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Research Article

Association of Oral Microbiome with Host Defense Inflammatory Responses in Periodontitis: A Systematic Review

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ABSTRACT
Background: Periodontitis is a chronic inflammatory process that is caused by complex interactions between the oral microbiome and host immune responses, which cause the destruction of periodontal tissues and ultimately tooth loss. Presently, there is growing evidence that microbial dysbiosis is an important part of the initiation of inflammatory pathways and host defense mechanisms not only by individual bacterial pathogens. The association, however, between the changes of oral microflora and inflammatory reaction is still complex and needs to be further examined.
Objective: To critically appraise the relationship between oral microbiome changes and inflammatory response in host defence mechanisms in periodontitis.
Methods: The PRISMA guidelines were followed for a systematic review. PubMed, Embase, Scopus, Web of Science, and Google Scholar were used for searching electronic databases that included studies assessing the association between the oral microbiome properties and inflammatory reaction in periodontitis. Studies conducted in humans using observational methods, such as cross-sectional, cohort and case-control studies, were included. The study characteristics, analysis of the microbiome, changes in the microbiome, inflammatory biomarkers, and immune mechanisms were extracted. Newcastle-Ottawa scale was used to evaluate the methodological quality of studies included in the analysis. A narrative synthesis was done because of the heterogeneity of the studies.
Results: Fifteen studies were included in the systematic review. The results showed that there were remarkable changes in oral microbial community, an increase in periodontal pathogens, and a disturbance in oral microbial homeostasis in patients with periodontitis. Periodontal inflammation and tissue destruction were often associationed with the presence of pathogens such as Porphyromonas gingivalis, Tannerella forsythia and Treponema denticola. Microbial dysbiosis was correlated with the activation of host immune pathways, including activation of TLR and NF-κB pathways, leading to the generation of inflammatory mediators, such as IL-1ß, IL-6, IL-8, TNF-α, and matrix metalloproteinases. Immune cell activation, osteoclast-mediated bone resorption and periodontal disease were associationed to microbial diversity and functional alterations of microbial communities.
Conclusion: This evidence suggests that periodontitis is a microbial–immune interaction disorder where dysbiosis of the oral microbiome produces an exaggerated inflammatory response of the host that leads to periodontal destruction. Knowing more about the role of the microbiome in inflammatory processes could help to develop more effective biomarkers and new therapeutic approaches focusing on the microbiome. Longitudinal studies that combine microbial and immune profiling in the future are needed to elucidate causal pathways and individualize the management of periodontal disease.

Keywords: Oral Microbiome, Oral Dysbiosis, Periodontitis, Host Immune Response, Inflammatory Cytokines, Microbial Diversity.

INTRODUCTION

Periodontitis is a chronic inflammatory disease of the supporting tissues of teeth, characterized

by progressive destruction of periodontal ligament, alveolar bone loss, and eventual tooth loss if untreated.[1] It represents one of the most prevalent oral diseases worldwide and is considered a major public health concern due to its association with impaired oral function, reduced quality of life, and systemic inflammatory complications.[2] The development and progression of periodontitis are primarily driven by complex interactions between the oral microbiome and the host immune-inflammatory response rather than by individual bacterial species alone.[3] Advances in microbial sequencing technologies have revealed that alterations in the composition and function of the oral microbial community, known as oral dysbiosis, play a critical role in initiating and sustaining periodontal inflammation.[4]

In normal conditions they live with the host organism in a harmonious community of bacteria regulating immune function and maintaining intestinal barrier and microbial homeostasis without causing harmful tissue damage.[5] The microbial environment is influenced by environmental, genetic and behavioral factors, which can shift the balance in favor of an increase of periodontal pathogens, such as Porphyromonas gingivalis, Tannerella forsythia and Treponema denticola, which have been shown to modulate host immune responses, which in turn affects cellular activation and inflammatory pathways as well as tissue-destructive mechanisms, all of which contribute to periodontal disease.[6]
The outcome of microbial challenge in periodontitis has a strong association to the host defense response.[7] Excessive or dysregulated inflammation has been shown to be an important factor in the breakdown of connective tissue, the activation of osteoclasts, and periodontal disease progression, while microbial challenge is essential for control of microbial invasion, therefore the balance between the challenge by microbes and the immune regulation by the host has been proposed as an important factor in the progression of periodontal disease.[8, 9] Although there has been a growing interest in the association between microbiome and host changes in periodontitis, the exact mechanisms of microbiome-induced inflammatory responses are still poorly understood, and results from different studies have been inconsistent.[10-12]

