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Review Article

Oral Microbiome and Digestive Diseases

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Abstract

The implications of the oral microbial community with the intestinal microbiota and the participation in inflammatory bowel diseases and colorectal and pancreatic cancer due to the effect of dysbiosis and pathogenic bacteria of the oral cavity are reviewed. To update the knowledge on the link between the oral microbiota and the repercussion of dysbiosis caused by pathogenic bacteria in chronic digestive diseases kas been the reason for the review. There was evidence of a relationship between oral and intestinal microbiota, participation of the oral-intestinal axis, role of dysbiosis in the oral cavity and pathogens such as *Porphyromonas gingivalis, Klebsiella pneumoniae* and *Fusobacterium nucleatum* in inflammatory bowel disease and digestive cancer. Recent advances on oral-intestinal microbiota links, influence of dysbiosis and pathogenic oral bacteria in the pathogenesis of inflammatory bowel diseases and in colorectal and pancreatic cancer, and the value of oral cavity hygiene in health were reviewed.

***Keywords**: Microbiomes; Oral Microbiota; Intestinal Microbiota; Dysbiosis; Oral Health; Digestive Diseases; Colorectal Cancer and Pancreatic Cancer*

Introduction

Preserving oral health is representative of a challenge for human health. The medical-odontological scientific community has drawn attention to its importance and the meaning of integration of policies related to oral health and general health, in expression of the interaction with systemic diseases [1]. In this context, the epidemiology of periodontitis with a high global prevalence and its correlation with the metabolic syndrome [2] stands out, drawing attention to the prevalence of periodontal disease in developing countries as a health problem [3].

The oral microbiome and its microbiota (OM) is one of the most diverse and abundant in the human body, it is the second largest, preceded by the intestine, and noted for its participation in oral health and different systemic diseases [4] and is related to oral diseases, such as dental caries, periodontitis and cancer of the oral cavity [5] while the intestinal microbiome (IM) has a complex heterogeneous community of resident commensal microorganisms, which participate in a series of beneficial effects for digestion, nutrient production, detoxification, protection against pathogens and in the regulation of the immune system [6].

The oral cavity is dominated by facultative organisms that ferment sugar, such as *Streptococcus* and *Actinomyces* species [7]. It has been postulated that oral microorganisms in their transit to the intestine can maintain their viability and alter the homeostasis of the host's

microbiome, by displacing the community of commensal bacteria producing short-chain fatty acids (SCFA); since oral taxa can be directly immunogenic [8,9].

In periodontitis and other diseases that affect the periodontium, there is an association with the development of plaque biofilms with dysbiosis associated with cause-effect inflammation that drives the development to chronicity and the consequent destruction of the dental support [10,11]. Oral dysbiosis is characterized by the presence of *Porphyromonas gingivalis*, supported by accessory pathogens, such as *Streptococcus gordonii*; *P. gingivalis* is one. specific bacteria in the mouth, with an effect on the microbial community as it is a common presence in periodontal disease, which has also been implicated in colitis and homeostasis of the intestinal mucosa epithelium [12].

IM contains between 500 - 1000 bacterial species with a total concentration of 10^{12} - 10^{14} colony forming units (cfu). in the older child and the healthy adult [13,14]. The surfaces of the oral cavity contain diverse microbial communities, which can host approximately 50 different microbial species that make up OM at any location [15]. The referred surfaces are covered by a thin mucilaginous layer called plaque or biofilm, which modulates the attachment of bacteria to the dental and epithelial surfaces, while protecting the mucosa [16].

In the oral cavity, the role of dysbiosis has been described as a decisive element, which occurs in the same way as in the microbiome of the intestine, where its imbalance is decisive in different important pathologies, such as acute infectious diarrhea, especially of cause viral and bacterial; persistent diarrhea, nosocomial diarrhea due to *Clostridium difficile* and its recurrence; necrotizing enterocolitis, irritable bowel and inflammatory bowel diseases are among the main ones [17].

There is accumulated evidence about the close relationship between OM and systemic diseases, such as those of the Digestive System [15]. The linkage of the oral and intestinal microbiota is supported by the description of the "oral-intestinal axis [18] and supported by research in mice and studies in humans that described intramucosal connections between the oral cavity and the intestine, according to reports from patients with IBD [19].

