The oral microbiota as part of the human microbiota – links to general health

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Abstract

The human body is covered by billions of microorganisms including bacteria, virus, fungi, archaea and protozoa, which are collectively referred to as the human microbiome. The composition of the resident microbiome is shaped through millions of years of co-evolution with the host, with substantial site-specific variations due to characteristic ecological properties at each body site.

During the latest decades the development of sophisticated molecular methods has provided deep insight into the composition of the human microbiome, and today more than 900 different bacterial species have been identified from the oral cavity. Oral health is shaped by a symbiotic relationship between the resident oral microbiota and the host. However, local bacterial alterations as a consequence of ecological perturbations may result in dysbiosis, which is considered critical in the pathogenesis of the two major oral diseases, periodontitis and dental caries.

The composition of the oral microbiota has also been suggested to influence general health status, and dysbiosis of the oral microbiota has been linked with general medical diseases such as cardiovascular diseases, diabetes and cancer. Therefore, a symbiotic relationship between the oral microbiota and the host may potentially have positive effects reaching far beyond the borders of the oral cavity.

The purpose of the present review paper is to address latest findings linking the oral microbiota with general health status, and to discuss future perspectives of this area of research.

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Introduction

The human body is covered by billions of microorganisms including bacteria, virus, fungi, archaea and protozoa, which are collectively referred to as the human microbiome. Bacterial cells alone outnumber human cells by a 10-fold (1). The composition of the resident microbiota is the result of millions of years of symbiotic co-existence between the host and the microbes, which is why today the human body and the microbes that line the inner- and outer body surfaces are collectively referred to, as a unity called the holobiont (2). General health (including oral health) is built upon a symbiotic relationship (harmonic co-existence) of the resident oral microbiota and the host immune system. Accordingly, alterations in either of the components, such as loos of bacterial diversity or an over reactive adaptive immune reaction towards the resident microbiota, may create dysbiosis (imbalance), which in turn can lead to general and oral diseases.

The Human Microbiome Project (HMP) founded by National Institutes of Health (NIH) was initiated in 2007, with the aim of characterizing the healthy human microbiome in samples collected from 300 American volunteers (1;3). In 2013, data from 4.788 samples collected from multiple body sites (females: 18 body sites, males: 15 body sites) in 242 participants of the HMP were presented with emphasis on structure, function and diversity of the healthy human microbiome (4). Data demonstrated that each body site was harbored by a distinct microbiome, which in terms of composition and functionality reflected the ecological characteristics present at each particular body site. Furthermore, correlation of microbial community compositions and host phenotypic characteristics, such as ethnicity, age and gender were reported, which partly underline the complex symbiotic relationship between the host and the resident microbiome in general health (4). The dataset from HMP now serves as a valuable tool containing phylogenetic (16S rRNA) and functional (metagenomic) information on healthy reference microbiomes from various body sites, which can be used for comparison with microbiome data collected from individuals with general medical and oral diseases (3).

In the latest decade, a fast growing attention is being paid to the role of the microbiome in sickness and in health. Accordingly, in 2010 a total number of 951 PubMed indexed papers with microbiome in the title were published, whereas in 2018 this number was increased by 10-fold (9050 PubMed index publications). The intestinal (gut) microbiome and the oral microbiome are the two most complex microbiomes found in the human organisms, and those are also the two microbiomes, which have been studied in most detail in health and disease (5;6). When technological progress is made, new techniques have often initially been applied in studies on the gut microbiome, and then subsequently used in studies on the oral microbiome. The gut and the oral cavity are both part of the gastrointestinal tract, and the gut microbiome and the oral microbiome are both critically involved in digestion (7;8). Therefore, dysbiosis in one part of the gastrointestinal microbiome may compromise homeostasis in other parts. Accordingly, this review paper will focus firstly on the role of the gut microbiome and secondly on the role of the oral microbiome in general health status. Finally, future therapeutic possibilities in modulating and transferring microbiomes to establish and maintain oral and systemic health will be discussed. Throughout the text taxonomic terms such as phylum, genus and species will be used in order to describe the findings from different studies on the gut and oral microbiome. Phylum level is a very broad characterization, whereas genus and species level are more precise characterizations of the microorganism described.

