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# THE EFFECTS OF ORAL MICROBIOME ON SYSTEMIC HEALTH

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## ABSTRACT

The oral microbiome, a diverse community of microorganisms, plays a critical role in maintaining oral and systemic health. Disruptions in this microbiome, known as dysbiosis, are associated with oral diseases like dental caries and periodontitis, as well as systemic conditions such as diabetes, cardiovascular disease or cancer. The oral microbiota varies across individuals and within different regions of the oral cavity, influenced by factors like oxygen levels, nutrient content, and immune response. Emerging research highlights the microbiome's potential role in conditions like stunting in children and neurodegenerative diseases. The oral microbiome is also linked to systemic diseases. For example, oral bacteria have been detected in the lungs of cystic fibrosis patients and are associated with respiratory infections like pneumonia. In gastrointestinal diseases, oral microbiome imbalances are linked to conditions such as inflammatory bowel disease (IBD) Additionally, endocrine disorders like diabetes and obesity show strong correlations with oral microbiome changes. Maintaining a balanced oral microbiome is crucial for preventing and managing these diseases. Treatment strategies must focus on preserving the microbiome's integrity while targeting pathogenic bacteria. As research continues to uncover the complex relationships between oral health and systemic diseases, interdisciplinary collaboration between dentistry and medicine will be key to advancing preventive and therapeutic approaches.

**KEYWORDS:** Oral microbiome, systemic disease, health, prevention.

## INTRODUCTION

The new millennium has brought forth extraordinary opportunities for dentistry, encompassing technological advancements, precision science, and enhanced professional connectivity and collaboration. However, significant challenges persist in achieving individual and population-level oral health. The burden of oral diseases remains one of the most prevalent global health conditions and is projected to increase in the absence of a sufficiently trained and equitably distributed workforce.[1]

The oral cavity is defined as a reflection of general health. According to Seymour, "You cannot have general health without oral hygiene" statement that are widely accepted. The oral cavity is the common ground for dentistry and medicine, which are professions aimed at enhancing patient health and quality of life.[2] Both fields believe that the interventions made will have a positive impact on the patient's well-being, health, and quality of life. It is estimated that more than 100 systemic diseases and over 500 medications cause oral findings and symptoms commonly seen in elderly individuals. It has been reported that Hippocrates treated diseases by extracting infected teeth. However, the relationship between oral diseases and systemic diseases was not well understood until recently. This lack of understanding of these processes has slowed the interaction and collaboration between dentistry and medicine. Although bidirectional relationships between oral health and systemic diseases are better understood over time, more research in this area is needed. As the effects of oral health on systemic health are clarified and proven, there should be closer relationships between dentistry and medical professionals. In any case, the impact and importance of oral health on general health have become focal points for many practitioners in the United States, as well as the World Health Organization.[3]

The oral cavity is colonized by a diverse array of microorganisms, commonly referred to as the oral microbiome. Research on the oral microbiome has heightened awareness of the critical balance between the host and the microbial species that coexist within it. This balance is of vital importance for maintaining oral health throughout all stages of life. It is now recognized that changes in the oral microbiota significantly contribute to the development and progression of various oral diseases.[4-5] The oral microbiome is of great importance to health, as it can lead to both oral and systemic diseases. It exists within biofilms throughout the oral cavity, creating an ecosystem that sustains health in a balanced state. However, disruptions in this balance can allow pathogenic organisms to emerge and cause disease. Disturbances in the delicate balance of the microbiome, known as dysbiosis, have been linked to oral diseases such as dental caries and periodontitis, as well as noncommunicable conditions like diabetes and cardiovascular disease. Emerging evidence suggests that the oral microbiome may also contribute to the development of stunting in children.[6]

