Journal of Surgery
McMillan A and Brooks AE. J Surg 9: 1992
www.doi.org/10.29011/2575-9760.001992
www.gavinpublishers.com
Commentary

Oral Microbiome Dysbiosis and Surgical Outcomes

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Citation: McMillan A, Brooks AE (2024) Oral Microbiome Dysbiosis and Surgical Outcomes. J Surg 9: 1992 DOI: 10.29011/2575-9760.001992

Received Date: 03 February, 2024; **Accepted Date:** 07 February, 2024; **Published Date:** 09 February, 2024

Abstract

The oral microbiome is complex with a diverse composition of bacteria, viruses, and fungi. The microbiota can be affected by both genotypic and environmental factors such as stress and infection. Our published, preliminary data titled, "The Effect of Physical and Psychological Stress on the Oral Microbiome" indicates that stress can impact the composition of the oral microbiome which supports the current understanding that microbiome dysbiosis can predispose to oral and systemic diseases. [1] Recent research has emerged on the effects of gut microbiota dysbiosis and postoperative outcomes; however, oral microbiota dysbiosis in the context of postoperative complications remains to be explored.

Keywords: Dysbiosis; Gut microbiome; Operative outcomes; Oral microbiome

Introduction

The oral microbiome is complex with a diverse composition of bacteria, viruses, and fungi. There are 6 broad bacterial phyla that comprise the core oral microbiome, including *Firmicutes, Actinobacteria, Proteobacteria, Fusobacteria, Bacteroidete*s, and *Spirochetes*. [2] However, the oral microbiome also has a variable aspect that can be influenced by genotypic and environmental factors such as age, genetics, stress, smoking, and infection. [3,4] If the dynamic balance of the microbiota is disturbed, beneficial microbiota might be impeded by the proliferation of more aggressive pathogenic species with disease-causing capabilities. [5] Although there are still many unknowns regarding oral microbiome composition and its effects on human health, literature has begun to show that oral microbiome, which is easier to obtain than gut microbiome, dysbiosis has the potential to cause oral and systemic disease, such as cardiovascular, neurodegenerative and respiratory diseases. [6] In our research on the effects of stress on oral microbiome composition, the preliminary data indicated that stress can impact the composition of the oral microbiome and cause an increase in microbiota that are associated with various pathogenic potential. [1] The impact of the oral microbiome on both mental and physical health is not a completely novel concept. However, this is a disconnect. While current literature convincingly suggests that gut microbiome dysbiosis may impact postoperative outcomes, oral microbiome dysbiosis in the context of postoperative complications remains to be explored.

Oral Microbiome Dysbiosis and Systemic Health

The oral microbiota have become well known for their role in in-situ or distant tumor progression due to microbial dysbiosis, colonization, and translocation. [7] *Porphyromonas gingivali* and *Fusobacterium nucleatum* are two examples of oral microbiota that have been linked to carcinogenesis. [7] *Fusobacterium nucleatum* from the oral cavity is considered a critical factor in colorectal cancer development and *Porphyromonas gingivalis* has been strongly associated with pancreatic cancer. [7] In a meta-analysis, six studies with a total of 863 pancreatic cancer cases and 906 controls determined a total of 12 to 17 species and clusters of bacteria such as *Porphyromonas, Fusobacteria*, *Bacteroidetes*, *Streptococcus* and *Pasteurellaceae*, were correlated with pancreatic cancer. [7,8] Further, in a prospective study with 80 patients who were suspected to have a pancreatic tumor prior to biopsy or surgery found

Streptococcus and *Leptotrichina* was associated with a higher risk of pancreatic cancer. [9] Although microbiota that is found in the oral microbiome has been detected in pancreatic tumors, the cause for this shift in cancer patients remains unknown due to the multitude of genetic and environmental factors that play a role in the oral microbiome composition. [10] Additionally, pancreatic

tumors contain their own microbiome. Recent studies have shown that pancreatic tumors contain select bacteria that are significantly increased than those found in the oral or gut microbiome. [11] An increase in intra-tumoral *Mycoplasma* generates resistance to the common chemotherapy gemcitabine used to treat pancreatic cancer. [12] Whereas a greater abundance of *Pseudoxanthomonas*, *Saccharopolyspora*, and *Streptomyces* predict a greater long-term survival. [12] The current proposed mechanisms of systemic inflammation, direct inoculation, transient bacteremia or analogous environments causing oral microbiome dysbiosis and subsequently pancreatic carcinogenesis has not yet been confirmed. [10] The effects of socioeconomics, genetics, race, ethnicity, age and smoking on the oral microbiome can also play a role in systemic health as shown for pancreatic carcinogenesis, posing a challenge to demonstrate a causal link between oral microbiome dysbiosis predisposing patients to pancreatic cancer. [10] Despite promising prospects for utilizing oral microbiome dysbiosis in precision medicine, the review highlighted multiple research gaps, including understanding oral microbiome effects on postoperative outcomes.