The gut microbiome in health and disease

The gut microbiome is the most complex found in the human organism. The predominant part of the gut microbiome is constituted by bacteria (the microbiota) with as much as 1500 different bacterial species identified (9). In addition, the gut is also colonized by archaea, yeast and viruses. The four dominant bacterial phyla in the gut are Bacteriodetes, Firmicutes, Actinobacteria and Proteobacteria (9). The composition of the gut microbiota varies considerably between individuals, and is largely influenced by diet and lifestyle. The composition of the gut microbiota is also influenced by genetics. Accordingly, a closer resemblance of the gut microbiota has been reported in identical twins compared to siblings, which in turn have closer resemblance than individuals, who are not genetically related (9;10). Furthermore, the composition of the gut microbiota is also influenced by lifestyle, with differences in nutrition and dietary preferences as the main contributors (8;11–13). In fact, it has been suggested that the gut microbiota may be divided into four characteristic ecosystems (enterotypes) (14). Three of those enterotypes associate with health, which is presumably compatible with an omnivore type diet, a fibre rich vegetarian diet and a high protein high fat diet, respectively. The fourth enterotype seems to associate with dysbiosis of the gut microbiota for example in patients with inflammatory diseases and diarrhea, with high numbers of Escherichia coli (14). However, the use of enterotypes in characterizing the gut microbial community composition is still somewhat controversial (15).

The composition of the gut microbiota is constantly stressed by endogenous and exogenous perturbations. For example, traveling causes a transient but fully reversible compositional change of the gut microbiota (16;17). Antibiotics also induce substantial changes to the gut microbiota (18). However, a recent study in healthy young adults reported the gut microbiome to be resilient to antibiotics, since the composition of the gut microbiota was almost completely recovered six months after antibiotic treatment (19).

The gut microbiota is believed to be critically involved in maintenance of homeostasis and general health. For example, reciprocal interactions of the gut microbiota and the immune system are considered instrumental in adaptive immune homeostasis (20;21). Furthermore, dysbiosis of the gut microbiota has been reported to associate with diabetes (22–25). Therefore, a symbiotic gut microbiota presumably impacts not only health of the gastrointestinal tract, but also general homeostasis of the human body.

The oral microbiome

The oral microbiome is the second most complex found in the human organism. The oral microbiota is comprised of bacteria, which harbor the surfaces of the oral cavity such as the buccal mucosa, the tongue and the teeth (7). Today, more than 900 different bacterial species have been isolated from the oral cavity (26), and taxonomic information can be retrieved in the Human Oral Microbe Database (HOMD) (27). Firmicutes is the predominant bacterial phylum of the oral cavity with Streptococcus as the predominant bacterial genus (28). The oral microbiota shows high intra-subject diversity, including major differences in the oral microbiota identified at different sites in the same individual (3). In general, the composition of the oral microbiota found at each surface is shaped partly by ecological properties but also by endogenous and exogenous perturbations (29). The buccal mucosa is characterized by an aerobic environment with a high epithelial turn-over, which is why the buccal microbiota is somewhat simple and primarily constituted by Streptococcus sp. The tongue on the other hand has a lower degree of epithelial desquamation and crypts with anaerobic conditions. Therefore, the most complex microbiota of the oral cavity is found on the tongue (28).

The oral microbiota is characterized by minor inter-subject variation compared to that of the skin (3). That is, the oral microbiota in two non-related individuals is more comparable than their correspondent skin microbiota. However, in oral health the oral microbiota identified at various surfaces shows personalized characteristics, which are relatively stable over time, as long as oral health is maintained (30). Oral health is built upon a symbiotic relationship between the microbiota and the host immune system (31;32). The symbiotic relationship on the other hand, may be compromised as a consequence of ecological perturbations such as impaired oral hygiene (33), hyposalivation (34), smoking (35;36) and dietary habits (37;38), which in turn may cause dysbiosis of the oral microbiota. Such compositional changes of local microbial biofilms are critically involved in initiation and progression of the two major oral diseases, periodontitis and dental caries (29;32). Thus, a healthy symbiotic relationship between the resident oral microbiota and the host immune system is obviously essential in maintenance of oral health.

The oral microbiome and general health

The oral microbiota may compromise general health in several ways. First of all members of the oral microbiota can gain access to the circulation as a consequence of gingival and periodontal inflammation (39;40), but also from periapical infections (41). In fact, the total area of the periodontal ulcer in patients with generalized untreated periodontitis may be as large as 20 cm2, which corresponds to the surface area of the fist (42). It is therefore not surprising that transient bacteremia after tooth brushing and dental procedures occurs more often in patients with untreated periodontitis than in healthy controls (39). Nor is it peculiar that bacterial DNA has been identified in distant sites of the cardiovascular system such as heart valves and atherosclerotic plaques in patients with untreated periodontitis (43;44). This has collectively been referred to as the focal infection theory, which stress that members of the oral microbiota are capable of inducing disease at distant body sites, if they gain access to these areas of the human organism (45). The focal infection theory is definitely not the new kid on the block. In fact, the focal infection theory dates back as long as to Hippocrates, and today it is still considered the explanatory model of endocarditis and pneumonia caused by oral microorganism (45).

