REVIEW ARTICLE

Oral Dysbiosis and the Gut

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Abstract

The oral cavity and the gut are distinct organs having specific microbiomes. However, studies in animals and humans have indicated that oral bacteria can overcome the physical and microbial barrier and colonize the gut, especially in the small intestine. The oral microbiome is associated with oral and systemic diseases. The bacteria mainly implicated in causing oral dysbiosis—*Porphyromonas gingivalis* and *Fusobacterium nucleatum*—on colonizing the gut alter the intestinal microbiome, creating dysbiosis in the gut microbiome and promoting the immune and inflammatory responses resulting in gastrointestinal diseases. This area of research, although still in its infancy, highlights the need for a coordinated approach to the treatment of periodontitis and development of gastrointestinal disease and also evaluation of emerging microbiome-based therapeutic approaches in the treatment of disease.

Keywords: Gastrointestinal disease, Gut dysbiosis, Oral diseases, Oral dysbiosis, Periodontitis.

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Introduction

The oral cavity of a healthy adult constitutes a complex microbial ecosystem of around 700 different microbial species constituting bacteria, viruses, and fungi, which maintain a stable mouth environment.[1] These microbes are members of Firmicutes (mainly *Streptococcus*), Proteobacteria, Fusobacteria, Actinomycetes, Haemophilus, and Bacteriodetes as determined by the Human Microbiome Project Consortium, 2012 implemented by the US National Institute of Health.[2] The bacterial species present mainly in the oral cavity are *Streptococcus*, *Fusobacterium*, *Gemmella*, *Veillonella*, *Granulicatella*, *Bacteroides*, *Pasteurella*, *Prevotella*, *Neisseria*, and *Corynebacteria*. The oral microflora is present on the teeth, buccal mucosa, tongue, and soft and hard palates as well as in the gingival, supragingival, and subgingival margins. The saliva contains up to 10^8 microbes/mL besides nutrients and components with antimicrobial activities.[3] The oral microbes coexist by forming polymicrobial communities called the "biofilms."[4] The complex equilibrium between these resident species in the oral cavity in a healthy state is "symbiosis." Hence, a normal stable oral microbiome exists in the oral cavity of the human host. The oral microbiome is most abundant in the human body secondary to the gut microbiome. Any imbalance in the oral microbiome could affect the gut also. The objective of this review is to explore the link between the oral microbiome and the health of the gut.

Oral Dysbiosis

Any alteration in the healthy state of the oral cavity by modifiable factors enhances the pathogenicity of the oral microflora, furthering the progression of oral diseases. This state is of oral dysbiosis. These modifiable factors include salivary gland dysfunction resulting in a change in flow and composition of saliva, poor oral hygiene, improper dietary habits like excessive consumption of sugar and carbonated drinks, and smoking.[5] These factors change the natural balance of oral microbiota toward markedly increased numbers leading to oral diseases like caries and periodontitis. A dysbiotic microenvironment can occur in many distinct habitats of the mouth including smooth surface enamel, pits and fissures, proximal sites, exposed root surfaces, resulting in the formation of dental plaque biofilm and initiating "oral dysbiosis." In this state of oral dysbiosis, there is a loss of community balance or diversity in the biofilm, making a single or few species predominating.[6] Oral dysbiosis is generally initiated by *Porphyromonas gingivalis* and *Fusobacterium nucleatum* manifesting in the form of periodontal diseases or even oral cancers.[7] *P. gingivalis* is also associated with a disruption of the immune response. The relation between periodontal disease and systemic diseases like cardiovascular diseases, diabetes mellitus, and respiratory diseases has been well documented.[8] A change in the oral microbiome has been related to the pathogenesis of rheumatoid arthritis, a most frequently occurring autoimmune disorder worldwide.[9] In chronic inflammations like periodontitis, a loss of tolerance against self-antigens perpetuates increased inflammatory events promoting autoimmune disorders.[10] In recent years, oral dysbiosis is now linked to various diseases including that of the gut (Flowchart 1).