It is documented that a large number of oral microorganisms progress through saliva through the digestive tract, which allows establishing a close association in the pathogenesis of digestive diseases. These include cancers, such as colorectal [20] and pancreatic cancer [21] inflammatory bowel diseases, especially Crohn's disease [19] and conditions related to metabolic syndrome, such as non-fatty liver disease alcoholic. Likewise, the interrelation of the oral microbiota and diseases not related to the digestive system is described, which include rheumatoid arthritis [22], cardiovascular diseases [23], and adverse effects of pregnancy, between or after [24] (Table 1).

Inflammatory Bowel Disease
Cancers
- Cancer of the mouth
- Esophagus cancer
- Colorectal cancer
- Pancreatic cancer
Metabolic syndrome:
Liver disease:
- Nonalcoholic fatty liver disease
- Nonalcoholic Steatohepatitis

Table 1: *Periodontitis and associate digestive diseases.*

Inflammatory bowel diseases

It is recognized in Crohn's disease, and ulcerative colitis, are related to an imbalance in the composition of the intestinal microbiota (dysbiosis). In patients with IBD, complex interactions between microorganisms and the host occur, since there is a breakdown in the

mechanisms established by the immune system to promote the separation between symbiotic microorganisms and the epithelium of the intestinal mucosa with the effective destruction of penetrating microorganisms. associated with suppression of the activation of inappropriate responses of T cells to resident microorganisms [25]. The alterations of the intestinal microbiomes in patients with IBD show a reduction in their diversity and changes in the bacterial composition. These changes include loss of the bacterial phylum of *Firmicute*s and an increased abundance of the phyla *Proteobacteria* and *Bacteroidetes* [26] The intestinal colonization of oral bacteria has been shown to be a participant in the pathogenesis of IBD [26]. On the other hand, periodontal disease is recognized as a significant risk factor and contributes to many systemic diseases, including IBD. Subjects with IBD harbor large amounts of bacteria from the oral microbiota, which presumably have infiltrated the intestinal microbiota [26].

Genetic, dietary and environmental factors have been described in the pathogenesis of IBD related to the participation of the oral and intestinal microbiomes [27], with the consequent increase in the association of the incidence of periodontitis and IBD [28]. Recent studies have shown that *Bacteroidetes* are significantly increased with a concurrent decrease of *Proteobacteria* in the salivary microbiota of IBD patients. The notable changes achieved with the development of the 16S rRNA gene sequencing methods have made it possible to learn about the dominant bacterial species that cause periodontitis infections that are most frequently associated with IBD. These oral bacteria can travel to the intestine, where they settle and disturb (dysbiosis) the balance of MI, even favoring the development of chronic inflammatory diseases, which correspond to *Porphyromonas gingivalis, Klebsiella pneumoniae, Enterobacter spp., Neisseria spp., Prevotella nigrescens* and *Fusobacterium spp.*, indicating aberrations of the oral microbiota and their major contribution to dysbiosis [19]. *Fusobacterium nucleatum* has been reported to be enriched in IBD [26].

Klebsiella pneumoniae

In this context, for example, *K. pneumoniae*, a bacterial species that, in humans, is normally found in the oral sphere and very rarely in the intestine; It was observed in research that dysbiosis caused by ingestion of antibiotics, by disturbing the balance of the intestinal microbiota; it can lead to colonization in the intestine of *K. pneumoniae*. This colonization triggers an immune response, and therefore, chronic intestinal inflammation, which contributes in patients with IBD and other intestinal diseases to create a suitable environment for the implantation of oral bacteria. Likewise, these findings suggested bacteria from the oral cavity may be potentially pathogenic, with the ability to aggravate intestinal diseases [29].

Likewise, the accumulated results of different experimental studies in mice have argued the interrelation between the microbiota of the oral cavity and the intestinal microbiota in the pathogenesis of IBD [29]. Dysbiosis in the oral microbial community in mice with imitation of oral periodontitis phenotypes when compared with healthy controls and later, when inducing colitis, bacteria of oral origin colonized both environments. In other hand, mice with periodontitis were susceptible to infection by potentially pathogenic bacteria (pathobionts) from bacteria of oral origin. In turn, the studies by Rautava., *et al.* [30] described in similar mouse models with colitis a significant association between the microbial profiles of saliva and the proximal intestinal profiles that reflected the proportion of intestinal inflammation [31].

