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The Oral Microbiome as a Bridge Between Oral and Systemic Health: Associations, Mechanisms, and Intervention Strategies

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ABSTRACT
The oral cavity, as the entry point of the human body, harbors a complex and dynamic microbial community known as the oral microbiome. In recent years, accumulating evidence has revealed that the oral microbiome is not only closely associated with oral diseases but also serves as a critical bridge linking oral health to systemic health. This review summarizes the bidirectional associations between the oral microbiome and major systemic diseases, including cardiovascular diseases, diabetes mellitus, neurological disorders, and respiratory diseases. We elaborate on the underlying mechanisms by which oral microbial dysbiosis contributes to systemic pathogenesis, such as the translocation of pathogenic microorganisms and their metabolites, the induction of chronic inflammation, and the modulation of host immune responses. Additionally, we discuss potential intervention strategies targeting the oral microbiome to simultaneously improve oral and systemic health, including probiotic/prebiotic supplementation, targeted antimicrobial therapies, oral hygiene management, and dietary interventions. Finally, we highlight the challenges and future research directions in this field, such as the establishment of causal relationships between oral microbiome alterations and systemic diseases, the development of personalized microbiome-based intervention strategies, and the application of multi-omics technologies in mechanism exploration. This review provides a comprehensive overview of the role of the oral microbiome in the crosstalk between oral and systemic health, offering new insights for the integrated prevention and treatment of oral and systemic diseases.

Keywords: Oral Microbiome; Systemic Health; Microbiota Dysbiosis; Inflammatory Response; Intervention Strategies; Multi-omics; Causal Relationship

1. Introduction

The oral microbiome, consisting of hundreds of microbial species including bacteria, fungi, viruses, and archaea, forms a complex ecological network that interacts dynamically with the host [1]. Under physiological conditions, the oral microbiome maintains a state of homeostasis, playing important roles in nutrient metabolism, immune system development, and resistance to pathogenic colonization [2]. However, under the influence of various factors such as poor oral hygiene, unhealthy diet, smoking, and systemic diseases, the balance of the oral microbiome is disrupted, leading to dysbiosis [3]. Oral microbiome dysbiosis is well-known to be the primary driver of oral diseases such as dental caries, periodontitis, and oral malodor [4]. In recent decades, with the advancement of microbiome sequencing technologies and multi-omics research, the association between the oral microbiome and systemic health has attracted increasing attention [5].

The „oral-systemic link“ has become a hot topic in medical and dental research. A large number

of epidemiological studies and basic research have confirmed that oral microbiome dysbiosis is closely associated with the occurrence and development of various systemic diseases, including cardiovascular diseases (CVDs), type 2 diabetes mellitus (T2DM), Alzheimer's disease (AD), and chronic obstructive pulmonary disease (COPD) [6]. For example, periodontal pathogens such as Porphyromonas gingivalis and Aggregatibacter actinomycetemcomitans have been detected in atherosclerotic plaques, suggesting a potential role in the pathogenesis of atherosclerosis [7]. Additionally, oral microbiome alterations may affect glucose metabolism by inducing systemic inflammation, thereby increasing the risk of T2DM [8]. These findings indicate that the oral microbiome is not an isolated ecological system but a key node connecting oral health to systemic health.

Despite the growing evidence supporting the oral-systemic link, the underlying mechanisms remain not fully elucidated, and the causal relationships between oral microbiome alterations and most systemic diseases have not been clearly established. Moreover, effective intervention strategies targeting the oral microbiome to improve both oral and systemic health are still in the exploratory stage. Therefore, this review aims to systematically summarize the associations between the oral microbiome and major systemic diseases, elaborate on the potential mechanisms, and discuss the latest progress in microbiome-targeted intervention strategies. This review is expected to deepen the understanding of the oral-systemic link and provide new ideas for the integrated prevention and treatment of oral and systemic diseases.