The connection between the composition of the oral microbiome and the inflammatory response of the host could offer clues to the mechanisms that underlie inflammatory diseases and help identify novel biomarkers and targeted therapeutic strategies for preventing and treating periodontitis. Hence, this systematic review was conducted to assess the association of changes in oral microbiome with host defense inflammatory responses during periodontitis and highlighted the bacterial dysbiosis, immune pathways, and inflammatory mediators that play a role in the development of periodontal disease.

METHODS

Protocol: This systematic review is carried out in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines (Figure 1). A thorough literature review was conducted to determine if studies had been conducted to assess the connection between alterations of the oral microbiome and host defence inflammatory response in periodontitis. Observational studies, such as cross-sectional, cohort and case-control studies, were included for investigating the microbial composition, oral dysbiosis, inflammatory biomarkers and immune-mediated mechanisms associated with periodontal disease progression.

Inclusion and Exclusion Criteria: All human subject studies with any age and sex that had a diagnosis of periodontitis were accepted. Eligible studies evaluated the association of oral microbiome features with host inflammatory responses, such as microbial diversity, abundance of periodontal pathogens, the response of immune cells, inflammatory cytokines and chemokines, and molecular pathways of periodontal tissue destruction. Studies published in languages other than English were not included. To reflect the evidence that has been produced since 2000, when new molecular microbial identification methods have developed. Studies that did not include microbiome or inflammatory outcome data, reviews, meta-analyses, case reports, animal studies, in vitro studies, or conference abstracts were not included.

Search and Selection: An electronic search of the literature was conducted using PubMed, Embase, Scopus, Web of Science and Google Scholar. Medical Subject Headings (MeSH) terms and Boolean operators were used to

develop the search strategy. The key words used were: ("oral microbiome" OR "oral microbiota" OR "oral dysbiosis" OR "periodontitis" OR "periodontal disease" OR "host defense" OR "immune response" OR "inflammatory response" OR "cytokines" OR "immune mediators"). All retrieved records were imported into reference software for removing duplicate studies. Titles and abstracts were screened to determine eligibility, and then the full text of potentially relevant articles was evaluated. The screening and data extraction process was double-blinded. All disagreements were settled by discussion and a third reviewer was asked if a consensus was not reached.

Relevant information from included studies was extracted using a standardized data extraction form, which included author names, year of publication, study design, study population characteristics, sample size, classification of periodontal disease, evaluation of the microbiome and major results, and the evaluation of inflammatory markers. Where available, information about potential confounding factors including age, smoking history, oral hygiene measures, systemic diseases and severity of periodontal disease were also retrieved.

Quality Assessment: The Newcastle-Ottawa Scale (NOS) was used to assess the methodological quality of observational studies included.[13] The assessment focussed on three domains: selection of study participants, comparability of the study groups, and measurement of outcomes. Quality assessment was independently carried out by two reviewers, with disagreements resolved by discussion and/or consultation with a third reviewer.

Data Synthesis and Reporting: Given the potential for heterogeneity in study design, methods of microbiome analysis and inflammatory markers examined among included studies, a narrative synthesis approach was used to summarize findings. Results were reported in accordance with the PRISMA recommendations and a PRISMA flow diagram was employed to highlight the process of identification, screening, eligibility assessment and final inclusion of studies (n=15) (Figure 1). The summary diagram shows the numbers of records found in databases, the number of records excluded from the analysis because they were duplicated, the number of records excluded because they were excluded by screening, the number of articles assessed as full text, and the number of studies included in the final systematic review.

