Review Article

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Association of Oral Microflora with Various Systemic Disorders – A Review

Abstract:

Emerging evidence suggests that the oral microbiome plays a pivotal role not only in maintaining oral health but also in the etiology and progression of a wide range of systemic disorders. This review presents findings from recent literature examining the correlation between oral microbial dysbiosis and various systemic diseases—including cancer, obesity, cleft lip and palate (CLP), pulmonary conditions such as pneumonia and COPD, cardiovascular diseases, and neurogenic disorders like Parkinson's disease (PD). The mechanisms linking oral microbiota to systemic pathologies primarily involve chronic inflammation, immune dysregulation, metabolic disruption, and microbial translocation. In cancer and cardiovascular diseases, key oral pathogens have been implicated in tumorigenesis and atherogenesis, respectively. In obesity and metabolic syndrome, they contribute to systemic inflammation and insulin resistance. In CLP, impaired microbial balance worsens healing outcomes, while in pulmonary diseases, aspirated oral bacteria act as reservoirs for respiratory pathogens. In PD, oral dysbiosis may exacerbate neuroinflammation and increase the risk of aspiration pneumonia. These associations underscore the diagnostic and therapeutic potential of oral microbiota, positioning them as viable targets for early intervention, risk stratification, and management of systemic conditions.

Key-words: .....

Introduction:

The human oral cavity is home to a complex and dynamic microbial community that extends its influence well beyond the mouth. Harbouring over 700 microbial species,[1] the oral microbiota is traditionally studied in the context of dental diseases. However, growing evidence reveals strong correlations between oral dysbiosis and systemic disorders.[2] From cardiovascular disease to cancer and neurodegeneration, the mouth may serve as both a mirror and a contributor to overall health. This article explores the evolving role of oral microflora in the pathogenesis of various systemic diseases, including:

1. **Cancer**
2. **Obesity**
3. **Cleft Lip and Palate**
4. **Pulmonary Disease**
5. **Cardiovascular Disease**
6. **Parkinson's Disease**

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1. Cancer:

Over the years, epidemiological research has identified several well-known risk factors for cancer, including age, heredity, diet, tobacco use, chronic viral infections, and inflammation. Due to the strength of these associations, there was limited consideration of other possible contributors like bacterial infections. However, pivotal discoveries in the early 1990s recognized *Helicobacter pylori* as a causative agent for gastric cancer, shifting the understanding of microbial involvement in oncogenesis. In 1994, the World Health Organization officially listed *H. pylori* as a definite cause of

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human cancer. Since then, evidence has continued to grow, supporting the association between various microorganisms, including oral microbes, and cancer development.[3]

Oral bacteria such as *Fusobacteriumnucleatum*, *Porphyromonasgingivalis*, and *Treponemadenticola* are commonly identified in cancerous tissues and are believed to contribute to cancer progression through multiple pathways.[3] These pathogens are known to stimulate chronic inflammation by triggering immune responses, leading to the secretion of pro-inflammatory cytokines like IL-6 and TNF-α, which assist in tumor initiation and growth.[3] Additionally, bacterial by-products like hydrogen sulfide and butyrate interfere with the cell cycle and promote DNA damage.[4]

Studies have shown that cancer patients often exhibit higher levels of anaerobic bacteria such as *Prevotella* and *F. nucleatum*, which aid immune evasion and tissue invasion.[5] Moreover, oral microbes may affect gene regulation through epigenetic mechanisms, either activating oncogenes or silencing tumor suppressor genes.[6] The pro-inflammatory microenvironment induced by these bacteria, as well as therapeutic strategies that aim to restore microbial balance, are areas of growing interest in cancer prevention.[7] Altogether, these findings underscore the active role of oral microbiota in cancer biology and their potential as tools for early diagnosis and intervention.

2. Obesity:

Obesity is recognized as a chronic disease that contributes to a wide range of conditions, including type 2 diabetes, cardiovascular disease, hypertension, and certain cancers. It also has adverse effects on periodontal health. The pro-inflammatory cytokines produced by adipose tissue are thought to initiate systemic processes that link obesity and periodontal diseases.