Oral Dysbiosis and the Gut

Though the gut has barriers to prevent microbes from entering like acid of the stomach, probiotic bacteria, and immune cells, oral bacteria can get in causing the gut microbiome to become unbalanced and in a state of "dysbiosis" leading to a variety of unhealthy conditions including inflammatory bowel disease (IBD), HIV infection, liver cirrhosis, colon cancer, primary sclerosing cholangitis, and gastroesophageal reflux disease.[11]

In a study on the human microbiome project, it was found that bacteria of the oral cavity and stool overlapped in around half

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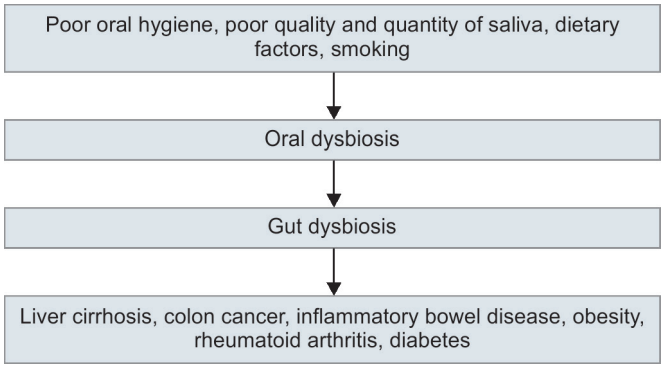
Flowchart 1: Factors showing factors causing oral dysbiosis, which may cause gut dysbiosis leading to gastrointestinal diseases



(45%) of the subjects.[12] Dysbiosis in periodontal disease facilitates systemic dissemination of oral bacteria. A study on animals found a direct effect of oral administration of *P. gingivalis* on the composition of the gut microbiome as well as inflammatory changes in tissues and organs.[13] Oral bacteria like *Actinobacteria*, *Fusobacteria*, *Bacilli*, *Clostridia*, and *Proteobacteria* overcome the gut barrier and can survive in the germ-free gut.[14] These bacteria alter the gut microbiota causing intestinal dysbiosis promoting inflammatory responses leading to colorectal cancer tumorigenesis.[15] This intestinal dysbiosis results in various disorders such as obesity, diabetes, IBD, allergies, autism, colorectal adenomas, and initiating tumorigenesis. *P. gingivalis* has been extensively associated with intestinal dysbiosis in periodontitis. Various studies have shown intestinal dysbiosis induced by gut translocation of oral bacteria. *P. gingivalis*, when orally administered to C57BL/6N mice twice a week for a total of 5 weeks, induced endotoxemia 16Sr RNA pyrosequencing showed an alteration in intestinal microbes with increased oral bacteria mainly *P.gingivalis*.[16]

Intestinal dysbiosis by *P. gingivalis* also aggravates arthritis as shown by Sato et al.[17] When *P. gingivalis* and *P. intermedia* were administered in DBA/1 mice with exponentially collagen-induced arthritis, it led to endotoxemia, inflammation, and disruption of the intestinal barrier, intestinal dysbiosis, and increased inflammatory response leading to aggravation of arthritis. Autoimmune disorders, such as rheumatoid arthritis, are also now being linked to a changed oral and gut microbiome which results in the loss of tolerance against self-antigens and increased inflammatory reactions aggravating arthritis.[9] Oral bacteria-induced intestinal dysbiosis is linked with the development of obesity and insulin resistance.[18] When *P. gingivalis* W 83 was administered orally in C57BL/6 mice twice weekly for a 5 week period, altered intestinal microbiota composition with increased *Ruminococcus* species was observed. The metabolomic study further revealed enhanced biosynthesis of amino acids like alanine, glutamine, histidine, tyrosine, and phenylalanine.[19]