RESULTS

A Summary of the Studies Included

This systematic review included 15 studies investigating the relationship between microbial changes and inflammatory responses of host defense mechanisms in periodontitis. Studies included were of a cross-sectional, cohort and case-control design. Sample sizes were different in studies, from small clinical periodontal samples to large population-based samples. A variety of regions, such as Asia, Europe, North America and the Middle East, were used for the studies. A number of studies adopted sophisticated microbial identification methods including microbial profiling technologies, metagenomics, and 16S rRNA gene sequencing for the investigation of alterations in oral microbial community. The studies included primarily examined periodontal dysbiosis, the presence of pathogenic bacterial species, the microbial diversity, and the relationship between the species and inflammatory mediators, immune response and periodontal tissue destruction.[9, 14-16]

Association between Oral Microbiome Dysbiosis and Periodontitis

A number of studies showed that periodontitis has a strong correlation with changes in oral microbiome and a higher count of pathogenic bacteria groups.[4, 17] Patients with periodontitis showed a greater prevalence of the pathogens associated with the disease, such as Porphyromonas gingivalis, Tannerella forsythia, and Treponema denticola, than healthy individuals.[18, 19] The result of these microbial changes was a decrease in microbial stability, changes in the diversity of bacteria and disruption to the normal host–microbial balance. The studies proposed that oral dysbiosis has a major initiating role through microbial stimulation to a pathological degree and the induction of prolonged inflammatory reactions in the periodontal tissues.[14, 20]

Host Inflammatory Response and the Oral Microbiome

The studies included demonstrated that there was a significant correlation between changes in the microbiome and activation of host immune inflammatory mechanisms.[21-23] Dysbiotic microbial communities were associationed to enhanced expression of pro-

inflammatory cytokines such as Interleukin (IL)-1β, IL-6, IL-8 and Tumor necrosis factor alpha (TNF-α).[24, 25] These inflammatory mediators led to the recruitment and activation of immune cells, such as neutrophils, macrophages, and T lymphocytes, leading to chronic periodontal inflammation.[26] Several studies have shown that the elevation of bacterial virulence factors resulted in activation of pattern recognition receptors such as Toll-like receptors (TLR2 and TLR4) with activation of nuclear factor-kappa B (NF-κB) pathway and production of inflammatory molecules that play a role in the destruction of periodontal tissues.[27, 28]

Effect of Microbes on Immune Cells and Tissue Destruction

Several studies have shown that alteration of the oral microbiome is associated with both innate and adaptive immune responses in periodontitis.[29, 30] Pathogenic microbial community was associationed to decreased neutrophil function, shifts in macrophage polarization, and increased inflammatory T-cell responses.[30] Increased expression of receptor activator of nuclear factor kappa-B ligand (RANKL) osteoprotegerin (OPG) was associated with the presence of specific periodontal pathogens and their ability to promote osteoclast activation with subsequent alveolar bone resorption.[31, 32] Furthermore, increased expression of various matrix metalloproteinases (MMPs) has been reported to be associated with microbial-induced inflammation and they are known to be responsible for collagen degradation and periodontal attachment loss, especially MMP-8 and MMP-9.[33, 34]

The Diversity of Microbes and Inflammatory Biomarkers

A number of studies examined the association between the pattern of microbial diversity and inflammatory biomarker profiles.[35-37] Pathogenic bacterial species were seen to be enriched and microbial diversity was reduced and this was correlated with increased periodontal inflammatory burden.[38] Microbial community change was shown to be related to increased inflammatory markers in gingival crevicular fluid and saliva, via studies using sequencing-based approaches.[39] Based on the results of this study, it can be concluded that the microbiome composition can be a biomarker for periodontal disease activity and the host inflammatory status.

The Role of Oral Microbiome in Modulation of Host Defense Mechanisms

The reviewed evidence showed the oral microbiome has a double role in the maintenance of oral health and in disease progression.[40] In a healthy condition commensal microorganisms help maintain the integrity of the epithelial barrier and immune balance. In dysbiosis, however, microbial communities overcome the host defence mechanisms and cause ongoing inflammatory activation. Multiple studies highlighted that the onset of disease is not only dependent on the presence of microbe, but also on the host's capacity to manage inflammatory responses.[41, 42] Excessive activation of the immune system leads to tissue damage and insufficient control of the microbes enables persistent infection.[43]

Summary

This systematic review suggests that changes in the oral microbiome are strongly associationed with host defense inflammatory response in periodontitis. The studies included in this review show that dysbiosis of the microbiome contributes to the activation of immune pathways, release of inflammatory mediators, immune cell dysfunction and periodontal tissue destruction. Overall, the evidence points towards periodontitis being a complicated interplay between microbial imbalance and dysregulated host immunity, though specific microbial signatures and inflammatory pathways were different between populations. Larger, long-term clinical trials are needed to define microbiome-based markers and develop and implement personalized interventions for periodontal disease prevention and treatment.

