochracea, Eikenella corrodens, Enterococcus faecalis, Parvimonas micra, Streptococcus intermedius, Streptococcus sobrinus* during radiotherapy, and a rise of *Actinomyces naeslundii, Pseudomonas Aeruginosa, Prevotella nigrescens*, and the *Enterobacteriaceae* family after the treatment.

Mougeot et al[38] made a longitudinal study on patients affected by head and neck cancer, analyzing their OM at baseline, 6 months, and 18 months after radiotherapy, and evaluating the development of caries. They demonstrated a cariogenic role for *Prevotella melaninogenica* and a protective role for *Abiotrophia defectiva*.

Villafuerte et al[39] made a systematic review from observational studies describing the changes in OM during chemo and/or radiotherapy in adults and children. In pediatric population they found an increase of gram-positive species like *Lactobacillus, Streptococcus mutans, Streptococcus viridans*, and of some gram-negative, such as *Capnocytophaga*, while in adults they reported an increase in both gram-positives *Streptococcus* spp. and *Staphylococcus* spp. and gram-negatives *E. coli, Klebsiella* spp, *Pseudomonas* spp, *Veillonella* spp.

These findings confirm the hypothesis that important changes occur in the oral environment during high impact treatments for cancer like chemo and radiotherapy.

Liver diseases

Oral dysbiosis has been found in different liver pathologies like cirrhosis, hepatocellular carcinoma, non-alcoholic fatty liver disease, and viral liver disease[40].

Zhao et al[41] reported a decrease of the abundance of *Bacteroidetes* and an increase of *Proteobacteria* and *Gracilibacteria* in patients affected by Hepatitis B; the relative abundance of *Actinomyces*, *Porhyromonas, Bergeyella, Centipeda, Alysiella, Bulleidia,* and *Pseudoramibacter* was significantly different in patient with Hepatitis B compared to the healthy controls.

Abe et al[42] found a relation between OM dysbiosis and inflammatory markers in patients affected by autoimmune liver diseases. In particular, they discovered a significant increase of genus *Veillonella* in these patients [OR (95% CI): 1.49 (1.14-1.94); p=0.003] and a significant association between the presence of *Veillonella* and the levels of salivary IgA in patients affected by primary biliary cholangitis and autoimmune hepatitis and, only in this second group, also with levels of IL-1β, IL-6, and IL-8.

THE IMPACT OF ORAL MICROBIOTA ON ORAL DISEASES

Caries

Caries represents a common teeth disease from childhood to old age, which, if not well treated, could lead to the development of more aggressive tooth diseases, such as pulpitis.

Since the role of diet is fundamental in the etiopathogenesis of caries, the review article by Giacaman RA[11], states that caries should be considered the result of an ecological sugars dysbiosis caused by an impairment of the oral pathobiont.

Until now, although the only plaque member whose role has been confirmed in the development of the caries is *Streptococcus mutans*[43,44]. Several studies showed the importance of the entire bacterial environment in the development of this disease, underlining also the role of *Lactobacillus, Actinomyces, Veillonella*, and *Neisseria*[45].

Some studies demonstrated that the composition of the OM among children affected by tooth decay is different if compared to healthy subjects. In their work, Hurley et al[46], showed that the most represented phyla in patients affected by caries were *Firmicutes* and *Bacteroides*, with a high abundance of *Streptococcus mutans*, *Prevotella* spp., *Bifidobacterium* and *Scardovia* spp. Moreover, Gamboa et al[47] showed that adequate educational intervention improving oral hygiene was feasible and efficient in reducing *Streptococcus mutans* levels in the saliva of children.

Jiang et al[48], compared OM in an elderly population affected by tooth decay with healthy controls and found an increase of the relative abundance of *Proteobacteria* as phylum and *Haemophilus* as genus in patients, while *Comamonas*, *Ruminococcaceae*, *Lactobacillus*, *Megasphaera*, and *Leptotrichia* were more abundant in the controls.

Periodontal Disease

Periodontitis is a pathological entity, which can lead to progressive destruction of gum and alveolar bone. Nowadays, it is well known that dysbiotic microbial communities can sustain the local inflammatory process in the context of periodontal disease[49].

A meta-analysis was performed by Guerra et al[50] considering a total of 2111 patients. The authors found that *Porphyromonas gingivalis* and *Streptococcus mutans* represented a risk factor for periodontitis development [OR (95% CI): 2.93 (0.98-8.87) and 0.77 (0.89-3.54), respectively], while *Aggregatibacter actinomicetemcomitans* [OR (95% CI): 0.52 (0.33-0.83)] was protective for the same disease. *Fusobacterium nucleatum*, *Prevotella intermedia*, *Tannerella forsythia*, *Streptococcus sanguis*, and *Treponema denticola* showed a possible weak risk in the development of periodontitis, while *Lactobacillus* and *Staphylococcus aureus* had a protective action, even if not statistically confirmed.

In another work by Chen et al[51], the authors analyzed 76 samples from subgingival plaques (50 patients affected by periodontal disease and 26 controls). The authors discovered a greater abundance in patients of genera *Porphyromonas, Treponema, Tannerella, Filifactor,* and *Aggregatibacter*, while genera *Streptococcus, Haemophilus, Capnocytophaga, Gemella, Campylobacter,* and *Granulicatella* were more abundant in healthy controls.

Torres et al[52] have identified a new organism involved in the development of the periodontal disease. Using a comparative metagenomics read-classification approach, the authors found that *Candidatus Bacteroides periocalifornicus*, is omnipresent in the plaque of subject affected by periodontal disease and it is strictly related to the "red-complex", a group of very virulent pathogens, involved in the process of destruction of soft tissues and bone.

CONCLUSIONS

During the last year, several studies confirmed a relation between lifestyle (i.e., diet, smoke, alcohol intake) and systemic diseases (i.e., diabetes, liver diseases, cancer therapies) with OM.

Many studies reported the link between OM and the development of oral diseases, like tooth decay and periodontitis.

However, further studies are needed to deepen our knowledge on OM and its regulation, improving the prevention of the most common oral diseases linked to inflammatory conditions.

Conflict of Interest

The authors declare that they have no conflict of interest.

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