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From harmony to havoc: Oral dysbiosis as the gateway to periodontitis

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Abstract
The oral microbiome, the second largest and most diverse microbial community in the human body, is essential for maintaining oral and systemic health. Under homeostatic conditions (eubiosis), commensal microorganisms support immune regulation, metabolic processes, and colonization resistance. Disruption of this balance (dysbiosis) leads to ecological and functional shifts in the subgingival biofilm, favouring pathogenic species.
The polymicrobial synergy and dysbiosis model emphasizes that periodontitis is not caused by a single pathogen but results from cooperative and competitive microbial interactions that amplify pathogenicity. Tissue breakdown is primarily mediated by the host's dysregulated immune-inflammatory response rather than direct microbial action. Advances in diagnostic approaches, including 16S rRNA sequencing, metagenomics, and biomarker analysis in gingival crevicular fluid and saliva, provide valuable insights into microbial ecology and disease activity.
Emerging therapeutic strategies, such as probiotics and prebiotics, aim to restore microbial balance and modulate inflammation, offering promising adjuncts to conventional periodontal therapy. A deeper understanding of the shift from eubiosis to dysbiosis is critical for developing targeted and personalized approaches to periodontal disease management.#

Keywords: Biofilm, immune dysregulation, microbiome analysis, oral dysbiosis, periodontitis, probiotics, virulence factors

Introduction

The oral microbiome is the second largest and one of the most diverse and complicated groups of microbes in the human body. This complex community consists of numerous commensals, symbiotic, and potentially pathogenic microorganisms, encompassing over 700 prokaryotic species, in addition to fungi, viruses, and protozoa [1]. Bacteria are the most common prokaryotes found in the mouth. These microbes are embedded in a self-produced extracellular polymeric matrix called biofilm, which is made up of polysaccharides, proteins, lipids, and DNA from outside the cell. This matrix is very important for microbial colonization and the structural stability of the microbial community [2].
Under physiological conditions, the oral microbiome exists in a state of homeostasis dominated by commensal and beneficial species. Disruption of this equilibrium, referred to as oral dysbiosis, is frequently characterized by the overgrowth of Gram-negative bacteria. Such microbial shifts are often precipitated by inadequate oral hygiene practices, unfavourable dietary patterns, and other environmental influences [3]. Mounting evidence links oral dysbiosis not only to local pathologies, including dental caries, periodontitis, and oral malignancies, but also to systemic conditions such as cardiovascular disorders and metabolic diseases, notably diabetes [4].
Dysbiotic microbial consortia often establish synergistic interactions that enhance immune evasion, nutrient acquisition, and persistence within pro-inflammatory niches [5]. Among the most clinically significant outcomes of dysbiosis is periodontitis, a condition driven by a dysregulated host immune-inflammatory response to alterations in the microbial ecosystem. Periodontitis is recognized as a polymicrobial infection, wherein diverse bacterial taxa act in concert to promote chronic inflammation and progressive breakdown of periodontal structures in genetically or environmentally susceptible individuals. Globally, periodontitis represents a major public health challenge, ranking as the sixth most prevalent disease and affecting approximately 743 million people worldwide [6].

Healthy Oral Microbiome

The oral cavity harbors a diverse array of microorganisms that together constitute a dynamic and highly complex ecosystem. Under physiologic conditions, this microbial community exists in a balanced state referred to as eubiosis. Distinct ecological niches within the mouth including the tongue, buccal mucosa, hard palate, tooth surfaces, and gingival sulcus provide unique environments that support the colonization and growth of specific microbial groups [7].
Commensal microorganisms serve essential protective functions by limiting the adhesion and proliferation of pathogenic species. In addition, they contribute to key metabolic activities, such as nitrate reduction, which results in the generation of nitric oxide, a molecule with well-documented roles in host defense and vascular health [8]. Beyond these functions, a stable oral microbiome plays a pivotal role in modulating and sustaining host immune homeostasis.
Several host-derived mechanisms further contribute to oral health maintenance. Saliva, through its continuous secretion, buffering capacity, and antimicrobial constituents including lactoferrin, lysozyme, and defensins restricts bacterial overgrowth and facilitates microbial clearance. The oral epithelium provides an additional line of defense by forming

a tightly regulated barrier, while natural desquamation of epithelial cells assists in the removal of adherent microbes. Moreover, both innate and adaptive immune responses remain actively engaged in regulating the oral microbiota, promoting the persistence of commensal organisms while constraining the proliferation of potentially pathogenic species [9].

Transition from Eubiosis to Dysbiosis

The transition from a state of oral eubiosis to dysbiosis is a pivotal event in the initiation and progression of periodontitis. This shift is not merely an increase in the quantity of bacteria, but a fundamental alteration in the composition and metabolic activity of the subgingival microbial community. This allows for the maturation of the biofilm, creating increasingly anaerobic conditions and a nutrient-rich environment from gingival crevicular fluid (GCF) and host tissue breakdown products [10]. As the oxygen tension decreases, strict anaerobes, which are often associated with pathogenicity, begin to thrive, outcompeting the facultative anaerobic commensals that characterize health.