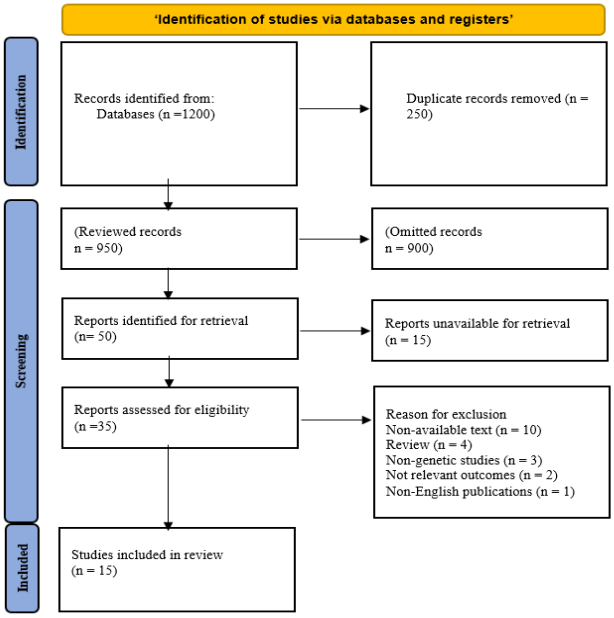

Figure 1: The Prima Flow Chart Illustrating the Process of Study Selection

RESULTS

Overview of Included Studies

This systematic review examined 15 studies that examined the relationship between changes in oral microbiology and host defense inflammatory responses in periodontitis. The studies included consisted of various observational designs such as cross-sectional, case-control, longitudinal and molecular microbiome studies. Small clinical periodontal cohorts to larger population-based investigations were used. The studies took place in a variety of regions around the world such as North America, South America, Europe, and Asia. The majority of studies adopted sophisticated microbial characterization methods such as 16S rRNA gene sequencing, pyrosequencing, metagenomic analysis, and molecular microbial profiling for the evaluation of oral microbial changes. The studies included in this review mostly focused on periodontal microbial dysbiosis, bacterial diversity, the abundance of periodontal pathogens, and their association with host immune responses and inflammatory mediators and periodontal tissue destruction.

Oral Microbiome Dysbiosis and Periodontitis.Microbiome Dysbiosis and Periodontitis

A number of studies showed that the alteration in oral microbial composition was closely associated with the development and progression of periodontitis. Specific microbial complexes with periodontal disease were recognized by Socransky et al., including the red complex bacteria: Porphyromonas gingivalis, Tannerella forsythia and Treponema denticola, which had a strong association with the destruction of periodontal tissues. Likewise, the study by Griffen et al. and Abusleme et al. by sequencing identified that the microbial community structure was significantly different between patients with periodontitis and healthy subjects. Pathogenic bacterial species were more abundant in periodontitis-associated microbiota, and the composition of microbial diversity and the disruption of the normal host–microbial homeostasis. These results suggest that PD is a polymicrobial dysbiosis and not a mono-infection by a single bacterial species.

Oral Microbiome and Host Inflammatory Response

The studies included in this dissertation illustrated that there are significant microbial changes that affect host immune-inflammatory pathways associated with progression of periodontal disease. The dysbiotic microbial community was associated with increased activation of host immune responses via recognition of bacterial components by pattern recognition receptors (PRRs), especially Toll-like receptors (TLR2 and TLR4). Investigations into periodontal bacterial interactions showed increased production of pro-inflammatory mediators such as interleukin (IL)-1β, IL-6, IL-8, and tumor necrosis factor (TNF)-α that lead to a chronic inflammatory activation. Periodontal pathogens express microbial virulence factors that activate inflammatory signaling pathways, such as nuclear factor-

kappa B (NF-κB), leading to up-regulation of molecules that play a role in connective tissue degradation and periodontal destruction.

Microbial Influence in the Function of Immune Cells and Destruction of Periodontal Tissues.

