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IBD, MALIGNANCY AND ORAL MICROBIOTA: ANALYSIS OF THE LITERATURE

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ABSTRACT

The human microbiota, in adults, varies in number and species based on the location in the gastrointestinal tract. The highest concentration is at the intestinal level, where mainly Bacteroidetes, Actinobacteria, Firmicutes and Proteobacteria are found. Instead, in

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the oral cavity, five major phyla exist: Firmicutes, Actinobacteria, Proteobacteria, Bacteroidetes, and Fusobacteria. Variations in the microbiota cause dysbiosis, which is responsible to a great extent for the onset of many diseases including inflammatory bowel disease (IBD) and colorectal cancer (CRC). In some cases (8 - 10%) IBD has shown oral manifestations that may reflect a change in the composition of the oral microbiota. This work relates, through a meta-analysis of the literature, how variations of the oral microbiota, or the combination of micro-organisms that inhabit the oral cavity, can influence the onset of IBD and CRC.

Keywords: Inflammatory Bowel Disease, malignancy, oral microbiota, dysbiosis

INTRODUCTION

Microbiota is the focus of numerous scientific studies which depict that changes in the composition of the microbiota, indicated by the term dysbiosis, predispose the individual to the onset of many diseases, including inflammatory bowel disease (IBD) and colorectal cancer (CRC) [1]. The term "microbiota" indicates the plethora of bacteria that inhabit the human gastrointestinal tract. In adults the microbial flora colonizes all the traits of the digestive system, however it varies in number and species according to location in the gastrointestinal tract [2].

The concentration is highest at the intestinal level where it is estimated to be present in 10^{14} CFUs (Colony Forming Units) with about 500 different microbial species organized in colonies [1, 2]. In fact, the bacterial species that are present at the level of the small and large intestine are divided into four main groups (Bacteroidetes, Actinobacteria, Firmicutes and Proteobacteria), with the most represented species are being Lactobacillus, Streptococcus, Bifidobacterium, Clostridium and Enterobacteriaceae [3].

Another site of the gastrointestinal tract in which there is a large concentration and diversity of bacteria is the oral cavity, where they form the oral microbiota. There are about 280 different species of bacteria in the oral cavity. They can be divided into five different major phyla (Firmicutes, Actinobacteria, Proteobacteria, Bacteroidetes, Fusobacteria), and they belong to bacterial species such as Streptococcus, Eubacterium, Actinomyces, Campylobacter, and Prevotella [4, 5].

The microbiota, exerts various physiological functions both in gut and in the oral cavity. In the gut, the microbiota can promote synthesis of short-chain fatty acid (SCFAs), inhibit the growth of pathogenic bacteria, facilitate the absorption of nutrients and mineral salts as well as the synthesis of vitamins, participate to immunity through interaction and stimulation of the gut associated lymphatic tissue (GALT). The microbiota also reduces the cellular permeability through the increase of the tight junctions and produces compounds important for the health of the organism [6, 7].

In the oral cavity microbiota establishes symbiotic relations with the host that determine benefits to both the bacterial species and the host. Furthermore, the oral microbiota helps to keep under control the growth and proliferation of pathogenic bacteria and prevents their adhesion to the surfaces of the oral cavity [8]. Therefore, any alteration of the microbiota, which is defined by the term dysbiosis, can cause diseases in gut or in the oral cavity or both.

Inflammatory Bowel Disease and Oral Manifestations

Inflammatory Bowel Disease (IBD) is a spectrum of chronic inflammatory bowel diseases that involve the entire gastrointestinal tract, from the mouth to the anus with a typical segmental distribution of the lesion, in the case of Crohn's disease (CD), or the last part of the intestine, colon and rectum, in the case of ulcerative colitis (UC). At the base of IBD etiology there is a set of conditions including genetic predisposition, diet, lifestyle, vitamin D deficiency, drugs, geographic and epidemiologic factors and deregulation of the immune system, all situations that lead to change in composition of the microbiota and consequently to dysbiosis [1, 2, 7, 9, 10].

In IBD, there are bowel-specific symptoms such as abdominal pain, abdominal colic, nausea, fever, fatigue, weight loss, and diarrhea, in addition to nonspecific extra intestinal manifestations such as arthritis, endocarditis, thyroiditis, alopecia, psoriasis, and uveitis [1, 2, 7, 9].

