LITERATURE REVIEW

The Oral Microbiota: a Literature Review for Updating Professionals in Dentistry-Part II

La microbiota oral: una revisión de literatura para la actualización de profesionales en odontología-Parte II

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ABSTRACT: In the first part of this literature review, published in October 2019 in this journal, we summarized the conceptual background of the oral microbiota, and the main methods used in microbiology to characterize oral organisms. We also presented the most studied bacteria species in the oral microbiota. In this second part, we will discuss the evidence regarding the biological plausibility linking the oral microbiota dysbiosis and systemic diseases, as well as the main factors and mechanisms suspected in this association.

KEYWORDS: Microbiota; Oral hygiene; Systemic Diseases; Holistic health; Continuing Education.

RESUMEN: En la primera parte de esta revisión de literatura, publicada en esta revista en octubre de 2019, se resumieron los antecedentes conceptuales de la microbiota oral y describieron los principales métodos utilizados en microbiología para caracterizar los microorganismos orales. Asimismo, se presentaron las especies bacterianas mejor estudiadas de la microbiota oral. En esta segunda parte, se explorará la plausibilidad biológica que vincularía la disbiosis de la microbiota oral y las enfermedades sistémicas, así como las características que podrían influenciar la composición de la microbiota oral.

PALABRAS CLAVE: Microbiota; Higiene oral; Enfermedades sistémicas; Salud holística; Educación continua.

INTRODUCTION

Humans and microorganisms have evolved simultaneously, allowing a beneficial mutual adaptation (1). The oral microbiota shows a peculiarity compared to the normal microbiota of other body sites, since it includes not only commensal species, but also the main microorganisms responsible for the two most common diseases in humans: dental decay and periodontitis (2). Therefore, the correct balance between commensal and opportunistic species (with a pathological potential) plays an important role in maintaining a good oral health (3).

The relationship between microorganisms and the human body is dynamic, and is shaped early in life (4). The form of acquisition of the microbiota (natural delivery or c-section) and feeding (natural or artificial lactation), influence the composition of the oral and systemic microbiota (5). Oral microbiota have two main functions: to prevent pathogenic colonization, and to educate the immune system to identify pathogenic bacteria (4). However, changes in the environment (e.g. pH, oxygen tension, etc.), or changes of the immune status can cause a modification from a commensal community to a pathogenic population: a dysbiosis. Despite the known relationship between oral microbiota and general health (6), the potential biological and social mechanisms relating oral diseases and systemic health have not been fully elucidated (7).

The aim of this work is to review current evidence regarding the biological plausibility linking oral and systemic diseases via the oral microbiota. For this, we will first present the most prevalent oral diseases and their possible impact on systemic health. Second, we will synthesize the endogenous and exogenous factors that can modify oral microbiota. The hypothesis discussed is that the oral microbiome could influence general health, through dysbiotic changes, that can operate both locally and at distance (8).

LOCAL IMPACT OF ORAL DYSBIOSIS: CARIES AND PERIODONTITIS

Dental caries is the most common non-communicable disease in the world. According to the World Health Organization (WHO) "dental caries develops when bacteria in the mouth metabolize sugars to produce acid that demineralizes the hard tissues of the teeth" (9). In fact, dental caries is a dysbiotic disease characterized by a process where the presence of free sugars from diet, produce an imbalance of oral microbiota provoking a shift from symbiotic microorganisms of low cariogenicity, to a high cariogenicity population of bacteria (7).

Periodontitis is defined as "an inflammatory disease of supporting tissues of teeth caused by specific microorganisms or groups of specific microorganisms, resulting in progressive destruction of the periodontal ligament and alveolar bone with periodontal pocket formation, gingival recession or both" (10). It has been suggested that periodontal diseases are a source of chronic inflammation that can have effects on systemic inflammation (11). Periodontal disease can increase the probability to develop certain systemic diseases or alter the natural course of existent conditions; such as cardiovascular diseases, diabetes mellitus, preterm labor, and low-birth-weight, among others (12-16).