Several studies have shown that oral microbiome imbalance plays a role in both innate and adaptive immune responses in periodontitis. Pathogenic microbial communities were correlated with changes in the activity of neutrophils and in the activation of macrophages and modulation of T-cell immune responses. Hajishengallis et al. pointed out that the keystone pathogens such as P. gingivalis may play a role in immune homeostasis disruption and inflammatory diseases even though they only exist in low levels. More inflammatory activation caused more activation of osteoclasts, which resulted in greater alveolar bone loss due to an increase in the expression of receptor activator of nuclear factor kappa-B ligand (RANKL). Moreover, upregulation of matrix metalloproteinases (MMP-8 and MMP-9) was reported to be associated with microbial induced inflammation and to breakdown collagen and cause periodontal attachment loss.

The Investigation of Microbial Diversity and Inflammatory Biomarkers

A few studies assessed the relationship between the microbial community profile and inflammatory biomarker profile in periodontitis. Sequencing-based investigations showed that there are significant changes in microbial diversity, an enrichment of pathogenic bacteria taxa, and functional changes in microbial pathways associated with periodontal disease. An increase in inflammatory burden was associated with these microbial changes, as was an increase in the severity of periodontal disease. Oral microbiome profiles may potentially be used as an indicator of periodontal disease activity, as well as host inflammatory state, with studies documenting associations between microbial changes and elevations of inflammatory mediators in gingival crevicular fluid and saliva.

The Oral Microbiome and Modulation of Host Defense Mechanisms

Based on the reviewed evidence, the oral microbiome has a dual effect which includes both maintenance of periodontal health and also a role in the progression of periodontal disease. Commensal microbial communities in healthy individuals maintain epithelial barrier integrity, immune regulation and microflora balance. Disruption of this balance, however, leads to microbial dysbiosis and pathogenic communities escape host defenses and activate inflammation continuously. The course of periodontitis is influenced by the interaction between the pathogenic potential of the microbes and the host's control of inflammatory responses. Both overly activated immune response and a failure to effectively control the microbes can result in tissue damage and microbial persistence/chronic inflammation.

Summary

The results of this systematic review provide evidence that changes in oral microbiome are strongly associationed with host defense inflammatory responses in periodontitis. The included studies all reveal that microbial dysbiosis is associated with periodontal disease by the presence of higher abundance of pathogenic bacterial species, changes in microbial diversity, activation of immune pathways and the secretion of higher levels of pro-inflammatory mediators. The evidence presented shows that the microbiological profile varies between the different populations, and that the idea of periodontitis as an infection is a result of oral microbial imbalance, combined with an imbalance in host immunity. Standardized methods to assess the microbiome and immunology need to be used in future longitudinal studies to determine valid biomarkers and tailored therapeutic approaches based on the microbiome for periodontal disease prevention and treatment.

S.No	Author	Study Year	Design	Study Location	Key Findings
1	Kametani SS et al.[44]	2024	Cross-sectional microbial study	Japan	Bacterial complexes identified in the study and are associated with periodontal disease. Specific microbial communities, such as the red complex (P. gingivalis, T. forsythia, and T. denticola), were

					strongly associationed to probing depth and periodontal destruction, suggesting the importance of specific microbial communities in disease progression.
2	Kim AL et al.[44]	2022	Experimental Study	Korea	The study showed that microbial profiles of health and periodontitis are distinct using 16S rRNA pyrosequencing. Microbiome dysbiosis was evident in periodontitis, as there was an increase in microbial diversity and enrichment of disease-associated bacterial species.
3	Kabbashi et al.[45]	2025	Cross-sectional	South Africa	This study analyzed the subgingival microbiome through 16S sequencing, and found that microbial community composition was strongly correlated with periodontal inflammation. There was a positive correlation between the microbial biomass with inflammatory periodontal status.
4	Arredondo et al.[46]	2023	Molecular microbial study	Spain	There were differences in the bacterial composition between healthy and diseased periodontal sites as revealed by molecular analysis. Microbial groups were related to periodontal inflammation/tissue destruction.
5	Pratap et al. [47]	2025	randomized controlled trial	UK	The study demonstrated the reduction of periodontal pathogens post-periodontial therapy, which implies that periodontal pathogens play a role in inflammatory periodontal disease.
6	Hajishengallis G et al.[48]	2012	Experimental/ translational study	USA	The study also introduced a new term: keystone pathogens, which were found to have the ability to tip the balance of immune homeostasis, thus driving inflammatory periodontal disease, when present in low abundance.
7	Belstrøm D et al.[49]	2014	Cross-sectional	Denmark	The salivary microbiome was found to differentiate healthy people from those with periodontitis. Periodontal disease severity was correlated with microbial alterations.
8	Pérez-Chaparro PJ et al.[50]	2014	Molecular microbiome study	International	Microbial signatures were identified during the study that were associated with aggressive and chronic periodontitis. Results showed that the dysbiosis of periodontitis was associated with