Metabolic syndrome, a cluster of metabolic abnormalities that increase the risk for type 2 diabetes and heart disease, has been found to be more prevalent in individuals with moderate to severe periodontitis than in those with none or mild forms. A cohort study also observed that deeper periodontal pockets and greater loss of alveolar bone were correlated with chronic metabolic syndrome.[8] The proposed mechanism includes impaired insulin sensitivity, decreased antioxidant potential, and elevated oxidative stress, forming a potential bi-directional relationship between metabolic syndrome and periodontitis.[8]

Endotoxins like LPS released from *P. gingivalis* and *F. nucleatum* are capable of activating inflammatory pathways that involve cytokines such as IL-1β and TNF-α, disrupting insulin signalling and contributing to fat cell dysfunction.[8] 16S rRNA analysis comparing oral microbiota from healthy, obese, and diabetic individuals has revealed that inflammatory bacteria like *Prevotella*, *Leptotrichia*, and *Porphyromonas* are more abundant in obese individuals, promoting systemic inflammation and insulin resistance.[9] Another study reported the presence of *Selenomonasnoxia* in nearly all obese children sampled, suggesting its possible involvement in metabolic regulation through mechanisms like nutrient absorption and hormonal signaling.[10] Additionally, microbial imbalance in the oral cavity may alter taste perception, leading to increased preference for sugary or fatty foods, thereby intensifying weight gain.[11] Oral microbes can also influence gut microbiota through saliva ingestion, further amplifying systemic effects. These findings support the hypothesis that oral dysbiosis may contribute to the development and maintenance of obesity and related disorders, making oral microbiota a potential target for intervention.

3. Cleft Lip And Palate:

During the early stages of gestation, the successful fusion of orofacial structures is critical for normal development of the lip and palate. A failure in this fusion process results in orofacial clefts, presenting as cleft lip, cleft palate, or both. Affecting approximately 1 in 700 live births, cleft lip and/or palate (CL/P) ranks among the most common congenital craniofacial anomalies.[12]

Individuals with CLP show notable changes in their oral microbiota due to differences in anatomy, compromised oral function, and frequent surgical treatments. Next-generation sequencing techniques have revealed increased levels of anaerobic bacteria such as *P. intermedia* and *F. nucleatum* in these patients, suggesting a need for tailored microbial therapies.[12] Elevated levels of disease-associated species like *F. nucleatum*, *S. mutans*, and *P. gingivalis* contribute to ongoing inflammation and delayed wound healing.[13] These bacteria can activate inflammatory cytokines, disrupting tissue regeneration.[13] Moreover, immune system imbalance in CLP patients—specifically a shift in the ratio of pro- to anti-inflammatory cytokines—complicates healing and raises the risk of infection.[14] Pathogens in cleft-affected areas are also associated with a higher likelihood of post-operative complications such as wound breakdown and localized infections.[15]

The inclusion of oral microbiota profiling in CLP management has been recommended to allow early detection of dysbiosis and guide pre-surgical treatment planning.[16] These insights emphasize the importance of early microbial intervention in improving surgical outcomes and overall oral health in individuals affected by CLP.

4. Pulmonary Diseases

Pulmonary disorders can be broadly categorized into infections, malignancies, and diseases that obstruct airflow. This section primarily focuses on pneumonia and chronic obstructive pulmonary disease (COPD).

Pneumonia, an inflammatory condition of the lungs, is typically caused by microbial infections.[17] One common complication observed in patients on mechanical ventilation is ventilator-associated pneumonia (VAP), defined as a severe lung infection that occurs in individuals requiring respiratory support.[17] COPD, on the other hand, is a chronic obstructive lung condition characterized by long-term airflow limitation, breathlessness, persistent cough, and sputum production.

Research exploring the connection between oral health and respiratory diseases has indicated that bacteria commonly found in dental plaque and saliva may serve as a source of infection, potentially increasing the risk for pneumonia.[18] The pathogens responsible for community-acquired pneumonia frequently overlap with those present in the oropharyngeal region, including *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, *Porphyromonasgingivalis*, *Bacteroidesgracilis*, *Eikenellacorrodens*, *Fusobacteriumnucleatum*, *Actinobacillusactinomycetemcomitans*, *Peptostreptococcus*, *Clostridium*, and *Actinomyces*. In contrast, nosocomial pneumonia tends to involve organisms like *Pseudomonas aeruginosa* and *Staphylococcus aureus*, which are not typical residents of the oral cavity.[19]