## Oral Microbiome

The oral microbiota encompasses various niches and environmental interactions, including the teeth, dental plaque, periodontal spaces and pockets, the dorsum of the tongue, and other mucosal surfaces. The oral microbiota is composed of archaea, fungi, protozoa, and predominantly bacteria. Through 16S rRNA profiling of a healthy oral cavity, resident bacteria have been classified into six broad groups. Firmicutes, Actinobacteria, Proteobacteria, Fusobacteria, Bacteroidetes, and Spirochaetes collectively constitute 96% of the total oral bacteria. Most of these bacterial species in the oral cavity are defined as members of the 'normal microbiota' and generally exhibit commensal characteristics. The state of oral health is inherently associated with the presence of an ecologically balanced and diverse microbiome that engages in mutual relationships with the host. Biodiversity is essential for health, as it sustains a mutually beneficial relationship between the host and the microbiome.[7-8]

The oral microbiome exhibits variations from person to person and even within different regions of the oral cavity in the same individual. To understand this diversity and dynamic relationship, the oral cavity can be examined as distinct ecosystems based on morphological and physiological differences. As development progresses, various habitats begin to emerge within the oral cavity. Depending on different anatomical and physiological structures, oxygen levels, nutrient content, temperature, and the host immune response, certain groups of microorganisms become more dominant in these habitats.[9-10]

## The Relationship of Oral Microbiome with Systemic Diseases

It has long been known that the oral microbiome serves as a reservoir for infections in other parts of the body. The pathogenicity of the oral microbiota should not be thought to be limited solely to the oral cavity. While initial theories suggested focal infection-based dissemination, evidence-based studies in the current concept have demonstrated that these diseases are multifactorial conditions with multiple risk factors, rather than simple infections. For example, periodontitis can be considered a manifestation of systemic diseases and genetic disorders such as diabetes mellitus, Papillon-Lefevre syndrome, hypophosphatasia, neutropenia, Chediak-Higashi syndrome, leukemias, histiocytosis, acrodynia, AIDS, Down syndrome, and Ehlers-Danlos syndrome. Additionally, Streptococcus gordonii, a pioneer colonizer of the oral flora and commensal microorganisms, is an opportunistic pathogen associated with endocarditis.[11-12] Below, these and similar diseases are classified and listed.

### Respiratory System Diseases

When examining the respiratory system and lungs, oral bacteria have been detected in the lungs of patients with cystic fibrosis. Bacteria colonizing the oropharynx, including Streptococcus pneumoniae, Haemophilus influenzae, and Mycoplasma pneumoniae, are recognized as sources of community-acquired pneumonia. In one study, individuals hospitalized due to pneumonia were found to have periodontal pathogens such as P. gingivalis, F. nucleatum, Prevotella oralis, Campylobacter gracilis, Fusobacterium necrophorum, and Aggregatibacter actinomycetemcomitans, in addition to the pathogens causing the disease. Furthermore, a study involving hospitalized children and adults who received periodontal treatment and maintained good oral hygiene reported a reduction in the incidence of pneumonia.[13-14]

### Gastrointestinal System Diseases

With the increase in research, it has once again been proven that gastrointestinal system diseases are associated with the oral microbiome. Inflammatory Bowel Disease (IBD) is one of the earliest diseases to be linked. Today, there is compelling evidence for the relationship between the oral microbiome and liver cirrhosis and gastrointestinal cancers. Compared to healthy individuals, children with celiac disease on a gluten-free diet have a less diverse salivary microbiome and show an increase in microorganisms associated with caries (e.g., Rothia, Porphyromonas, Gemellaceae, Prevotella, Streptococcus, and Lachnospiraceae).[15-16] In a study conducted by Docktor et al., it was shown that in children with Crohn's disease, bacterial diversity in tongue colonization was significantly reduced, and Fusobacterium and Firmicutes species were the most altered.[17] Therefore, the observation of these oral findings, which reflect changes and dysbiosis in the intestinal mucosa of Crohn's patients, has emphasized the importance of developing diagnostic tools for systemic diseases based on oral biomarkers. However, it remains unclear whether this pronounced dysbiosis leads to a greater susceptibility to oral diseases such as caries in Crohn's patients.[15-17]