Digestive cancers

In 2018, the WHO estimate of the main causes of death worldwide (9.6 million) from cancer corresponded to lung tumors (18.4%), colorectal cancer (9.2%), stomach cancer (8.2%) and liver cancer (8.2%), with esophageal cancer occupying sixth place and pancreatic cancer in seventh place [32,33], figures that show the interest of the oral microbiota and its dysbiosis and the link in different diseases [34,35].

The oncogenic participation of bacteria in the pathogenesis of cancers is recognized, as occurs in the interrelation between *Helicobacter pylori* and gastric carcinoma (GC) and some gastric lymphomas (MALT). Gastric cancer is triggered mainly by *H. pylori* infection,

which has been classified as a type I carcinogen and a preclinical risk factor and the first example of bacterial infection associated with carcinogenesis. There is evidence of dentobacterial plaque, in individuals with periodontitis, it is a reservoir of *H. pylori* [36]. Recent advances report a complex interaction with the gut microbiota during gastric carcinogenesis, characterized by reduced bacterial diversity and increased microbial dysbiosis [36].

The epidemiology of digestive cancers linked to the oral microbiota shows a relationship with esophageal, colon and pancreatic cancer [37]. Recent studies report evidence on the role of the microbiota of the oral cavity and its dysbiosis is involved with cancers of distant organs, not located in the head and neck, as it happens, with the development of digestive cancers, an argument controversial since years ago. Three main mechanisms have been proposed in pathogenesis: chronic inflammation, microbial synthesis of carcinogenic substances, and integration of the intestinal barrier [38]. Likewise, oral pathogens are decisive in colorectal cancer (CRC) [20] and pancreas [39] related to two species in particular *Fusobacterium nucleatum* and *Porphyromonas gingivalis* (the latter in pancreatic adenocarcinoma) [40].

Porphyromonas gingivalis

It is an anaerobic gram-negative bacterium closely associated with periodontal disease (gingivitis and periodontitis), that is found on the surface of the teeth. It is part of the microbial community of the biofilm of the mouth that colonizes the subgingival area and regulates the immune function of the host, whose alteration decisively influences the events of periodontal disease. There is evidence for a link between periodontal disease and oral cancer, *P. gingivalis* may play an important role in the development of oro-digestive carcinogenesis independently of periodontitis [41]. Multiple publications have implicated. *P. gingivalis* with digestive cancers [41,42].

Esophagus cancer

The worldwide incidence corresponds to the eighth place for tumors and the sixth with the highest mortality [32,33]. In central China it is reported in the highest frequency, although in recent years it has increased in Western Europe and America [37]. Two types of cancer are described: squamous cell (90%) and adenocarcinoma, which it is of higher mortality. Gao., *et al.* described the link between *P. gingivalis* and esophageal cancer and postulated the limitations for early diagnosis and importance in the progression of this type of cancer [42]. The infection rate of *P. gingivalis* is much higher in cancers of the esophagus than of the stomach, which is related to the effect of acid [41,43].

Colorectal cancer

It is the digestive cancer with the highest incidence, ranks second worldwide. Different mechanisms have been postulated in the participation of OM in the production of dysbiosis in CRC [44] which are numbered below:

Participation of oral bacteria in the intestinal environment:

1. Role of oral polymicrobial biofilms in CRC.
2. Metabolic properties of oral cavity bacteria in the colon.
3. Virulence factors of oral bacteria to inhibit apoptosis, modulate inflammation and the immune response in the colon.

To date, there is no reliable marker for the detection of CRC with high sensitivity for early diagnosis. In this direction, different studies have been carried out in search of reliable biomarkers, since fecal occult blood and fecal immunity methods have low sensitivity. In research in animal and human models, changes in the composition of the microbiota of the colon and fecal mucosa have been reported. by the development of bacteria normally located in the oral cavity versus benign colon polyps and healthy controls. This finding supports the microbial role in the pathogenesis of CRC and its value as a diagnostic factor [45].