ORAL MICROBIOTA IN CARIES PROCESS

Streptococcus mutans has been considered, since its discovery in the 1920s, as the aetiologic bacteria causing caries. More recently, and with the introduction of DNA-based studies, other species were isolated from carious lesions and appear to have a role in the process of tooth decay. Other studies have revealed the presence of other types of microorganisms associated with caries development, including *Bifidobacterium*, *Prevotella*, *Propionibacterium*, *Scardovia*, *Actinomyces* and

fungi (e.g Candida albicans) (17-19). *Scardovia wiggsiae* have been described as an etiological agent of severe early childhood caries. Other groups are related to specific caries types, such as, *Veillonella*, *Rothia*, and *Leptotrichia* in enamel caries and *Streptococcus sanguinis*, *Atopobium*, *Schlegelella*, *Pseudoramibacter*, and *Lactobacillus* in dentin caries (20). Additionally, dental caries is characterized by the bacteria acid production due to the availability of fermentable carbohydrate, which can lower biofilms pH. This process selects a group of acidogenic and acid-tolerant Gram-positive bacteria (*Lactobacilli* and *Streptococcus mutans)* (21), inducing a pathogenic biofilm community (22).

Studies have suggested a link between dental caries and systemic health. For instance, *Streptoccocus mutans* (SM), one of the most important caries-related bacteria, is suspected of being a causative bacterium in Infectious Endocarditis (IE), in persons with underlying heart diseases (23). The possible route of infections hypothesized, is in the case of severe caries, where the infection extends to the pulp chamber, SM could travel through the blood vessels reaching the heart and colonizing injured heart tissue (23). In general, there is few information supporting direct biological mechanisms associating caries and human's health. Research examining these association highlight a nutritional path (24), being quite difficult to disentangle the possible direct effect of dental caries from confounding factors (e.g. lifestyles and behaviors) (25).

ORAL MICROBIOTA IN PERIODONTITIS

Oral cavity is rapidly colonized by microorganisms transmitted from the mother's vaginal, fecal, skin and buccal microbiota. Facultative anaerobic bacteria, such as, *Streptococcus* and *Actinomyces* are the first colonizers. In a second moment, strict anaerobic bacteria, such as, *Veillonellae* and *Fusobacteria* come into play

(26). In the subgingival environment, oxygen is reduced, which also favors strict anaerobes (e.g. Bacteroidaceae, Spirochaetes) (22).

The inflammatory reaction provokes a gradual loss alveolar bone and soft tissues. The majority of pathogenic bacteria intervening in periodontal disease have been described in literature. Some of them have also been found in pathological processes in some systemic diseases. Researchers have hypothesized that periodontal disease can impact systemic health trough periodontal factors or metafactors (e.g. Lipopolysaccharide) (27), and via the inflammatory response, causing local and systemic effects (28).

In dysbiosis, anaerobic Gram-negative bacteria colonize the periodontal microenvironment, including *Fusobacterium*, *Porphyromonas* or *Prevotella* (27). The best-known group of bacteria related to periodontits is called the "red complex", including *Porphyromonas gingivalis*, *Tannerella forsythia* and *Treponema denticola*. However, additional microorganism have also been cited in the development of the disease: *Filifactor alocis* and *Peptoanaerobacter stomatis*; *Firmicutes phylum* (*Dialister* spp., *Megasphaera* spp. and *Selenomonas* spp.); *Prevotella*, *Desulfobulbus* and *Synergistes* (22).

Nowadays there is a large literature that explains the role of chronic periodontitis on the onset, aggravation and maintenance of metabolic diseases. Several mechanisms have been explored, and we will summarize them below.

THE BIOLOGICAL PLAUSIBILITY LINKING THE ORAL MICROBIOTA AND SYSTEMIC DISEASES

Endogenous human microbial communities participate in multiple systemic functions; hence the alteration of the function and composition of the microbiota can have consequences for general health (5). For instance, it is known

that microorganisms possess local and systemic metabolic, physiological and immunological functions. Microbes play a role regarding the host immune system responses and maturation, food digestion, energy generation, regulation of fat storage, and maintaining the balance between inflammatory processes, among others (7,29).

The main hypotheses about the possible pathways linking oral and general health comes from the following observations: i) poor oral health can cause systemic inflammation (30); ii) oral chronic diseases have effects on general health (8,14), and iii) chronic and dental diseases share a vast majority of risk factors (31). Evidence of the associations between oral health and systemic diseases comes from several epidemiological studies, showing higher odds of having a systemic illness in patients suffering from chronic periodontitis (32). However, the possible pathogenic mechanisms that could explain how the oral microbiota can influence general health are not completely understood. Some hypotheses have been advanced, mainly regarding bacteremia, inflammatory processes and the host immune responses.