2. Associations Between Oral Microbiome and Systemic Diseases

The oral microbiome is involved in the pathogenesis of various systemic diseases through multiple pathways. Below, we summarize the associations between the oral microbiome and several major systemic diseases, based on the latest epidemiological and microbiological evidence.

2.1 Cardiovascular Diseases

Cardiovascular diseases, including atherosclerosis, myocardial infarction, and stroke, are the leading causes of death worldwide [9]. Accumulating evidence suggests that oral microbiome dysbiosis is an important risk factor for CVDs. Epidemiological studies have shown that patients with periodontitis, a typical oral disease caused by microbiome dysbiosis, have a 1.2-2.0 fold increased risk of developing CVDs compared to healthy individuals [10]. Microbiological studies have further confirmed that periodontal pathogens such as P. gingivalis, T. denticola, and A. actinomycetemcomitans can translocate from the oral cavity to the systemic circulation and colonize in atherosclerotic plaques [7]. Metagenomic analysis of atherosclerotic plaque samples has identified oral microbial DNA, including that of P. gingivalis and Streptococcus mutans, which are rarely found in healthy vascular tissues [11].

In addition to periodontal pathogens, changes in the composition of the oral microbiome are also associated with CVD risk factors. For example, a study involving 1,215 participants found that the abundance of Veillonella parvula in saliva was positively correlated with blood triglyceride levels, a key risk factor for atherosclerosis [12]. Another study showed that the oral microbiome diversity was significantly lower in patients with coronary artery disease compared to healthy controls, and the relative abundance of Firmicutes was increased while that of Bacteroidetes was decreased [13].

2.2 Diabetes Mellitus

Diabetes mellitus, especially T2DM, is a metabolic disease characterized by insulin resistance and hyperglycemia, which can lead to various complications [14]. There is a bidirectional relationship between

the oral microbiome and T2DM. On one hand, T2DM can disrupt the oral microbiome balance, increasing the risk of oral diseases such as periodontitis. On the other hand, oral microbiome dysbiosis can exacerbate insulin resistance and promote the progression of T2DM [8]. Epidemiological studies have shown that the prevalence of periodontitis in T2DM patients is 2-3 times higher than that in non-diabetic individuals, and severe periodontitis is associated with poor glycemic control [15].

Microbiological studies have found that the oral microbiome of T2DM patients is significantly different from that of healthy individuals. For example, the relative abundance of P. gingivalis, Tannerella forsythia, and Fusobacterium nucleatum is significantly increased in T2DM patients with periodontitis [16]. Additionally, a metagenomic study showed that the oral microbiome of T2DM patients has enhanced metabolic pathways related to lipopolysaccharide (LPS) synthesis and amino acid fermentation, which may contribute to systemic inflammation and insulin resistance [17].

2.3 Neurological Disorders

Neurological disorders such as AD, Parkinson's disease (PD), and multiple sclerosis (MS) are characterized by progressive neuronal damage and dysfunction [18]. In recent years, the „gut-brain axis" has been widely studied, and the „oral-brain axis" has gradually attracted attention as an extension of the gut-brain axis. Evidence suggests that the oral microbiome may be involved in the pathogenesis of neurological disorders through multiple pathways. For example, P. gingivalis has been detected in the brains of AD patients, and its virulence factor gingipain can cleave tau protein, a key component of neurofibrillary tangles in AD [19].

Epidemiological studies have shown that periodontitis is associated with an increased risk of AD and PD. A 20-year follow-up study found that individuals with severe periodontitis have a 2.3 fold higher risk of developing AD than those with mild or no periodontitis [20]. Microbiological studies have also found significant differences in the oral microbiome between neurological disorder patients and healthy controls. For example, the relative abundance of P. gingivalis and F. nucleatum is increased in the oral cavity of AD patients, while the abundance of beneficial bacteria such as Streptococcus sanguinis is decreased [21]. Additionally, the oral microbiome of PD patients is characterized by decreased diversity and increased abundance of periodontal pathogens [22].

