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Review

CORRELATION BETWEEN ORAL DYSBIOSIS AND ORAL PATHOLOGIES

R.A. Assanti[1] and P. Daliu[2]

[1]Multidisciplinary Department of Medical-Surgical and Dental Specialties, University of Campania "Luigi Vanvitelli", Naples, Italy;
[2]Dental School, Albanian University, Tirana, Albany

**Correspondence to:*
Remo Antonio Assanti, DDS
Multidisciplinary Department of Medical-Surgical and Dental Specialties,
University of Campania "Luigi Vanvitelli",
Naples, Italy
e-mail: remoantonio.assanti@unicampania.it

ABSTRACT

Numerous microorganisms inhabit the human oral cavity, including bacteria, viruses, fungi, archaea, and protozoa, forming a complex ecological community that impacts oral and systemic health. Microbiota-associated diseases are the most dominant oral diseases, such as dental caries and periodontal diseases. Furthermore, increasing shreds of evidence have sustained that many systemic diseases are associated with alterations in the oral ecosystem, like tumors. The present control of dental plaque-related diseases is nonspecific and focuses on removing plaque by mechanical means. Due to this actuality of the oral microbiome, new strategies founded on the microbiome's modulation that aim to support and reestablish a healthy oral ecosystem are gaining ever greater importance. The present review aims to describe the concept of dysbiosis and its correlation with pathological processes that can affect the oral cavity.

KEYWORDS: *bacterium, fungi, viruses, protozoa, archaea, microbioma, microbiota*

INTRODUCTION

The oral microbiome consists of microbial groups in different habitats in our mouth, such as teeth, cheeks, tongue, palates, gingiva, and tonsils. It is the second most diverse habitat of the human body after the gut microbiome, prevalently residing bacteria besides fungi, viruses, protozoa, and archaea (1). More than 700 bacterial species are colonizing in the mouth (2) with a specific bacterial composition based on its location. The hard palate represents the site with the least relevant bacterial composition, while the bacterial presence is increased in the gingival plaque. Bacteria such as Eubacterium and Prevotella are significantly associated with the back of the tongue. The papillary structure and the low redox potential of its surface could explain its distinctive specific bacterial association (3). The anaerobic environment of subgingival plaque may explain the bacteria site-specific association. In the oropharynx, the distribution of Firmicutes,

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Proteobacteria, and Bacteroidetes were similar to that of saliva, and the presence of Proteobacteria was increased compared to the mouth (4). Moreover, the bacteria present in the oral cavity can undergo continuous mutations dictated by factors that can be external or internal. Furthermore, their evolution is related to age/dentition stages (5,6) and lifestyles (7,8).

Although the oral microbiome plays an essential role in maintaining health, specific ecological changes in the microbiome can driveway some bacteria to cause various oral diseases (9).

The present review aims to describe the concept of dysbiosis and its correlation with pathological processes that can affect the oral cavity.

Method of bacterial cohabitation

The oral microbiome keeps the oral cavity healthy by preventing the expansion of pathogens (however already present in the environment) rather than preventing their invasion. Through the structural, metabolic, and chemical interactions that are triggered between bacteria equilibrium and stability are maintained in the resident microbial community in favor of non-pathogenic bacterial species (10).

Symbiosis can be mandatory, meaning that one or both symbiotics depend entirely on each other for survival, or optional when they can generally live independently. Symbiosis is also classified by physical attachment; the symbiosis in which organisms have a bodily union is called conjunctive symbiosis, and the symbiosis in which they are not in a union is called disjunctive symbiosis (11). Inside the oral cavity, bacteria can coexist with each other in three ways:

- mutualism: the particular relationship between species that mutually benefit from coexistence and are unable to live in isolation;
- commensalism: it is a non-obligatory interaction between two living beings in which one takes advantage of the other's nourishment or waste without causing suffering or disturbance. One organism between the two benefits from the other, and the other is neither harmed nor helped;
- parasitism: it is a form of biological interaction, generally of a trophic nature, between two species of organisms, one of which is called a parasite and the other a host. Unlike mutualistic symbiosis, the parasite benefits at the host's expense, creating biological damage to it.