### Nervous System Diseases

Alzheimer's disease is a chronic, neurodegenerative disorder that leads to progressive cognitive impairment and is the leading cause of dementia in individuals over the age of 65. It is known that the disease arises from inflammation caused by infections in the central nervous system due to viruses, particularly Human Herpes Simplex Virus 1 (HSV-1), and bacteria such as Helicobacter pylori, Chlamydophila pneumoniae, and Borrelia burgdorferi, or from the effects of auto-immune antibodies

targeting neural structures. Periodontal pathogens like Treponema denticola and Porphyromonas gingivalis have been identified in the cerebrospinal fluid and neuronal ganglia of these patients. These pathogens, which also play a role in the aetiology of periodontal disease, have been argued to contribute to the onset or progression of Alzheimer's disease. In Parkinson's patients, it has been observed that the oral bacterial microbiota primarily consists of potential opportunistic pathogens such as Prevotella, Prevotellaceae, Veillonella, Solobacterium, Veillonellaceae, Lactobacillaceae, and Coriobacteriaceae, while species like Capnocytophaga, Rothia, Kingella, Leptotrichia, Actinomyces, and Leptotrichiaceae are found in lower proportions in these patients. Maintaining good oral health should be recognized as a potential preventive measure or risk-reducing strategy against neurodegenerative diseases.[18-20]

**Endocrine System Diseases**

The progression and prognosis of endocrine system diseases are closely related to the internal environment of the individual. Oral microbiomes influence and can be influenced by this internal environment, enabling us to identify correlations between endocrine system diseases and oral microbiomes. Diabetes, obesity, and pregnancy complications have been proven to be associated with oral microbiomes. [21-22] Diabetes mellitus is characterized by hyperglycemia, inflammation, and high oxidative stress, which can lead to systemic complications. Periodontitis is known as a significant complication of diabetes, and studies have shown that the periodontal microbiome in diabetic individuals differs from that of normoglycemic individuals. It has also been demonstrated that predominantly gram-negative species causing periodontal diseases are recognized by the body as an infection, thus linking periodontal diseases to diabetes mellitus through the mechanism of insulin resistance. In individuals with Type I diabetes, an increase in the severity of periodontal diseases has been observed across various age groups. [23-24] Obesity has also been found to be associated with the oral microbiome. Given the widely recognized inflammatory nature of obesity, Goodson et al. identified bacterial changes in the saliva of overweight women. Bacterial species can serve as biological indicators of overweight status, and oral bacteria may contribute to the pathology leading to obesity.[25] The oral microbiota is known to be associated with intrauterine colonization in the fetus. Studies have shown that adverse pregnancy outcomes, such as preterm birth, low birth weight, and neonatal sepsis, are more common in women with periodontal diseases. Fusobacterium nucleatum is the most significant periodontal pathogen responsible for these complications during pregnancy. F. nucleatum is a highly prevalent oral microorganism associated with both periodontal disease and pregnancy complications. This bacterium has been isolated in amniotic fluid, cord blood, and the fetus. Additionally, Porphyromonas gingivalis, Prevotella intermedia, Tannerella forsythia, and Treponema denticola have been shown to be other periodontopathogens contributing to pregnancy complications.[26]

**Immune System Diseases**

The oral microbiome is associated with human immune system diseases such as human immunodeficiency virus (HIV) and rheumatoid arthritis (RA).

In children infected with HIV, the presence of a generally weakened immune system compromises oral health. [21]

Rheumatoid arthritis (RA) is an autoimmune disorder associated with increased mortality due to cardiovascular and other systemic complications. However, the aetiology of RA remains unexplained. While studies on genetic predisposition to RA have implicated genes such as HLA-DRB1, TNFAIP3, PTPN22, and PADI4, environmental factors have also been shown to contribute to disease pathogenesis,

and microbial triggers may play a role in RA.[27] In one study, children with juvenile idiopathic arthritis (average age of 13) exhibited an increased antibody response to Porphyromonas gingivalis, one of the main species associated with periodontal diseases, and showed higher symptoms of periodontal disease, similar to adults with typical rheumatoid arthritis.[28] In another study, dysbiosis detected in the gut and oral microbiomes of RA patients partially improved after treatment. Changes in the gut, dental, and salivary microbiomes distinguished RA patients from healthy individuals, and this could be used to evaluate treatment responses. Specifically, Haemophilus spp. was not isolated in RA patients across all three sites and showed a negative correlation with serum autoantibody levels, while Lactobacillus salivarius was detected at high levels in RA patients across all three sites and was present in increased amounts in highly active RA cases. Functionally, the redox environment, transport, and metabolism of iron, sulphur, zinc, and arginine were altered in the microbiomes of RA patients. The use of microbiome colonization for prognosis and diagnosis may be recommended.[21]

