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The Oral Microbiome And Periodontal Disease: Biofilm, Dysbiosis And The Immune System

O Microbioma Oral e a Doença Periodontal: Biofilme, Disbiose e o Sistema Imunológico

El Microbioma Oral y la Enfermedad Periodontal: Biopelícula, Disbiosis y el Sistema Inmune

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ABSTRACT

The human microbiome is defined as the entire genomic content of the microorganisms inhabiting a particular human body site. Emerging evidence suggests the importance of a balanced microbiota to maintain proper immune response to provide health to the full body, oral tissues, and stomatognathic functions. Periodontitis (PD) is a chronic inflammatory disease affecting the teeth's supporting tissues. The etiology is multifactorial and subgingival dental biofilm stimulates an inflammatory and immune response. The association between the oral microbiome and PD is critical, as the disease is mainly triggered by an imbalance in the oral microbial community, known as dysbiosis. The article intends to describe the imbalance in the oral microbiota that leads to the development of periodontitis. To sustain an integrative literature review 53 articles published in English were analyzed. The oral microbiome influences the process and outcome of periodontal disease. The alteration in the composition of oral microflora is an indicator of the initiation of diverse diseases.

Keywords: Biofilm, Dysbiosis, Microbiota, Periodontics.

RESUMO

O microbioma humano é definido como todo o conteúdo genômico dos microrganismos que habitam um determinado local do corpo humano. Evidências emergentes sugerem a importância de ter uma microbiota equilibrada para manter

uma resposta imunológica adequada, não apenas para proporcionar saúde a todo o corpo, mas também aos tecidos orais e às funções estomatognáticas. A periodontite (DP) é uma doença inflamatória crônica que afeta os tecidos de suporte dos dentes. A etiologia é multifatorial e o biofilme dentário subgengival estimula uma resposta inflamatória e imunológica. A associação entre o microbioma oral e a DP é crítica, pois a doença é desencadeada principalmente por um desequilíbrio na comunidade microbiana oral, conhecido como disbiose. O artigo pretende descrever o desequilíbrio da microbiota oral que leva ao desenvolvimento da periodontite. Para sustentar uma revisão integrativa da literatura foram analisados 53 artigos publicados em inglês. O microbioma oral tem influência no processo e no resultado da doença periodontal. A alteração na composição da microflora oral é um indicador do início de diversas doenças.

Palavras-chave: Biofilme, Disbiose, Microbiota, Periodontia.

RESUMEN

El microbioma humano se define como el contenido genómico completo de los microorganismos que habitan en un lugar particular del cuerpo humano. La evidencia emergente sugiere la importancia de tener una microbiota equilibrada para mantener una respuesta inmune adecuada no solo para brindar salud a todo el cuerpo sino también a los tejidos bucales y las funciones estomatognáticas. La periodontitis es una enfermedad inflamatoria crónica que afecta los tejidos de soporte de los dientes. La etiología es multifactorial y el biofilm dental subgingival estimula una respuesta inflamatoria e inmune. La asociación entre el microbioma oral y la PD es fundamental, ya que la enfermedad se desencadena principalmente por un desequilibrio en la comunidad microbiana oral, conocido como disbiosis. El artículo pretende describir el desequilibrio en la microbiota bucal que conduce al desarrollo de la periodontitis. Para sustentar una revisión integradora de la literatura se analizaron 53 artículos publicados en inglés. El microbioma oral influye en el proceso y el resultado de la enfermedad periodontal. La alteración en la composición de la microflora bucal es un indicador del inicio de diversas enfermedades.

Palabras clave: Biopelícula, Disbiosis, Microbiota, Periodoncia.

1. INTRODUCTION

The human body consists of its cells and microorganisms that are found both inside and outside the human body (Pisano 2023). Commensal microorganisms are of fundamental importance to the host, as they perform important tasks, such as contributing to host health, counteracting pathogenic bacteria, contributing to the regulation of host homeostasis and balance, and modulating the immune response (Herrera *et al*., 2022; Pisano 2023).