Microbiome Dysbiosis and Postoperative Outcomes

The oral cavity and the gut are the two largest microbial environments. [13] Although the oral cavity and gut are connected anatomically with one another, the microbiome profiles are distinct due to the oral-gut barrier (Figure 1). [13] The oral microbiome can translocate to the gut through oral-gut barrier disruption from factors such as decreased bile acid pool, gastric acid and mucosal integrity. [14] The gut microbiota can translocate to the oral cavity with both intra- and inter-personal manners, such as contaminated foods or fluids. [14] The implication of the translocation of microbiota between the oral cavity and the gut in pathogenesis of cancer has been understudied to date; however, gut microbiome dysbiosis and its effects on postoperative outcomes is becoming more clear. A study on the impact of gut microbiome dysbiosis on postoperative complications in visceral surgery determined the occurrence of anastomotic leakage is highly suggested to be related to gut microbiome composition. [15] Additionally, a review on gut microbiota in the setting of gastrointestinal reconstructive surgery concluded gut microbiota dysbiosis can lead to the postoperative complications of pouchitis, malabsorption and diarrhea but also increase the levels of *Faecalibacterium prausnitzii* that helps to reduce inflammation in the gastrointestinal tract and improve postoperative healing.[16] Some of the pathogenic bacteria that increase significantly after gastrointestinal surgery are *Enterobacteriaceae, Enterococcus, Staphylococcus*, and *Pseudomonas*. [16] Postoperative complications after gastrointestinal surgery has been shown to alter the gut microbiome due to factors such as the stress of surgery, tissue ischemia, exposure to oxygen, types of reconstruction and neoadjuvant chemotherapy. [17] Surgical stress has been shown to increases levels of *Escherichia* and *Enterococcus*, ischemia-reperfusion injury increases the abundance of *Escherichia* species in the gut, and in colorectal tumor samples the presence of *Fusobacterium nucleatum* is associated with a decreased overall survival rate. [16] Recent studies have shown that in obesity, the gut microbiome has decreased microbial richness associated with increased body weight. [18,19] In fact, gut microbiome changes post-bariatric surgery has been proposed as one of the beneficial outcomes of the procedure. [18] The alteration in microbiota composition after bariatric surgery has been shown to not only help with weight loss but in maintaining the weight lost. [20] Bariatric surgery increases microbial richness and *Streptococcus* species and causes a decrease in levels of bacteria that have a negative correlation with the satiety hormone leptin such as *Bacteroides, Clostridium,* and *Prevotella*. [20] Although the causative role of the gut microbiome on surgical outcomes is known, additional studies to serially track the composition pre and post-operatively is warranted to create personalized bowel preparation and guide postoperative management for patients [21].

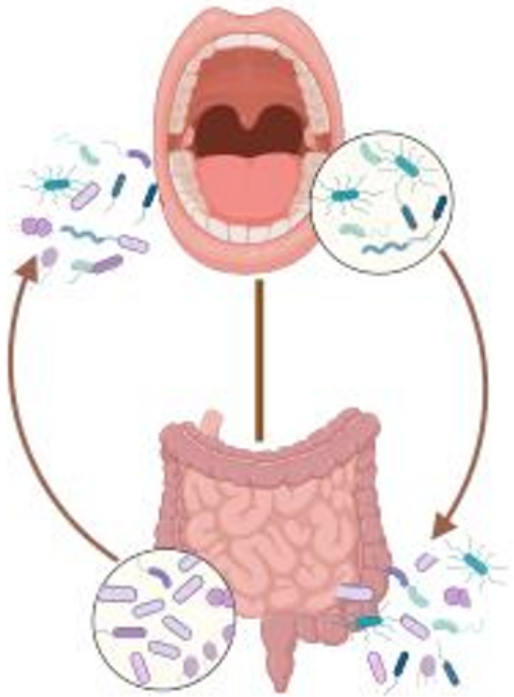

Figure 1: Created with BioRender.com. The oral cavity and the gut are the two largest microbial environments. [13] The oral cavity and gut are connected anatomically with one another; however, the microbiome profiles are distinct due to the oral -gut barrier.[13] Current studies have shown the oral and gut microbiomes can translocate amongst each other leading to dysbiosis that can promote disease deposition [14].

Discussion

The development of next-generation sequencing has allowed the composition of the oral microbiome to be more thoroughly analyzed and compared between healthy and non-healthy indivudals. [22] As the composition of a healthy microbiome is decoded, its potential integration into personalized medicine to prevent and treat disease is promising. The importance of the oral microbiome in predicting the development of oral or systemic diseases has been recognized but research in oral microbiome dysbiosis and postoperative outcomes is lacking.

This could be attributed to limited larger prospective studies with well-defined cohorts to identify associations between microbiome dysbiosis and surgical complications or the lack of pre-and post-operative screening for dysbiosis. However, the evidence for the association between microbiome dysbiosis and surgical outcomes as well as systemic health is strengthening and should continue to be explored. As oral microbiome disease associations continue to be revealed, modifying the microbiome to prevent or treat disease disposition is the next step in incorporating the oral microbiome into precision medicine [23].

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