Keystone Pathogen Hypothesis proposed by Hajishengallis (2012) highlights the role of keystone pathogens microbial species present in low abundance but with a disproportionately large impact on the microbial community in the onset of periodontal disease. Among these, *Porphyromonas gingivalis* is a prime candidate due to its ability to transform commensal microbes into pathogenic ones. It exerts both direct effects on microbial gene expression and indirect effects via host immune modulation. *P. gingivalis*, often termed the “master of subversion,” manipulates innate immunity by inhibiting toll-like receptor-4 (TLR-4) activation and promoting deceptive cross-talk between TLR-2 and the complement system, impairing phagocyte function. It also induces ineffective phagocytosis through Complement Receptor 3 (CR-3) signaling and suppresses interleukin-12 (IL-12) production, while inhibiting IL-8 to cause chemokine paralysis of neutrophils.

Despite its low abundance, *P. gingivalis* initiates chronic, ineffective inflammation, aiding immune evasion and nutrient acquisition for other pathogens. This dysbiosis drives destructive immune responses, ultimately contributing to the irreversible tissue damage seen in periodontitis.

The Polymicrobial Synergy and Dysbiosis (PSD) model posited by Hajishengallis (2012) asserts that periodontitis arises from intricate microbial communities of indigenous organisms functioning synergistically. These communities exhibit characteristics superior to those of individual species, with unique functions that enhance their overall pathogenicity. Their integration is supported by structural assembly, nutritional interdependence, and chemical signaling.

The "driver–passenger" model explains disease progression: keystone pathogens (drivers) initiate dysbiosis by disrupting immune surveillance and manipulating host responses. Pathobionts (passengers), like *Filifactor alocis*, *Selenomonas*, and *Desulfobulbus*, exploit this altered environment, eventually dominating and advancing disease. Accessory pathogens (e.g., *Streptococcus gordonii*) enhance interspecies cooperation, promoting survival in resource-limited settings, echoing the Black Queen Hypothesis. Conversely, antagonistic interactions also occur, reflecting the Red Queen effect, where bacteria evolve to compete.

This dynamic interplay both synergistic and antagonistic shapes the microbial community and its disease-causing potential, described as nososymbiocity disease arising from microbial coexistence in a susceptible host. This modern understanding moves beyond the idea of single-pathogen causation to a complex, hierarchical microbial network that drives immune dysregulation [11].

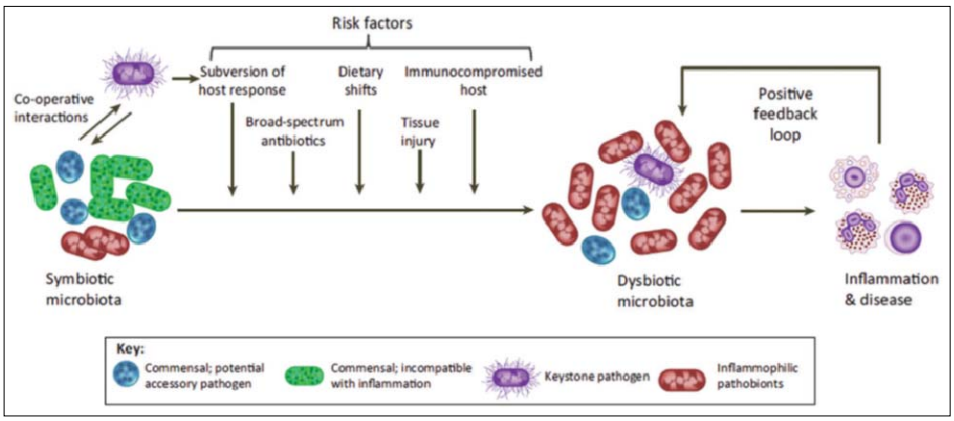

Fig 2: Polymicrobial synergy and dysbiosis model

Mechanisms of Periodontal Tissue Destruction in Dysbiosis

The progression of periodontitis from microbial dysbiosis to tissue destruction is a complex sequence by the harmful interaction between microbial virulence factors and an exaggerated, dysregulated host inflammatory response. While bacteria initiate the disease, the majority of tissue damage is caused by the host’s own immune response, which, in attempting to eliminate the infection, inadvertently damages the periodontal support structures.

a. **Direct Microbial Virulence Factors:** The dysbiotic subgingival biofilm especially keystone pathogens and their microbial allies play a direct role in tissue degradation through a range of virulence mechanisms:

- **Proteases and Enzymes:** Major pathogens like *Porphyromonas gingivalis* produce powerful proteolytic enzymes, notably gingipains (arginine-gingipain and lysine-gingipain), which are highly destructive. These enzymes degrade essential host

proteins such as collagen, elastin, immunoglobulins, and components of the complement system, thereby contributing to the breakdown of the periodontal ligament and alveolar bone. Additionally, other bacterial enzymes, such as collagenases and chondroitin sulfatases, further aid in the destruction of connective tissues and cartilage [12].