### Cardiovascular System Diseases

Cardiovascular system diseases (CVD) are a highly prevalent group of diseases, including congestive heart disease, cardiac arrhythmias, and coronary artery diseases, which rank among the leading causes of mortality.[29-30] Studies have shown a relationship between tooth loss and cardiovascular diseases. Additionally, dental caries and periodontitis, which lead to tooth loss, have been reported to increase the risk of ischemic stroke, with this risk being 400 times higher in individuals with periodontitis compared to those with widespread dental caries.[31] DNA samples from oral pathogens such as Tannerella forsythia, Fusobacterium nucleatum, Prevotella intermedia, Porphyromonas gingivalis, and Aggregatibacter actinomycetemcomitans, which are implicated in periodontal diseases, have also been identified in carotid atheromas. This finding is considered evidence of bacterial translocation. Compared to healthy individuals, both symptomatic and asymptomatic coronary heart disease patients have shown an increase in the periodontal pathogen Aggregatibacter actinomycetemcomitans in their saliva.[32]

### Neoplastic Diseases

A tumor is the abnormal growth or proliferation of tissue. It is believed that microbial-induced inflammation plays a role in approximately 15-20% of tumors observed in humans.[33] Some bacterial infections have been shown to be associated with colon, gallbladder, prostate, lung and oral cancers.34 The risk of gastrointestinal cancer is increased in individuals with conditions caused by oral bacteria, periodontal disease, or tooth loss.[35] When tumor tissues are examined, 52 different bacterial phylotypes have been isolated, including species such as Proteobacteria, Fusobacterium, Streptococcus, Prevotella, and Veillonella, which can adapt to the acidic and hypoxic environment of tumor tissue. Components of the oral microbiota may also be associated with tumors in distant regions. In a study of individuals with pancreatic cancer, levels of Streptococcus mitis and Neisseria elongata were found to be reduced in saliva. However, it remains unclear whether this result has diagnostic value or what the exact mechanism is. In recent literature, some studies have explored the potential relationship between diet, pancreatic cancer, colorectal cancers, and the oral microbiota, but sufficient evidence has not yet been established.[36]

## CONCLUSION

Imbalances in the oral microbiome have been associated with various diseases, particularly periodontitis. However, it is not yet fully understood whether these imbalances cause diseases or if diseases trigger the imbalances. Research has shown that certain bacteria increase or decrease under specific conditions, but the causal relationship behind these changes remains unclear. These two factors (imbalance and disease) may reinforce each other, creating a vicious cycle: the imbalance accelerates disease progression, while the disease further exacerbates the imbalance. Therefore, it is crucial to investigate the causal relationships between the oral microbiome and diseases in depth. Future research in this field could reveal the connections between specific diseases and oral microbiome imbalances, enabling the development of more effective prevention and treatment strategies.

In treatment approaches, it is equally important to preserve the overall structure of the oral microbiota as it is to inhibit the growth of pathogenic bacteria. For example, methods such as scraping the oral microbiota film can disrupt the entire ecosystem. Similarly, treatments targeting pathogenic bacteria may also inhibit the growth of beneficial bacteria. Therefore, during treatment, it is essential to focus on limiting the growth of pathogenic bacteria while maintaining the integrity of the oral microbiota. Additionally, supportive treatment measures should be implemented to enhance the stability and resilience of the oral microbiome. These approaches can promote the development of a healthier oral microbiome while reducing the colonization of other pathogens.

**Conflict of Interest:** The authors declare no competing interests.

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