In some cases of IBD, oral manifestations were observed which may reflect a change in the composition of the oral microbiota. Oral symptomatic manifestations in CD are relatively rare (8-10% of cases) [10, 11] and difficult to diagnose since they often overlap with other oral diseases such as orofacial granulomatosis [12, 13]. Oral lesions in the CD could involve the lips, buccal mucosa, gingiva and retromolar areas. They are mostly represented by granular gingival swelling, ulcers associated with hyperplastic mucosa, recurrent aphthous stomatitis, pyostomatitis vegetans (13) dysphagia, halitosis, gingivitis, caries and candidiasis [10, 11]. Moreover, in UC the oral symptoms are even rarer, as this disease affects mostly the last part of the intestine, and complications are represented by superficial hemorrhagic ulcers, pyostomatitis vegetans and aphthous ulcers [11, 13, 14]. However, it is important to note that often the oral mucosal lesions and dental tissues in IBD serve as an early indicator of IBD [15].

Analysis of the Literature

The authors analyzed the published studies, in particular those of the past 10 years, looking for correlations between IBD and the microenvironment of the oral cavity, with particular reference to the changes of the salivary microbiota as well as the change of various inflammatory molecules.

One of the first studies that correlate the IBD with the microbial flora of the oral cavity was made in 1986 by Thomas E. Van Dyke et al. [16]. In this study, a correlation between oral microbiota of patients with periodontal lesions and IBD was described. The study, through investigations conducted with dark-field microscopy, reported that, in patients with IBD and periodontal lesions, the microbiota consisted of furniture gram – negative bacteria, small and flagellates. In contrast, in patients with periodontal lesions but without IBD, the oral microbiota was composed of spirochetes, fusiform and filamentous [16].

Another study to be taken into consideration is the one performed by Zhang Li [17]. This study showed that the species of Campylobacter (especially Campylobacter concisus) detected in faecal samples and biopsies of patients with IBD may arise from the salivary microbiota and have a role in the pathogenesis of IBD. Campylobacter concisus, which normally colonizes the oral cavity, could be considered an initiator since it does not have a great ability to survive in

environments with strong inflammation. The hypothesis is that C. concisus has virulence factors that do not appear in the oral cavity, but only if the bacterium reaches the intestine. Once in the gut, C. concisus express their virulence factors giving way to the inflammatory process [17].

Another relevant study, conducted by Heba S. Said et al. [18] using molecular biology techniques such as pyrosequencing of the bacterial 16S rRNA gene. They showed significant differences between the salivary microbiota of patients with IBD and those of control patients. In particular, a significant increase was observed in the Prevotella kind in the salivary microbiota of patients with IBD, and a reduction of Streptococcus, a species normally abundant in salivary microbiota of healthy patients [18].

Regarding the inflammatory molecules related to IBD, Katarzyna Szczeklik et al. [19] conducted a study on pro - inflammatory molecules detected at the level of saliva in patients with CD. They demonstrated that in the saliva of patients who have the disease in the active phase, there was a high concentration of IL-1β, IL-6, and TNF-α, compared to control patients or patients with disease in remission [19].

Along the line, the results of another study by Stein et al. [20] showed a link between the presence of CD and the onset of periodontitis suggesting that periodontal microbiota may affect mucosal lesions [20].

The close relation between oral microbiota, IBD and colorectal cancer (CRC) was further supported by a recent study which highlighted how some bacteria, usually found in the oral microbiota in case of periodontitis (an inflammatory disease of the tissue surrounding the teeth and whose pathogenesis is related to a change in the composition of salivary microbiota) are also correlated with the onset CRC. Samples taken from CRC biopsies depicted the presence of a bacterium, Fusobacterium nucleatum, usually associated with periodontitis. This bacterium was not, however, found in the colonic mucosa samples taken from healthy patients. *F. nucleatum* is not the only bacterium that was found in the colic biopsies from patients with CRC. Other bacteria, such as those belonging to the family of *Porphyromonas*, have been detected in cases of CRC, and this suggests that the *F. nucleatum* species is a "driver," able to develop virulence factors that may induce colorectal tumorigenesis in association with other bacteria and other predisposing conditions [21].

CONCLUSION

The analysis of the literature showed a distinct difference, in the composition of the microbiota, between healthy patients and patients with IBD or CRC. These studies provided reasons to believe that the oral dysbiosis not only can causes oral lesions related to IBD but also that some bacteria in the oral cavity may predispose to IBD and CRC.

However, further studies are needed to clarify such a correlation between changes in the salivary microbiota and the appearance of oral manifestations in IBD. There is certainly a link between oral dysbiosis and oral symptoms of IBD very much like the link with intestinal dysbiosis, being one of the contributing factors that determine the onset of the disease. Again, it is of special interest to explore further the correlation between certain bacterial species present in the salivary microbiota and colorectal cancer, however, there are still very few studies on the subject and need further investigation.

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