The hypothesis of an inter-relationship between oral bacteria and increasing susceptibility of certain systemic diseases relates to the possible distal effects of bacteremia. This term refers to the presence of bacteria in bloodstream. Dental treatments, but also daily life activities, such as, eating, chewing gum or brushing can induce bacteremia (33). In most cases, it is quickly controlled by the immune system, eliminating the microorganisms from circulation. However, in some cases, notably in individuals with a compromised immune system, the oral organisms may not be eliminated, and may colonize certain distal sites raising the probabilities to systemic disease development. Recently, it was shown that some systemic bacteria could live in specific oral sites. For instance, Hemophilus influenzae, Pseudomonas aeruginosa and Trophyrema whipplei have been

found into the gingival sulcus. The other way around, oral bacteria, such as Porphyromonas gingivalis, Treponema denticola and Campylobacter rectus have also been found in systemic sites, like in atheroma plaques, valvular vegetations, joint cavities and pancreas (34). Additionally, not only bacteria can be introduced into bloodstream, but their bacterial products and endotoxins can also be released into systemic circulation. This can trigger inflammatory responses in specific sites elevating the risk of producing systemic diseases (35). A good illustration of a commensal oral-systemic relationships mediated by bacteria products, relates to the metabolism of nitrates from diet into nitrites. In the oral environment, and through bacteria processing, salivary nitrite becomes nitric oxide. Nitric oxide is a powerful vasodilator, that can be rapidly be absorbed and reach bloodstream, promoting cardiovascular health (36,37).

These evidences caused the resurgence of the so called "focal infection theory". This theory explains how "bacteria and/or bacterial products are disseminated from this source to distant parts, leading to disease in these organ systems" (35). However, it is from epidemiological studies that new questions arose about how oral health exerts an influence on general health. And this is the case of the epidemiological findings regarding periodontal disease. When it comes to bacteremia, a particular agent has been located at the center of the pathogenic hypothesis involved in a possible causal link between oral and systemic health: Porphyromonas gingvalis.

PORPHYROMONAS GINGIVALIS AND INFLAMMATION: FROM LOCAL TO SYSTEMIC INFLUENCES

P. gingivalis is a Gram-negative anaerobic bacterium that produces several virulence factors, such as cysteine proteinases, lipopolysaccharide (LPS), capsule, fimbriae, and outer membrane vesicles (38). This microorganism is typically found

in oral biofilms and is part of the very well-studied "red complex" (39). Moreover, *P. gingivalis* has been found in numerous non-oral sites, suggesting its implication in systemic diseases (40). Of all the microorganisms present in the oral microbiota, *P. gingivalis* is the most studied and has accumulated the greatest amount of scientific evidence on its role in systemic pathologies (41).

It has been described that *P. gingivalis* elicits the activation of human genes, many of which are related to systemic diseases such as Alzheimer's disease (AD), type 2 diabetes (T2D), and atherosclerosis (42). This bacterium induces systemic inflammation and is frequently found circulating, in atherosclerotic lesions, and in brain autopsies of AD patients (43,44).

Additionally, patients with these diseases have higher antibody titers against *P. gingivalis* or its secreted metabolites, and these antibodies have been described to cross-react with human antigens such as histones, cardiolipin, and oxidized-LDLs. When periodontitis was treated, a decrease in antibody titers was observed, as well as other inflammation biomarkers, including C-reactive protein, platelet activating factor, fibrinogen, IL-6 and haptoglobin (43).

In murine models, *P. gingivalis* LPS induced learning and memory impairment, inducing β-amyloid formation in microglia (44). Finally, in clinical trials, eradicating *P. gingivalis* in patients with periodontitis and rheumatoid arthritis (RA), prompted a clinical improvement of RA symptoms, with a decrease of anti-citrullinated peptide antibody titers (45,46).