Oral dysbiosis

Dysbiosis identifies an alteration of the human bacterial flora, and it is usually followed by an adjective that specifies the body district concerned (oral dysbiosis, vaginal dysbiosis, skin dysbiosis). Biofilm and other oral surfaces can be affected by what happens in the mouth, leading to an alteration of the balance between "good" and "bad" bacteria.

Any dental intervention can represent a disturbance of the normal oral microbiota. Even the diet can have a significant impact on the microbial environment: foods rich in sugar, acidic drinks (those without sugar), and smoking can all contribute to changing the oral environment, potentially making it more difficult for bacteria "the good overwhelm the bad" (12). As a result, maintaining good oral hygiene becomes more complicated than previously thought. Rather than simply fighting all bacteria indiscriminately, it is better to work towards supporting a healthy oral environment and maintaining natural balance (12).

It is clear to understand that a state of bacterial imbalance can negatively affect the oral district and the whole organism's health (13). The causes of this imbalance, as already mentioned, can be traced back to diet, drugs, incorrect lifestyles (smoking, alcohol, smog, little or no physical activity), and toxins. Exposure to these factors leads to the intestinal growth of non-beneficial bacterial strains at the expense of those beneficial to human health (13).

Toxins are invisible chemical compounds in the air, water, and food. Still, naturally, others are produced by the body itself and are the waste substances of the metabolic processes through a highly efficient internal chemical laboratory, which works constantly, or bacterial waste derived from the organism (13).

Dysbiosis occurs when the virulent microorganisms, which are often the same "friendly" organisms that, in a balanced state, are beneficial, transform into a pathogenic state without homeostasis. The problem, therefore, lies not in the presence of bacteria in the oral cavity but in their balance (14).

Oral dysbiosis and oral diseases

Interesting evidence emerges in the literature on the ability of the microbiota to educate the human immune system, for example, by allowing it to recognize pathogens or by directly stimulating various components of the innate and adaptive immune response (10).

The role of the oral microbiota on the immune system is not as well-known as that of other microbial communities in other human ecosystems. However, today it is possible to state, for example, that bacteria in the oral cavity selectively regulate the expression of the cytokine CXCL2 by determining the increase in neutrophils that "prepare" healthy gingival tissue (10).

In recent decades, research on the microbiota has focused on the role it plays in oral diseases rather than on the possible benefits for human health (as it has been done for the bacteria that reside in the intestine, genitourinary tract, and respiratory system). Recalling that it is possible to prevent diseases even by maintaining a good state of health, Kumar & Mason (10), therefore, stressed the importance of exploring the oral ecosystem and investigating the possible benefits that would arise from the presence of microorganisms in the oral cavity.

As mentioned above, with the interruption of microbiological homeostasis, a pathological process is triggered that sees the diversity of "healthy" populations decrease, and the prevalence of "pathological" populations increase. This way, the host's inflammatory/immune responses are established (14). The presence of an imbalance in the oral ecosystem can lead to the possible development of pathologies such as dental caries, periodontal diseases, and carcinoma.

Dental caries

Dental caries is the dissolution of the tooth structure by the acid produced as a result of the fermentation of dietary carbohydrates by oral bacteria (15). In individuals who repeatedly ingest high levels of carbohydrates, the frequency of acid production leads to a decrease in the buffering capacity of saliva. This, in turn, changes the composition of the oral microbiota, favoring aciduric microbial species. These species, notably Streptococcus mutans and Lactobacilli, continue to produce acid under acidic conditions, thus exacerbating the damage to dental hard tissues. Streptococcus mutans has been extensively studied for its cariogenic properties and has also been considered a specific pathogen (15).

To date, many bacterial species are recognized both in the biofilm and in the plaque, intent on producing acidogenic substances derived from the fermentation of dietary carbohydrates. Among these are present in addition to Streptococcus mutans and Lactobacilli, also Bifidobacterium, Propionibacterium and Scardovia (10).

However, in addition to acid production, some bacteria can raise the pH by producing ammonia from urea and arginine, which provide a mechanism to balance acid production and thus maintain homeostasis. What counts in developing a pathological process is not the identification of bacterial species but the consideration that the environmental characteristics pour on them (15).