- **Toxins:** *A. actinomycetemcomitans* produces leukotoxin, a pore-forming toxin that specifically targets and lyses human phagocytes (neutrophils and monocytes), hindering the host's primary immune defense and allowing bacterial proliferation. Metabolic byproducts such as butyrate (from *Fusobacterium nucleatum* and other anaerobes) also exert cytotoxic effects on host cells and modulate immune responses [13].

- **Biofilm Formation and Resistance:** The complex and highly organized architecture of the biofilm provide enhanced resistance against host immune defenses and antimicrobial therapies. Its extracellular polymeric matrix serves as a physical shield, limiting the access of antibodies, complement proteins, and antibiotics. This protective barrier enables pathogenic bacteria to persist within the subgingival environment and intensify their destructive impact [14].

b. Host Inflammatory Response the Central Role: Although direct bacterial action contributes to tissue damage, the host's inflammatory response triggered and sustained by the dysbiotic microbiota is the primary force driving periodontal destruction. The innate immune system is persistently stimulated by pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs) derived from the biofilm

- **Pattern Recognition Receptors (PRRs) and Cytokine Activation**

  Cells such as epithelial cells, fibroblasts, macrophages, and neutrophils express PRRs including TLR2 and TLR4 and Nucleotide-binding Oligomerization Domain-like receptors (NOD-like receptors) which detect microbial components like lipopolysaccharides (LPS), peptidoglycans, flagellin, and bacterial DNA. Recognition of these signals initiates intracellular pathways, primarily Nuclear Factor kappa B (NF-κB) and Mitogen-Activated Protein Kinase leading to the release of various pro-inflammatory mediators [15]. Key cytokines and chemokines involved include:

- **Interleukin-1β (IL-1β):** Stimulates matrix metalloproteinases (MMPs) and promotes osteoclast activation.

- **Tumor Necrosis Factor-alpha (TNF-α):** A central mediator of inflammation that accelerates bone resorption and soft tissue destruction.

- **Interleukin-6 (IL-6):** Plays a role in systemic inflammatory responses and osteoclast differentiation.

- **Interleukin-8 (IL-8):** Attracts neutrophils to the infection site, contributing to localized inflammation [16].

c. Immune Dysregulation: In chronic periodontitis, the host immune response becomes dysregulated. Instead of effective microbial clearance and inflammation resolution, there's a persistent, low-grade inflammatory state that ultimately becomes self-destructive. This involves:

- **Impaired Resolution of Inflammation:** In chronic periodontitis, resolution pathways, which are mediated by specialized pro-resolving mediators (SPMs) like resolvins and protectins, are frequently disrupted, resulting in inflammation and tissue damage mediated by neutrophils [17].

Diagnosis and Management Implications

Diagnosis relies on clinical parameters and radiographic assessment, while treatment primarily focuses on mechanical removal of bacterial plaque. However, the insights into microbial ecology open avenues for more targeted and personalized therapeutic approaches.

a. Current Diagnostic Approaches: Clinical diagnosis of periodontitis is based on the presence of signs such as gingival inflammation, bleeding on probing, increased probing pocket depth (PPD), clinical attachment loss (CAL), and radiographic evidence of alveolar bone resorption. These parameters reflect the cumulative effect of the disease process, but do not directly assess the microbial composition or the host's specific immune response.

b. Microbiome analysis using molecular techniques like 16S rRNA gene sequencing and metagenomics allows for detailed characterization of the subgingival microbial community, identifying specific pathogens and overall patterns of dysbiosis that deviate from health. Biomarker analysis in GCF or saliva can quantify host inflammatory mediators (e.g., PGE2, IL-1β, MMPs) and bacterial virulence factors, providing insights into disease activity, host susceptibility, and therapeutic response [18].

c. Probiotics and Prebiotics: Modulating the oral microbiome using probiotics (beneficial live microorganisms) or prebiotics (non-digestible compounds that selectively stimulate the growth or activity of beneficial bacteria) represents a promising, non-antibiotic approach. Recent systematic reviews suggest that certain probiotic strains (e.g., *Lactobacillus reuteri*, *Lactobacillus brevis*) have shown potential in inhibiting periodontopathogens, modulating inflammation, and contributing to the restoration of microbial balance [19].

Conclusion

Oral dysbiosis, characterized by an imbalance in the microbial community, is a key factor in the development of periodontitis. It triggers a chronic inflammatory response that leads to tissue destruction. Restoring microbial balance is essential for effective prevention and management of the disease.

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