However, the current periodontitis pathogenesis paradigm explains periodontitis from a general state of dysbiosis, rather than focusing in specific individual pathogens in the health-disease process (8). Also, *P. gingivalis* is unable to produce chronic periodontitis in germ-free mice even after colonization, suggesting that this bacterium needs commensal species to develop oral – and perhaps systemic- diseases (47), furthermore, the host immune response is involved in progression of these diseases.

ORAL MICROBIOTA AND HOST IMMUNE RESPONSE

For maintaining oral health, the host has to develop a controlled response from the immune systems to establish a host-microorganism homeostasis (48). Oral pathogens disrupt homeostasis by subverting the immune response and activating differential inflammation pathways (49). In this process, innate immunity is key, both in its cellular (neutrophils, macrophages and dendritic cells) and humoral (cytokines and complement) components (50-52). Thus, if local stimuli are mild and immune response is controlled, immunologic surveillance prevail (50), and neutrophils perform sentinel work in the oral epithelium and gingival crevice, acting as a barrier to oral plaque pathogens colonization (51).

However, if local microbiota pathogenicity is high due to keystone pathogens, namely *P. gingivalis,* that activate an immune response consisting of neutrophil protease release and causing oral bacteria destruction and epithelial damage (50). To protect themselves from collateral damage, epithelia secretes protease inhibitors, for instance secretory leukocyte protease inhibitor (SLPI) and elafin (51).

It has been reported that *P. gingivalis* "manipulates" inflammation host responses to better achieve a dysbiotic environment and creates a "nutritionally favorable" environment (48). For example, this bacterium secretes its own proteases called gingipains, that inactivate epithelial protease inhibitors and therefore maintain inflammation (51). Gingipains also inhibit IL-8 production and thus hamper immune cell chemoattraction, dysregulating immune response (53). In addition, gingipains cleave the complement C5 component, producing

its biological active entity, C5a. This interferes with intracellular signaling in phagocytes and inhibits actin polymerization and bacterial phagocytosis (53). Finally, *P. gingivalis* is intrinsically resistant to complement lytic action due to lipid A anionic structure of its LPS (54).

The result is that these disruptive mechanisms are the creation of a nutrient-rich niche, the protection of the dysbiotic microbial community, and the perpetuation of a local inflammation state that expands from local to low-degree chronic systemic inflammation, implicated in chronic disease pathogenesis (54).

Therefore, the hypothesized biological link with systemic disease is the chronic inflammation caused by periodontal diseases. In that sense, elevations of chronic inflammation biomarkers, such as C-reactive protein, have been described (55). Additionally, it has been reported that periodontal treatment has significantly reduced systemic disease markers. These findings provide strong evidence that periodontal disease is causally associated with either the genesis or progression of these systemic effects (56).

We have presented the main endogenous biological factors influencing oral microbiota. In the next section we will develop the role of the main exogenous factors that as, oral scientists, we should take into account to better understand the biological and social mechanisms potentially influencing the oral microbiota.

DETERMINANTS OF ORAL MICROBIOTA: THE EXOGENOUS FACTORS MODULATING ORAL MICROBIOTA

To better determine the real relationship between oral microbiota and general health, it is necessary to identify the main factors that can modify human oral microbiota. Oral (and general) diseases are multifactorial, as such, they have biological and social elements involved in their development. The latter elements relate mainly with human lifestyles, and therefore, are profoundly rooted in the individuals' social, cultural and economic characteristics. It is already known that social characteristics and lifestyles impact oral health, however, the interplay between social factors, oral microbiota and health remain unclear.

AGE AND SEX

At birth, infants born by vaginal delivery show communities similar to the mother's vaginal microbiota (*Lactobacillus*, *Prevotella*, and *Sneathia spp*). Babies born by C-section, show skin bacteria, such as, *Staphylococcus*, *Corynebacterium*, and *Propionibacterium spp*. After birth, the pioneer bacteria include Gram-positive *Streptococcus* and *Staphylococcus*. In the first month of life, the main genera detected are *Streptococcus*, *Haemophilus*, *Neisseria*, and *Veillonella* (57).

In children, there is a major event that shifts oral microbiota: teeth eruption (57). This provide new adhesion surfaces for colonization and promotes certain microorganisms, such as, *Streptococcus*. Exfoliation, in the establishment of permanent teeth, is also a major ecological event. With age, oral microbiota increase in complexity (7). Since oral microbiota is sensible to shifts in nutrition, it not surprising to detect differences during childhood when carbohydrates are incorporated in diet. Adolescence, with hormonal changes, can also influence oral microbiota, allowing an increase of Gram-negative anaerobes and Spirochetes (57).