In related studies in the bacterial population of the colon mucosa of cancer patients, biofilm formation comparable to those of the oral cavity was found. These colonies of bacteria cause an alteration in the expression of the genes of the cells of the colic mucosa, which suggest they are involved in the progression of cancer. Likewise, a negative correlation was observed in the intestinal concentration *of Lachnospiracae* and the low fiber diet, which allows us to affirm that oral bacteria in the colon tend to indicate the protective role through the diet. These studies by Flemer., *et al.* postulated OM analysis could potentially be used as a screening method for CRC and the detection of polyps [18,45].

Fusobacterium nucleatum

It is one of the most densely colonized bacterial species in the oral cavity and is known to be associated with periodontitis. *F. nucleatum* commonly resides in the oral cavity, but rarely in the intestine. Recently, many researchers have shown it is related to the development and pathogenicity of CRC. Komitiva., *et al.* [46] found identical strains of this bacterium in the tumor and oral cavity in CRC patients; however, the link between *F. nucleatum* in RCC and the oral cavity is not well understood [18,46].

Pancreatic cancer

Pancreatic cancer is one of the main causes of cancer mortality in developed countries and one of the most lethal malignancies reported in the world [32,33]. The two main types of pancreatic cancer tumors are adenocarcinoma (85%) and pancreatic endocrine tumors (less than 5%), with a 5-year survival of 8.2%). Many known risk factors contribute to PC, including alcohol use, chronic pancreatitis, genetic mutations, environmental hazards, type 2 diabetes mellitus, and smoking (25% in adenocarcinoma cases). Poor oral health is associated in multiple studies with an increased risk of developing pancreatic cancer [46-49].

A history of periodontal disease caused by *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* have been associated with pancreatic cancer and evaluated the imbalance of the oral bacterial community (specific gram-negative bacteria), twice greater in the presence of *P. gingivalis*, as the blood antibodies of said pathogen and the presence of the bacterium in the pancreatic ducts of humans have been demonstrated [50-52].

Conclusion

Studies by the Human Microbiome Project have revealed 29% of the human body's habitats reside in the gastrointestinal tract and 26% in the oral cavity, demonstrating that both constitute more than half of the total human microbial community. The oral microbiome has local and systemic effects and its dysbiosis intervenes in pathological processes, such as dental caries, periodontitis and cancer of the mouth. Likewise, the profiles altered by dysbiosis directly modulate systemic diseases, such as diabetes, cardiovascular diseases and rheumatoid arthritis. The link established through the oral-intestinal microbiota axis and the effects of dysbiosis is an obvious argument in favor of the implications in the pathogenesis of IBD and digestive cancers [26].

The oral and intestinal microbiomes are closely connected through interaction in the oral-intestine route by translocation of the bacterial barriers of both microbial communities, since in healthy states they are not invaded by pathogens for presenting an intact barrier that does not show increased intestinal permeability. Oral pathogens can interfere with the function of the intestinal barrier and invade the mucosa of the intestine, causing dysbiosis and chronic inflammation, as occurs in the pathogenesis of IBD. The growth of *P. gingivalis, F. nucleatum and K. pneumoniae* and other bacterial genera are key to the events described.

Research has shown the ability of bacteria to influence specific cells of the immune system, which determines many diseases, including the neoplastic response. It is recognized when the human microbial community in any place suffers dysbiosis, interacts with the immune system and causes damage to the state of health, both local and systemic. The possibility of dissemination of oral pathogens locally, in the blood or through the blood circulation, when passing to the systemic circulation, facilitates the presence of pathogens in an organ

(local or distant), modifies the immune response and stimulates the release inflammatory mediators, representing pathogenic events for a disease [48,53].

The increased incidence of IBD and digestive cancers in more recent years, such as CRC, are exponents of the importance of the oral-intestinal microbiota link and the importance of oral health. This concept provides arguments for pathogenesis and will be decisive for an accurate diagnosis/prognosis, as well as for effective treatment.

It is evident that compliance with oral health education measures through strict local hygiene are indispensable for the challenge of oral diseases, such as dental caries, gingivitis and, in particular periodontitis. Experts emphasize the use of traditional tooth brushing and the usefulness of dental floss, likewise, they recommend antiseptics, such as chlorhexidine mouthwashes or cetylpyridinium chloride, all required to prevent oral microbiota dysbiosis risk factors.

Conflict of Interest

The author declares no conflict of interest.

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