Periodontal diseases: gingivitis

Gingivitis is, perhaps, the most common bacterial disease in humans, with a prevalence in adults of over 90%, where bacterial plaque through stratification processes due to the presence of primary (Gram + aerobic) and secondary (Gram- anaerobic) colonizing bacteria adhere on the tooth surface through the interposition of the acquired film. The failure in constant removal of this bacterial biofilm produce the consequent microbial accumulation with an increase in gram-anaerobic species, endotoxins, and enzymes which, with their pro-inflammatory function, cause irritation and inflammation of the gums with subsequent increase in volume and spontaneous or induced bleeding. The disease is entirely reversible, and thanks to professional hygiene sessions and reasonable home control of the plaque, it is possible to obtain a "restitutio ad integrum" of the tissues, thus eliminating the clinical signs.

Periodontal diseases: periodontitis

Periodontitis is a common oral disease, the manifestation of which increases with increasing age (16). Often one gets the impression that it is a natural, almost inevitable, and physiological consequence of the aging process. It is essential to change this obsolete perception. It is mandatory to understand that periodontitis is an inflammatory disease linked to the oral microbiome and the individual's immune system (16).

It is also clear that the oral microbiota changes concerning different diseases. For example, in periodontitis, anaerobic bacteria are abundant in the oral cavity; these include Porphyromonas gingivalis, Tannerella forsythia, and Treponema denticola (the three members of the " red complex "). Furthermore, these bacteria are associated with the pathogenesis of some systemic diseases (16). The pathology manifests with deepening the physiological sulcus between the tooth surface and the marginal/free gingiva.

The onset and the course are also attributable to the host's susceptibility as bacterial plaque represents the leading cause but is not sufficient for developing the disease. As a consequence of the bacterial plaque's action, there is the alveolar bone's reabsorption with an accentuated mobility of the dental element and possible loss. The disease is irreversible, characterized by alternating periods of quiescence and activity (15).

Oral squamous cell carcinoma

Several mechanisms of action have been hypothesized regarding the role of the oral microbiota in cancer pathogenesis. Activation of inflammatory-driven cellular pathways of proliferation may have an essential role in the progression of oral carcinoma. Inflammatory mediators in this process cause or facilitate mutagenesis, cell proliferation, oncogene activation, and angiogenesis.

Martilla et al. (17) showed that oral microbial cultures can produce acetaldehyde (ACH), a carcinogenic agent, and that cultures from smokers generated significantly higher levels of ACH. *In vitro* characterization of the oral microbiome indicates that *Neisseria* species and *Candida* species are among the considerable microbial producers of ACH (18). The influence of OSCC risk factors on the carriage of ACH-generating microorganisms needs additional investigation. Microbially derived *N*-nitrosamine compounds are another potential carcinogen. Commensal bacteria and Candida spp can generate N-nitrosamines *in vitro* from nitrite and secondary amines (19). Community-level metabolomics strategies are required to define whether disturbances in the normal microbiota can form these and other toxic metabolites.

CONCLUSIONS

In conclusion, the oral microbial ecosystem plays an essential role in maintaining human health. The altered oral microbiota may be intimately associated with oral and systemic diseases. The balance of the microbiome is closely linked to that of the immune system: alterations of the former lead to disproportionate reactions of the latter, promoting inflammation and increasing exposure to oncological pathologies (20).

Furthermore, the salivary microbiome seems to be more sensitive to environmental factors and lifestyle habits rather than to genetically determined factors, thus confirming that a correct lifestyle can keep the pathogenicity of the salivary microbiome under control, thus also influencing the trend of dental diseases (21).

A more feasible and clinically practical goal would be to create a "hostile" environment for pathogenic strains and healthy for non-pathogenic bacteria, thus favoring disease control, modulating the microbiome, for example, with probiotics. The use of targeted probiotics could reduce the use of drug therapies, especially antibiotics, preventing drug resistance phenomena and adverse reactions.

Another prospect could be the early diagnosis of pathologies such as oral carcinoma through the analysis of the salivary microbiome profile, characteristically altered in these pathologies, just as is being done for the intestinal microbiome where for example, any alterations of the same can influence immune responses both locally and in organs distant from the intestine (21). The knowledge of oral microbiota's role in disease occurrence and development is far from complete. Forthcoming research exactly identifying the critical oral microbiota in health and disease will help to develop better practical tools for therapies.

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Conflict of Interest

The authors declare no conflict of interest.

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