This overlap suggests that the oral cavity could serve as a reservoir for respiratory pathogens, although direct evidence linking periodontal disease specifically to pneumonia remains limited.[18] However, further support for this association comes from studies evaluating the impact of oral hygiene interventions on pneumonia risk. Various preventive measures—such as chlorhexidine rinses, povidone iodine, denture cleaning, and mechanical techniques like toothbrushing and professional scaling—have been shown to reduce pneumonia incidence. Mechanical plaque removal has proven effective in reducing pneumonia among non-ventilated patients, although this benefit has not been consistently observed in ventilated individuals.[18,20]

Several biological mechanisms have been proposed to explain how oral microorganisms may contribute to respiratory infections:

1. Aspiration of oral bacteria into the lungs,
2. Modification of respiratory mucosal surfaces by enzymes from periodontal pathogens, promoting bacterial adhesion
3. Destruction of protective salivary pellicles that inhibit pathogen colonization,
4. Systemic cytokines originating from periodontal tissues that alter the respiratory epithelium, making it more susceptible to infection.[19]

As for COPD, although the evidence linking it to periodontal disease is not as robust, some studies have suggested that individuals with significant alveolar bone loss, dental plaque accumulation, and loss of clinical attachment may have an increased risk for COPD.[18]

To summarize, there is moderate evidence linking poor oral hygiene—specifically the presence of plaque and dental caries—to a heightened risk of pneumonia. The association between periodontal disease and COPD is less certain but still suggestive. Strong evidence supports the effectiveness of maintaining good oral hygiene to lower pneumonia risk in both hospitalized and community-dwelling populations.

5. Cardiovascular Diseases:

Atherosclerotic cardiovascular diseases (ACVD) refer to a group of diseases that comprise of fatal and non-fatal coronary heart disease (angina, myocardial infarction), ischemic cerebrovascular disease (stroke/TIA) and peripheral arterial disease.[21] Periodontitis has been associated with increased risk for various measures of ACVD independent of established cardiovascular risk factors.[21]

Substantial data was found to support that periodontitis can contribute to systemic levels of inflammatory mediators and markers associated with increased risk for CVD. [22] Inflammation plays a significant role in the pathogenesis of atherosclerosis, and the contribution of bacteria as initiators of inflammation has been established since long. Considering this, inflammation is being seen as the plausible link between periodontitis and atherosclerotic disease, with recent findings proposing that a local inflammatory nidus can increase vascular inflammation systemically.[23]

Accumulating evidence indicates that the incidence of ACVDis significantly higher among individuals with periodontitis or compromised periodontal health, in comparison to those without periodontitis or with more favorable periodontal status. This association appears to be independent of numerous established cardiovascular risk factors.[24]

One of the most biologically plausible mechanisms linking periodontitis to ACVD involves chronic oral infection facilitating the translocation of bacteria (or their by-products) into the bloodstream. This microbial entry triggers the host's inflammatory response through several interconnected pathways, including:

1) Elevated levels of systemic pro-inflammatory mediators;
2) Activation of both innate and adaptive immune systems;
3) Increased expression of thrombotic and hemostatic markers, originating from both systemic circulation and hepatic production;
4) Bacterial-induced dysregulation of serum lipid profiles;[21]
5) Migration of pathogen-harboring phagocytes to distant atheromatous sites.[23]

This host immune response favors atheroma formation, maturation and exacerbation.[21]

It has been demonstrated that periodontal treatment is moderately effective in reducing systemic inflammation, as reflected by decreased levels of C-reactive protein (CRP) and improvements in markers of endothelial function. Given that elevated CRP and impaired endothelial function are associated with an increased risk of future cardiovascular diseases, these findings are of clinical relevance. However, the evidence remains moderate regarding the impact of periodontal therapy on lipid profiles and its ability to reduce other biomarkers related to ACVD, including markers of inflammation, endothelial cell activation, arterial blood pressure, and subclinical manifestations of ACVD.[21]

Only scant evidence is available on the association of periodontitis with the incidence of secondary cardiovascular events in patients with established ACVD.[24]

In general, it is recognized that well designed intervention trials on the impact of periodontal treatment on prevention of primary and secondary ACVD, with hard clinical outcomes are needed.If such future studies corroborate the proposed connection and improve cardiovascular risk prediction, a diagnosis of periodontitis may contribute to cardiovascular risk stratification.[21]