Oral Dysbiosis and Liver

In the association of oral bacteria and gut microbiota, positive changes were seen after patients of nonalcoholic fatty liver disease having periodontitis were given periodontal treatment for 3 months.[20] Reduced serum levels of aspartate transaminase (AST) and alanine aminotransferase (ALT) were also observed. Periodontal treatment in cirrhosis was associated with reduced oral and intestinal dysbiosis.[21] In patients with liver cirrhosis, the gut microbiota is mostly replaced with oral bacteria. Bacterial species identified were mostly *Veillonella* and *Streptococci* that have oral origin suggesting oral bacteria may be related to the pathology of liver cirrhosis.[22] Dysbiosis of the oral microbiome has also been found to be associated with inflammatory reaction with the change in gut flora in patients with autoimmune liver disease (AILD) mainly primary biliary cholangitis (PBC). In patients of AILD having PBC and autoimmune hepatitis, there was a significant increase in *Veillonella* with a concurrent decrease in *Streptococcus* in the oral microbiota, patients with PBC showed significant increases in *Eubacterium*, *Veillonella*, and a significant decrease in *Fusobacterium* in the oral microbiota.[23] There was a positive correlation between the levels of IL-β, IL-8, and immunoglobulin A in saliva and relative abundance of lactobacillus in feces. Dysbiosis of oral microbiota may play a role in changes in gut microbiota in patients with AILD. Studies indicate that oral bacteria are able to disseminate into the colon, particularly *F. nucleatum* and *P. gingivalis* in conditions like periodontitis.[24]

Recent studies have identified oral bacterial species that were previously uncultivable like *Desulfobulbus*, *Synergites*, *Selemonas*, *Saccharibacteria,* and *Filifactor alocis*.[25] Still 20 to 60% of the bacterial species identified in the oral cavity are uncultivable.[26] *F. alocis* cocultured with *P. gingivalis* shows increased invasiveness for HeLa cells.[27] It has been identified now as a potential pathogen for periodontitis. This synergism could trigger inflammatory responses affecting the gut also, though no study has been reported so far. Additionally, many oral bacteria like *P. gingivalis* cause immune subversion.[28] This could possibly be in synergism with bacteria like *F. alocis*. Newer techniques like proteome analysis have contributed to the understanding of the process of oral dysbiosis by revealing the molecular mechanisms and proteases expressed by the oral bacteria. The oral proteins and their functions in relation to their effect on the gut need to be determined.

Oral Intervention in Systemic Diseases

It has been seen that people having good oral care require fewer healthcare expenditures.[29] Improving the oral hygiene of institutionalized patients in the intensive care unit has shown a positive impact on their systemic health.[30] Periodontitis and poor oral hygiene are linked with the development of coronary heart disease, and improving oral hygiene has shown to have a positive impact on the outcome of coronary heart disease.[31] In diabetes mellitus, its relationship with oral health is bidirectional, hyperglycemia negatively affects oral health and bad oral health can impact glycemic control negatively.[32] Treatment of periodontitis in diabetic patients has shown better control of blood glucose levels.[33]Oral hygiene has been linked to pregnancy and low-birth-weight infants. The change in oral flora in periodontitis has more anaerobes which initiate the inflammatory process resulting in myometrial contractions and preterm birth of the infant.[34]Treatment of periodontitis in pregnant women has shown a positive outcome of fetus health.[35] The oral bacteria in the dental plaque formed in oral diseases activate the proinflammatory cytokines produced by the monocytes and macrophages which can enter the systemic circulation and contribute to intestinal inflammation.[36] A recent meta-analysis has shown a significant association of periodontitis with IBD, that is, Crohn's disease and ulcerative colitis.[37] Oral intervention in gut diseases has not been explored so far.

Conclusion

The oral microbiome and the gut are linked as shown by several studies. Oral bacteria particularly *P. gingivalis* can cause intestinal dysbiosis by breaching the gut barrier. The importance of oral hygiene cannot be ruled out to maintain gut health. The prevention of colonization of the oral cavity by pathogens through regular oral care might have a positive impact on intestinal inflammation. However, this area of research needs further investigations on large patient size.

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