2.4 Respiratory Diseases

The oral cavity is closely connected to the respiratory tract, and the oral microbiome can directly affect the respiratory microbiome through microaspiration [23]. Chronic respiratory diseases such as COPD, pneumonia, and asthma are associated with oral microbiome dysbiosis. Epidemiological studies have shown that poor oral hygiene is a risk factor for COPD exacerbation, and periodontitis is associated with an increased risk of community-acquired pneumonia [24].

Microbiological studies have found that the oral microbiome of COPD patients is significantly different from that of healthy individuals. For example, the relative abundance of Haemophilus influenzae, Moraxella catarrhalis, and Streptococcus pneumoniae is increased in the oral cavity of COPD patients, which are also common respiratory pathogens [25]. Additionally, microaspiration of oral bacteria such as P. gingivalis and F. nucleatum can induce lung inflammation, exacerbating COPD symptoms [26]. In patients with asthma, the oral microbiome diversity is decreased, and the abundance of pathogenic bacteria such as Staphylococcus aureus is increased [27].

3. Mechanisms Underlying the Oral-Systemic Link

The oral microbiome affects systemic health through multiple mechanisms, among which microbial translocation, metabolic disturbance, and chronic inflammation are the most well-studied. These mechanisms are not mutually exclusive but interact with each other, jointly contributing to the pathogenesis of systemic diseases.

3.1 Microbial Translocation

Microbial translocation refers to the process by which microorganisms or their components cross the epithelial barrier and enter the systemic circulation [28]. The oral mucosa and gingival sulcus are important barriers preventing microbial translocation. However, in the case of oral inflammation (such as periodontitis), the epithelial barrier is damaged, and the permeability is increased, allowing oral pathogens to enter the systemic circulation [29]. For example, P. gingivalis can translocate from the oral cavity to the vascular wall, where it colonizes and promotes the formation of atherosclerotic plaques [7]. Additionally, oral pathogens can reach the lungs through microaspiration, leading to respiratory infections [23].

In addition to intact microorganisms, microbial components such as LPS, peptidoglycan, and DNA can also translocate into the systemic circulation. These components can be recognized by pattern recognition receptors (PRRs) such as toll-like receptors (TLRs) on host cells, triggering immune responses and inflammation [30]. For example, LPS from P. gingivalis can activate TLR4 signaling, inducing the production of pro-inflammatory cytokines and promoting vascular inflammation [31].

3.2 Metabolic Disturbance

The oral microbiome produces a variety of metabolites, including short-chain fatty acids (SCFAs), volatile sulfur compounds (VSCs), LPS, and amino acid metabolites, which can affect systemic health by entering the circulation [32]. For example, VSCs produced by oral anaerobic bacteria can induce oxidative stress and inflammation in vascular endothelial cells, promoting atherosclerosis [33]. Additionally, SCFAs produced by beneficial oral bacteria such as Streptococcus and Veillonella can regulate glucose metabolism and immune responses, while dysbiosis of the oral microbiome leads to decreased SCFA production, exacerbating insulin resistance [34].

Amino acid metabolites produced by the oral microbiome also play an important role in the oral-systemic link. For example, tryptophan metabolites produced by P. gingivalis can activate the aryl hydrocarbon receptor (AhR) signaling pathway, inducing immune suppression and promoting tumor progression [35]. Additionally, glutamate fermentation by oral bacteria can produce ammonia, which increases oral pH and promotes the growth of pathogenic bacteria, while also entering the circulation and affecting liver function [36].

3.3 Chronic Inflammation

Oral microbiome dysbiosis induces local inflammation in the oral cavity, which can spread to the whole body through the circulation, leading to systemic chronic low-grade inflammation [38]. Chronic inflammation is a common pathological basis of many systemic diseases, including CVDs, T2DM, and neurological disorders [39]. For example, periodontitis-induced inflammation leads to increased levels of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP) in the circulation [40]. These cytokines can damage vascular endothelial cells, promote the formation of atherosclerotic plaques, and induce insulin resistance [41].