Aging have been associated with a low-grade systemic inflammatory response and a decline in the immune system, also called inflammaging and immunosenescence (58). These mechanisms can modulate the inflammatory and immune response, causing gradual changes in the microbial community in elderly (58). However, the existent evidence is

few and limited by study designs, with nearly no evidence from longitudinal studies.

Regarding sex, some reports have emphasized the differences between men and women regarding caries development. The hypothesis is that sex/ gender interrelates with genetic variations, diet, hormonal fluctuations, salivary differences, and social factors, which can alter oral microbiota (59). However, more studies are necessary to identify a specific role of long-term sex/gender influences in oral microbiota, for health and disease.

DIET AND NUTRITION

It has been well described the role of sugar frequency consumption in the case of severe early childhood caries, where higher levels *Streptococcus mutans* and *Fusobacterium nucleatum* have been found (60). Despite being essential for gut microbiota, there is relatively little evidence showing the association between diet and oral microbiota (61). This can be partially explained by the fact that the principal substrate of oral microorganisms are endogenous, coming from saliva, crevicular fluid, degenerating cells and other bacterial metabolites (61). However, some studies point out the role of saturated fatty acids and vitamin C, linked to the alpha diversity and an increasing presence of Fusobacteria (61). In general, it appears that a fiber- and dairy-rich diet promotes a healthier composition of the oral microbiota (60).

HEALTH BEHAVIORS: SMOKING AND DRINKING

Smoking can disturb oral ecology. Cigarettes appear to increase saliva acidity (62), lower oxygen availability, have antibiotic effects, and provoke an immunological impairment in the host (63). Additionally, related to oxygen deprivation, it has

been suggested that it can create a favorable environment for anaerobes, such as *Veillonella* and *Actinomyces* (64).

Regarding drinking, oral bacteria can metabolize ethanol to acetaldehyde, a well-recognized carcinogen. However, it seems to be a difference in terms of the effect on microorganisms, according to the type of alcohol and frequency of consumption. Liquor appears to favor the development of Gram-positive bacteria, such the *Streptococcus*. One study showed that wine, when consumed moderately, does not provoke a destabilization of oral microbiota in the long term, and some of the wine organic acids (succinic, malic, lactic, tartaric, citric, and acetic acid) appear to be beneficial to overall oral microbiota, since they have an antibacterial activity against *Streptococci* (60]. However, this study was in vitro, and more evidence should accumulate to better understand the potential beneficial effect of alcohol in human oral microbiota.

SOCIODEMOGRAPHIC CHARACTERISTICS

Socioeconomic status (SES) is one of the leading determinants of oral diseases (65), showing bio-psycho-social characteristics (66). Oral health can be influenced by SES via health behaviors (67), psychosocial factors (68), but can also be directly linked via biological paths (69). Regarding oral microbiota, the association is less studied. However, some evidence points out the potential differences in microorganisms' composition and diversity. Low diversity of oral microbiota was found in groups with low SES (70). Additionally, it appears that SES can be reflected in the salivary bacterial profile (71). Similarly, some reports have suggested that culture and differences by geography, probably reflecting diet and host genetics, can modify the human oral microbiota (72).

CONCLUSION

The microbiota research has opened the possibility to a "microbiomic" epidemiology (56). While it is true that exploring oral microbiota in different health states could partially explain the links between oral health and certain systemic diseases, some methodological precautions have to be addressed. For instance, it is known that almost all the sociodemographic and the lifestyle variables, can act as confounders. In an epidemiological study is therefore essential to take into account all the potential confounders to run the most adapted statistical analyses, to prevent to observe spurious links between oral microbiota and systemic disease. Multi-disciplinary collaborations including dentists, epidemiologists, microbiologists, statisticians and bioinformatics will be crucial to continue moving forward. The hypothesis that oral microbiota can be part of the causal chain of systemic diseases is innovative, and central in terms of public health approaches, mainly regarding the integration of dental treatment in the preventive primary care in social security systems. In that sense, oral healthcare has to meet again with general healthcare to address health from a holistic perspective.

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