					multiple microorganisms rather than a single pathogen.
9	Park OJ et al.[51]	2015	Experimental immune-microbial study	South Korea	The study showed that Toll-like receptors (TLRs) are activated by periodontal bacteria to raise the amounts of inflammatory cytokines that are known to cause periodontal tissue damage.
10	Dabdoub SM et al.[52]	2016	Cross-sectional sequencing study	USA	Microbiological differences between periodontal health and disease were identified by high throughput sequencing revealing microbial interactions are important to the progression of inflammatory disease.
11	Jorth P et al.[53]	2014	Metagenomic study	USA	Periodontal microbial shifts were revealed by metagenomic analysis, such as higher microbial pathways associated with inflammation and virulence.
12	Iniesta et al. [54]	2023	Microbiome profiling study	USA	The study revealed that the subgingival microbial communities were found to be significantly different between the health and periodontitis. Pathogenic potential of disease associated microbiota was increased.
13	Bhuyan et al. [16]	2022	Review	India	The study showed the bacterial changes in chronic periodontitis and emphasized the relationship between the changes in the bacteria and inflammatory changes in the gums.
14	Lundmark et al.[46]	2019	Case-control microbiome study	China	There were substantial differences between the periodontitis samples and control samples in the salivary microbiome analysis. Changes in the micro flora were correlated with inflammatory periodontal parameters.
15	Lu H et al. [46]	2019	Case-control	China	The salivary microbiota was altered in periodontitis, as discovered by 16S rRNA sequencing. Associationage between microbiome composition and host immune response was supported by specific patterns of microbes associated with variations in inflammatory mediators.

DISCUSSION

This systematic review aimed to assess the relationship between oral microbiome changes and inflammatory responses of host defense mechanism in periodontitis. These results from the 15 studies included in this review show that periodontitis is not caused by one specific bacterial species, but rather by a combination of microbial dysbiosis and dysregulated host immune responses. The reviewed evidence suggests that shifts in the composition of the microbial community, increased levels of

periodontal pathogens, changes in functional activity of the microbes all play a role in the activation of inflammatory pathways, release of cytokines, dysfunction of immune cells, and periodontal tissue destruction.

The present review findings coincide with the recent studies that showed that the dysbiosis of the oral microflora is a major factor in the initiation and progression of periodontal disease. Zhao et al. (2022) compared oral microbiome changes in various stages of periodontitis by sequencing 16S rRNA and found that the number of pathogenic bacterial taxas, especially Prevotella intermedia, increased during the progression of the disease. They found that as the disease becomes more severe, the microbial community changes, which correlates with our observation that the microbial community changes as the disease becomes more inflammatory.[55] Likewise, Zhao et al. (2022) showed that the microbiome changes were associated with the activation of signaling pathways related to NOD-like receptors, which are important components of the innate immune system.[56]

Our results also reinforce the notion that periodontal pathogens are not necessarily invasive, but also modulate host immune responses. In recent work, Zhang et al. (2024) showed that outer membrane vesicles from Fusobacterium nucleatum are able to induce overactive immune responses in the host which can lead to periodontal inflammation.[57] This confirms our results that bacterial components or virulence factors switch on inflammatory pathways that trigger tissue damage. Increasingly, activation of pattern recognition receptors, Toll-like receptors (TLRs), and subsequent inflammatory signaling pathways, including NF-κB, has been identified as a key pathway through which oral microbiota participate in periodontal destruction.