The immune system plays a key role in the process of chronic inflammation induced by oral microbiome dysbiosis. Oral pathogens and their components can activate immune cells such as macrophages, dendritic cells, and T lymphocytes, leading to the production of pro-inflammatory cytokines and chemokines [42]. Additionally, long-term exposure to oral pathogens can induce immune tolerance, reducing the host's ability to clear pathogens and promoting chronic inflammation [43].

4. Intervention Strategies Targeting the Oral Microbiome for Improving Oral and Systemic Health

Given the important role of the oral microbiome in the oral-systemic link, targeting the oral microbiome to restore its homeostasis has become a potential strategy for improving both oral and systemic health. Currently, the main intervention strategies include probiotic/prebiotic supplementation, targeted antimicrobial therapies, oral hygiene management, and dietary interventions.

4.1 Probiotic and Prebiotic Supplementation

Probiotics are live microorganisms that confer health benefits on the host when administered in adequate amounts [44]. Probiotic supplementation can regulate the oral microbiome balance by inhibiting pathogenic bacteria, promoting beneficial bacteria, and modulating immune responses [45]. For example, Streptococcus salivarius K12 can inhibit the growth of oral pathogens such as P. gingivalis and F. nucleatum, reducing oral malodor and periodontal inflammation [46]. Additionally, Lacticaseibacillus rhamnosus GG can improve glycemic control in T2DM patients by regulating the oral and gut microbiomes [47].

Prebiotics are non-digestible food components that selectively promote the growth and activity of beneficial microorganisms [48]. Common oral prebiotics include inulin, fructooligosaccharides (FOS), and xylooligosaccharides (XOS) [49]. Prebiotic supplementation can promote the growth of beneficial oral bacteria such as Streptococcus and Bifidobacterium, restoring the oral microbiome balance [50]. For example, FOS supplementation can increase the abundance of Streptococcus sanguinis in the oral cavity, inhibiting the growth of S. mutans and reducing the risk of dental caries [51]. Additionally, synbiotics (a combination of probiotics and prebiotics) have shown better efficacy in regulating the oral microbiome and improving oral and systemic health than probiotics or prebiotics alone [52].

4.2 Targeted Antimicrobial Therapies

Traditional antimicrobial therapies such as chlorhexidine mouthwash and antibiotics can non-selectively kill oral bacteria, disrupting the microbiome balance and inducing antibiotic resistance [53]. Targeted antimicrobial therapies, which specifically target pathogenic bacteria without affecting beneficial bacteria, have become a research hotspot [54]. For example, bacteriocins produced by probiotics can specifically inhibit the growth of periodontal pathogens such as P. gingivalis and T. forsythia [55]. Additionally, phage therapy, which uses bacteriophages to specifically kill pathogenic bacteria, has shown potential in the treatment of periodontitis and dental caries [56].

Quorum sensing inhibitors (QSIs) are another type of targeted antimicrobial agent that can disrupt bacterial cell-to-cell communication, inhibiting biofilm formation and virulence factor production [57]. For example, lactonase-producing bacteria can degrade N-acyl-homoserine lactones (AHLs), a key quorum sensing signal molecule in Gram-negative bacteria, inhibiting the pathogenicity of P. gingivalis [58]. Targeted antimicrobial therapies have the advantages of high specificity and low side effects, and are expected to become a new direction for the treatment of oral microbiome dysbiosis-related diseases.

4.3 Oral Hygiene Management

Good oral hygiene is the foundation of maintaining oral microbiome homeostasis [59]. Regular oral hygiene practices such as tooth brushing, flossing, and interdental cleaning can effectively remove dental plaque, reducing the abundance of pathogenic bacteria [60]. For example, daily tooth brushing with fluoride toothpaste can reduce the number of S. mutans in dental plaque, preventing dental caries [61]. Additionally, professional oral cleaning such as scaling and root planning (SRP) can remove subgingival plaque and calculus, restoring the balance of the subgingival microbiome and alleviating periodontal inflammation [62].