6. Parkinson's Disease:

Parkinson's disease (PD) is an idiopathic neurological condition primarily marked by a resting tremor. As a progressive disorder, it gradually impairs mobility and leads to muscle stiffness. The hallmark symptoms—tremors and reduced motor control—often also hinder a patient's ability to maintain effective oral hygiene.[25]

Increasing attention has been given to the brain-gut axis in the pathogenesis of PD, underscoring a strong link between oral health, gut health, and neurological disorders. In this context, oral diseases are believed to potentially accelerate the progression of PD, with oral microbiome playing a particularly important role. Inflammatory responses triggered by oral infections can heighten systemic inflammation, thereby worsening PD symptoms. Moreover, periodontal disease not only causes pain and inflammation but also interferes with chewing, contributing to malnutrition—a frequent issue among PD patients. Cognitive decline may also be exacerbated by poor oral health, as chronic oral inflammation is associated with worsening neurological outcomes in PD.[26]

Additionally, limited oral mobility in PD patients facilitates accumulation of pathogenic bacteria, increasing the risk of infection and inflammation. Dysphagia, another common symptom, can cause aspiration of food, liquids, or saliva, potentially leading to aspiration pneumonia. Notably, this type of pneumonia affects nearly half of individuals with PD—three times more often than in age-matched individuals without the disease—and remains the leading cause of death in this population.[27]

Although the relationship between oral microbiota and PD has not been extensively explored, growing interest in the theory that PD may originate in the gut has prompted researchers to examine environmental risk factors involved in its development—shifting the scientific spotlight onto the human microbiome.[28] Multiple studies have reported a dysbiosis in both the oral cavity and the gut of individuals with PD.[28][29]

Significant differences have been observed in the oral microbiota of PD patients compared to healthy individuals. Specifically, samples from those with PD showed a higher prevalence of potentially pathogenic species, including members of the genera *Lactobacillus*, *Tannerella forsythia*, and *Prevotella intermedia*. Additionally, opportunistic pathogens such as *Streptococcus pneumoniae*, *Mycoplasma orale*, and *Streptococcus constellatus* were found in greater abundance.[27] Another study reported that even in the early stages of the disease, when oral health status appeared similar to that of control subjects, PD patients still exhibited higher levels of microbial groups like *Firmicutes*, *Negativicutes*, *Lactobacillaceae*, *Lactobacillus*, *Scardovia*, *Actinomyces*, *Veillonella*, *Streptococcus mutans*, and *Kingellaoralis*, while showing lower levels of *Lachnospiraceae* and *Treponema*. Furthermore, increased levels of the pro-inflammatory cytokine interleukin-1β were detected in the gingival crevicular fluid of PD patients, indicating a localized inflammatory environment.[28]

Overall, oral hygiene was generally poorer among individuals with PD, with more frequent occurrences of gingivitis.[25][27][28]

There is a considerable gap in understanding how individuals with PD utilize dental care services. Existing studies show wide disparities in oral health knowledge and access to dental

care across various subgroups. To assess whether the dental needs of this population are being adequately addressed—and to determine if they receive less dental treatment compared to other groups—comprehensive epidemiological investigations are needed.[29]

Further research is also needed to clarify the effects of PD medications on the oral microbiota and overall oral health.

Advancements in the research on correlation of oral microbiota and PD could pave the way for new diagnostic tools and therapeutic strategies aimed at enhancing the quality of life and longevity of individuals with PD. Notably, given that aspiration pneumonia remains the leading cause of death in this population, monitoring the oral microbiota could serve as a valuable, noninvasive, low-cost biomarker with potentially life-saving implications.[27]

Conclusion:

The findings of this review highlight the strong correlation between oral microflora and various systemic diseases, including cardiovascular, metabolic, autoimmune, and neurodegenerative disorders.In cancer and cardiovascular diseases, key oral pathogens have been implicated in tumorigenesis and atherogenesis, respectively. In obesity and metabolic syndrome, they contribute to systemic inflammation and insulin resistance. In CLP, impaired microbial balance worsens healing outcomes, while in pulmonary diseases, aspirated oral bacteria act as reservoirs for respiratory pathogens. In PD, oral dysbiosis may exacerbate neuroinflammation and increase the risk of aspiration pneumonia. The evidence underscores the importance of oral health in preventing or managing these conditions. These associations also emphasize the need for further research and a more integrated approach between oral and general healthcare to better address systemic health issues.

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