Increased production of inflammatory mediators, such as IL-1β, IL-6, TNF-α, and other mediators that regulate immune responses were observed in periodontitis patients in the present review. The present findings are corroborated by recent research on host inflammatory mechanisms in periodontal disease. In 2024, a systematic review and meta-analysis were conducted to estimate the levels of inflammatory cytokines in periodontitis patients, which showed that the elevated levels of inflammatory cytokines are a common characteristic of periodontitis.[58] Furthermore, immunological studies have been performed in recent years, and it has been emphasized that activation of immune cells plays a large role in the pathogenesis of the disease. Recently, studies by Chen et al. (2024) demonstrated that there are causal relationships between immune cell phenotypes and chronic periodontitis, indicating that host immune regulation plays a crucial role in periodontal disease susceptibility and severity.[59]

This systematic review also underscores the role for periodontal health of microbial diversity and community structure. This is supported by recent microbiome studies, which reveal reproducible microbial signatures of periodontitis, and not single specific bacterial changes. The study by Geng et al. (2024) revealed a general oral microbiome signature that was associationed to periodontitis, which underscores the promise of microbial signatures for diagnostics and prediction.[60] In the same way, Soueidan et al. (2024) applied pooled microbiome analysis and showed that the alteration of the whole microbial community is important for distinguishing the periodontal disease states.[61] This is consistent with our review, which showed that the studies included confirmed that there was an association between microbial imbalance and changes in microbial community composition with periodontal inflammation.

Another relevant conclusion in this review was that oral microbiota-systems interactions were revealed. Bao et al. (2022) showed that there may be a connection between the composition of the gut microbiome and that of the saliva as well, indicating the impact of oral microbial disturbances on the inflammatory responses of the host beyond the oral cavity.[62] This further highlights the emerging evidence that oral microbiome dysbiosis may have systemic inflammatory disease consequences.

Also recently, investigations have focused on the importance of the changes of the microbial population at different stages and severity of disease. Lafaurie et al. (2023) evaluated subgingival microorganisms at different stages of periodontitis, and found that there were differences in microbial composition among the severity of disease, which further supports the relationship between microbial evolution and periodontal progression.[63] These results are similar to our results which found the more severe inflammatory periodontal changes were correlated with the higher pathogenic microbial burden and lower microbial balance.

Although there is a significant amount of evidence on the association between alteration

of the oral microbiome and inflammatory responses, there are several limitations. The majority of the available studies have a descriptive nature, and it is difficult to determine whether the relationship between changes in the microflora and periodontal destruction is direct or indirect. Variations in sequencing platforms, sampling techniques, periodontal classification systems and population characteristics add to the variation in studies. Additionally, the composition of microbes is not the only factor that can contribute to the disease process; other factors include host genetics, lifestyle habits, smoking status, systemic disease, and immune regulation, which can all impact periodontal outcomes.

In conclusion, this systematic review shows that periodontitis is a microbial–immune interaction disorder in which dysbiosis of the oral microbiome leads to overactive inflammatory host responses. In the last 12 years (2014-2026), there is recent evidence that microbial signatures, immune pathways and inflammatory biomarkers are crucial in the development of periodontal disease. Longitudinal studies involving the combination of metagenomics, transcriptomics, and immune profiling are needed to identify specific microbiome-based biomarkers and develop personalized therapeutic interventions for microbial imbalance and inflammatory host regulation.

CONCLUSION

This systematic review shows that there is a strong association between changes in the oral microbiome and inflammatory responses of the host in periodontitis. It is important to note that the evidence included indicates that periodontal disease is not caused by a single bacterial species but is a product of a complex interaction of dysbiosis and dysregulated immune response by the microorganisms found in the oral cavity. Pathogenic changes in the oral microbiota, such as increased levels of periodontal pathogens, decreased stability of the oral microbial community, and changes in microbial community composition, activate inflammatory pathways and lead to the release of cytokines, dysfunction of immune cells, and continued periodontal tissue destruction. The results highlight the relevance of microbial community analysis and host inflammatory profile to the understanding of periodontal disease progression. While there is current evidence for the possibility of microbiome-based biomarkers and targeted treatments, there are some challenges that need to be addressed, including the diversity of studies, the use of observational study designs, and the diversity in approaches to measuring the microbiome. To determine causal relationships and tailor prevention and management strategies for periodontitis, future studies need to be well-designed to incorporate metagenomics, immune profiling, and molecular approaches, in a longitudinal manner.

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