Oral hygiene products such as mouthwashes and toothpastes containing probiotics, prebiotics, or natural extracts (such as tea tree oil and cranberry extract) can also help regulate the oral microbiome [63]. For example, mouthwash containing tea tree oil can inhibit the growth of P. gingivalis and reduce periodontal inflammation [64]. However, it should be noted that excessive use of antimicrobial oral hygiene products may disrupt the oral microbiome balance, so rational use is recommended.

4.4 Dietary Interventions

Diet is an important factor affecting the composition and function of the oral microbiome [65]. A balanced diet rich in fiber, vitamins, and minerals can promote the growth of beneficial oral bacteria, while a high-sugar, high-fat diet can promote the growth of pathogenic bacteria [66]. For example, a high-sugar diet increases the production of lactic acid by S. mutans, reducing oral pH and promoting dental caries [67]. Additionally, a diet rich in omega-3 fatty acids can reduce oral inflammation by regulating immune responses, improving periodontal health [68].

Functional foods containing probiotics, prebiotics, or bioactive compounds can also regulate the oral microbiome. For example, dairy products containing Lacticaseibacillus rhamnosus can reduce the abundance of S. mutans in the oral cavity [69]. Additionally, fruits and vegetables rich in polyphenols (such as green tea, grapes, and blueberries) can inhibit the growth of oral pathogens and reduce inflammation [70]. Dietary interventions are a safe and effective way to regulate the oral microbiome, and can be combined with other intervention strategies to achieve better results.

5. Challenges and Future Research Directions

Although significant progress has been made in the research on the oral microbiome and the oral-systemic link, there are still many challenges that need to be addressed. First, most current studies are observational, and the causal relationships between oral microbiome alterations and systemic diseases have not been clearly established. Second, the mechanisms underlying the oral-systemic link are complex and not fully elucidated, especially the interactions between the oral microbiome, gut microbiome, and host immune system. Third, the effectiveness of microbiome-targeted intervention strategies varies among individuals, and personalized intervention strategies have not been established. Fourth, the long-term safety and efficacy of new intervention strategies such as phage therapy and QSIs need to be further evaluated.

To address these challenges, future research should focus on the following directions: (1) Conducting large-scale, long-term prospective cohort studies and randomized controlled trials to establish the causal relationships between oral microbiome alterations and systemic diseases. (2) Using multi-omics technologies (metagenomics, transcriptomics, proteomics, and metabolomics) to comprehensively explore the mechanisms underlying the oral-systemic link, especially the interactions between the oral microbiome and host. (3) Developing personalized microbiome-based intervention strategies based on individual

oral microbiome profiles, genetic background, and lifestyle factors. (4) Exploring the combination of oral microbiome intervention with other systemic disease treatment strategies to improve treatment efficacy. (5) Establishing standardized methods for oral microbiome sampling, sequencing, and analysis to ensure the reproducibility and comparability of research results.

6. Conclusion

The oral microbiome is a key bridge connecting oral health to systemic health. Oral microbiome dysbiosis is closely associated with the occurrence and development of various systemic diseases such as CVDs, T2DM, neurological disorders, and respiratory diseases. The underlying mechanisms include microbial translocation, metabolic disturbance, and chronic inflammation. Targeting the oral microbiome to restore its homeostasis through probiotic/prebiotic supplementation, targeted antimicrobial therapies, oral hygiene management, and dietary interventions has shown potential in improving both oral and systemic health.

Despite the existing challenges, with the continuous advancement of research technologies and methods, the role of the oral microbiome in the oral-systemic link will be further clarified. Future research should focus on establishing causal relationships, exploring underlying mechanisms, and developing personalized intervention strategies. This will not only promote the development of integrated oral and systemic health care but also provide new ideas for the prevention and treatment of systemic diseases, ultimately improving the overall health of individuals.

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