The oral microbiota may also negatively influence general health status in more indirect ways. The oral microbiota is an integral part of oral homeostasis, which reside upon the symbiotic relationship with the immune defense systems of the host (7). On the other hand, local microbial alterations of the subgingival microbiota are critically involved in initiation and maintenance of destructive inflammatory reactions of the periodontium, which is the hallmark of periodontitis (32;46). Periodontitis associates with an increased risk of general diseases such as diabetes (47–49) and cardiovascular diseases (50–53). Furthermore, sufficient treatment of periodontitis improves clinical parameters of diabetes (54) and cardiovascular disease (55;56). One explanation to these findings is that local production of pro-inflammatory cytokines may spill-over from the periodontal lesions to the circulation, and therefore contribute negatively to the overall inflammatory status of the individual (57). This so-called «low-grade inflammation» theory is a matter of intense research activity, which may shed light on some of the mechanisms that link oral inflammation with general health status. Nevertheless, since the oral microbiota is implicated in local activation of the immune defense system, it is obviously an important piece in the low-grade inflammation puzzle linking oral inflammation with general health status.

Third, there are numerous association studies linking the composition of the oral microbiota with various general diseases. In such cases, presence of systemic disease may be looked upon as a perturbation effect, which stresses the oral microbiota. For example, the composition of the oral microbiota is modified by systemic diseases, such as diabetes, rheumatoid arthritis, and systemic lupus erythematosus, and as reviewed by Silva and co-workers disturbance of the oral microbiota in such cases is presumably a consequence of enhanced IL-17 mediated inflammation (58). In line, obesity has been reported to alter the composition of the subgingival microbiota in patients with type 2 diabetes (59). Furthermore, a recent study reported an association of subgingival microbiotas with liver cirrhosis in patients with periodontitis, which may be the consequence of a compromised immune system in patients with liver cirrhosis (60). Thus, there is evidence suggesting that the composition of the oral microbiota mirrors presence of systemic disease.

The oral microbiota has been suggested as a potential biomarker of different types of cancer. For example, it was demonstrated that the oral microbiota composition associates with staging of oral squamous cell carcinoma, and that cancer progression alters the composition of the oral microbiota (61). Furthermore, the composition of the tongue microbiota has been linked with gastric cancer, which is why the tongue microbiota has been suggested a possible marker for screening and early detection of gastric cancer (62). Likewise, the composition of the oral microbiota has been reported to possibly associate with risk of pancreatic (63), esophageal (64) and colorectal cancer (65). It is therefore possible that the oral microbiota may be used routinely in cancer screening and grading in a not so distant future.

Some general pitfalls apply to the pile of studies on the potential impact of the oral microbiota as a possible risk factor of general medical diseases. First of all, the majority of these studies are cross-sectional, which obviously hampers the possibility to draw any causal conclusions. Second, periodontitis associates with several systemic diseases including diabetes and cardiovascular disease. However, oral examination is seldom performed in such studies, which is why the impact of periodontitis is not known. Third, periodontitis shares important risk factors, such as smoking and diet with diabetes and cardiovascular diseases. Furthermore, smoking and diet itself impacts the composition of oral microbiotas such as the salivary and subgingival microbiota. Therefore, some reported associations may in fact be explained by shared confounding factors.

At the end of the day, it is not known whether alterations of the oral microbiota are a prerequisite for systemic diseases, or merely the consequence of systemic diseases. I.e. is it the hen or the egg? Thus, long term longitudinal studies in large populations are needed in order to evaluate if the oral microbiota is causally associated with increased risk of developing systemic diseases.

Future treatment possibilities

Using the oral microbiota as a screening tool for systemic health and disease

The oral microbiota may potentially be used in screening for systemic diseases at preclinical stages. When considering screening, the salivary microbiota may be preferred because of the ease and non-invasive nature of saliva sampling, as compared to other oral microbial sampling techniques (66;67). Furthermore, since saliva is sterile when entering the oral cavity (68), the salivary microbiota is composed of bacteria shed from oral surfaces (28). Several findings on the salivary microbiota in relation to oral health and disease may be looked upon as a proof of principle in using saliva-based screening for detection of disease. First of all, cross-sectional studies using different molecular techniques have shown that the composition of the salivary microbiota differs in patients with periodontitis (69;70) and dental caries (71;72), as compared to oral health. Second, longitudinal data have demonstrated the salivary microbiota to be personalized (73) and time-stable in oral health (30). Third, correlation between subgingival and salivary levels of proposed periopathogens have been reported in periodontitis patients (74–77), and finally, interventional studies have demonstrated that the salivary microbiota reflects local bacterial alterations caused by controlled perturbations, such as oral hygiene discontinuation (33) and non-surgical periodontal treatment (78;79). Therefore, the composition of the salivary microbiota has collectively been shown to correlate with oral health status, but future studies are needed to reveal if changes of the salivary microbiota precedes clinical sign of oral disease, or if such findings are merely the consequence of established oral disease. Interestingly, recent studies have shed light on the functional profiles of the salivary microbiota. Accordingly, it was reported that orally healthy individuals may be divided in salivary ecotypes based on the metabolomic profile of saliva, which correlated with the composition of the salivary microbiota (80). Likewise, metatranscriptomic analysis has shown functional characteristics of the salivary microbiota in patients with periodontitis and dental caries different from that of oral health (81). Several cross-sectional studies have demonstrated correlations of the salivary microbiota with general medical diseases such a liver cirrhosis (82), diabetes (83), and pancreatic cancer (84). However, at the moment large-scale prospective longitudinal studies are needed to evaluate the efficacy of using saliva-based screening of systemic diseases.

Shaping the oral microbiome

As oral health is built upon the symbiotic relationship between the resident oral microbiota and the host (85), it is reasonable to assume that oral homeostasis might as well reflect general health status. One example is that some oral bacterial species might be involved in management of blood pressure due to their ability to reduce inorganic nitrate to nitrite and nitric oxide (86). Therefore, shaping the composition of the oral microbiota could potentially influence general health status. Accordingly, the composition of the oral microbiota can be shaped in direct and indirect ways. Theoretically, direct shaping of the oral microbiota may be accomplished by means of either probiotics or microbiota transplants, whereas changing ecological conditions may indirectly shape the composition of the oral microbiota. Use of probiotics has been reported to induce quantifiable changes in the composition of the oral microbiota in orally healthy individuals (87), while transplantation of oral microbiotas on the other hand remains to be performed. However, fecal transplants are used in treatment recurrent Clostridium difficile infection (88). Indirect shaping of the oral microbiota can be achieved by controlling inflammation (89), which has been demonstrated by use of Resolvin E1 in a rabbit (90) and a rat model (91). Thus, it is possible that future prevention and treatment of oral and systemic diseases might involve direct and indirect shaping strategies of the oral microbiota. However, much research is needed before such treatment modalities might actually be implemented routinely in the dental office.

Conclusion

The advent of advanced molecular techniques has provided great insight on the oral microbiota in oral health and disease. Thus, today it is known that dysbiosis, rather than presence or absence of specific oral bacterial species, links the oral microbiota to periodontitis and dental caries. Potentially, the composition of the oral microbiota might reflect or impact systemic health. However, future large scale longitudinal studies are needed to address this question.

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Tidendes pris for beste kasuspresentasjon

Tidende ønsker å motta gode kasuspresentasjoner til tidsskriftet. Vi har derfor opprettet en pris som vi tar sikte på å dele ut hvert annet år, og neste gang ved NTFs landsmøte i 2020.

Prisen på 20 000 kroner tildeles forfatteren(e) av den kasuistikk som vurderes som den beste av de publiserte kasuspresentasjonene i løpet av to årganger av Tidende. Tidende ønsker med dette å oppmuntre til en type fagskriving som er etterspurt blant leserne og som bidrar til å opprettholde norsk fagspråk. Vi er ute etter pasienttilfeller som er sett og dokumentert i praksis og som beskriver kliniske situasjoner som bidrar til erfaringsgrunnlaget i tannhelsetjenesten. Vi er svært interessert i flere bidrag fra den utøvende tannhelsetjenesten i tillegg til kasus fra spesialistutdanningene. Ved bedømmelsen blir det lagt særlig vekt på: Innholdets relevans for Tidendes lesere, disposisjon, fremstillingsform og lesbarhet, diskusjon av prognose og eventuelle alternative løsninger samt illustrasjoner.