The human microbiome is defined as the entire genomic content of the microorganisms inhabiting a particular human body site. Nobel prize laureate Joshua Lederberg first coined the term “microbiome” as a community of commensal, symbiotic, and pathogenic microorganisms. It has also been noted that these microorganisms share physical space within the human body (Morrison *et al*., 2023).

The terminology “microbiome” and “microbiota” are often used interchangeably; however, this is inaccurate. The term “microbiome” refers to the collective genomes of the microorganisms residing within a given environment, while the term “microbiota” refers to the wide variety of microorganisms that reside within a given environment. Emerging evidence suggests the importance of having a balanced microbiota to maintain proper digestion, metabolism, and immune response not only to provide health to the full body

but also the oral tissues and stomatognathic functions as well (Herrera *et al*., 2022; Morrison *et al*., 2023; Pisano 2023).

Periodontitis (PD) is a chronic inflammatory disease affecting the teeth' supporting tissues (gums, periodontal ligament and alveolar bone) (Morrison *et al*., 2023). Therefore, the etiology is multifactorial and subgingival dental biofilm stimulates a host inflammatory and immune response, eventually leading to the irreversible destruction of the periodontium (Kwon, Lamster, Levin 2021). The association between the oral microbiome and PD is critical, as the disease is mainly triggered by an imbalance in the oral microbial community, known as dysbiosis (Herrera *et al*., 2022; Morrison *et al*., 2023).

The process of periodontal disease evolution occurs and how systemic diseases participate directly and indirectly in the pathogenesis situation. As a complex chronic inflammatory disease, periodontitis presents with a non-linear progression (Bezerra *et al.*, 2022). The article intends to describe the process of imbalance in the oral microbiota that consequently leads to the development of periodontal disease, yet, the study aims to discuss the role of biofilm, dysbiosis and the immune system in the aspect of periodontitis (Herrera *et al*., 2022).

2. THEORETICAL FRAMEWORK

Bacali *et al*., (2022) affirm that the oral microbiome, forming a biofilm that covers the oral structures, contains a high number of microorganisms. Biofilm formation starts from the salivary pellicle that allows bacterial adhesion–colonization–proliferation, co-aggregation and biofilm growth. Current methods to study the oral microbiome include cultures and microscopy, gel-based techniques, polymerase chain reactions methods, DNA microarrays and Next Generation Sequencing (NGS) techniques (Bacali *et al*., 2022; Ray, Pattnaik 2023)

The oral cavity hosts a large number of microorganisms, the totality of them being known as the oral microbiome, the oral flora or the oral microbiota that lives in the mouth (Bacali *et al*., 2022). These microorganisms coexist in a dynamic balance with the human host, playing an important role in oral and general health. The mouth offers a favorable habitat—appropriate humidity, temperature (37 °C) and pH (6.75–7.25) and abundant nutrients for various microbial species such as bacteria, protozoa, fungi and viruses (Bacali *et al*., 2022).

Disturbances of the symbiotic relationship between the host and the oral microbiome may cause oral and systemic diseases (Bezerra *et al*., 2022; Qilichovna, 2024). Microbes from oral biofilm can spread to other parts of the body through the respiratory or blood systems or to the digestive tract. Periodontitis is

a bacterially-triggered chronic periodontal inflammation resulting in progressive, irreversible destruction of the connective periodontal attachment and alveolar bone resorption and tooth loss (Bacali *et al*., 2022).

Periodontal (PD) disease is a chronic inflammatory disease of the oral cavity with its primary etiological factor being bacterial plaque. In the US, almost half of the population presents with some form of periodontal disease (Bezerra *et al*., 2022). Most studies have found that periodontitis affects a significant number of individuals before the age of 20 years and affects the majority of the adult population after the age of 35-40 years (Qilichovna, 2024)

The common forms of PD are associated with Gram-negative bacteria such as *Porphyromonas gingivalis* and *Prevotella intermedia*. Periodontitis is a highly prevalent disease. As it progresses, it causes serious morbidity in the form of periodontal abscesses and tooth loss and, in the latter stages, pain (Sczepanik *et al*., 2020).

Several authors have related systemic diseases to conditions of oral dysbiosis and vice versa. Thus, there may be a bidirectional relationship between the oral microbiota and systemic diseases; indeed, the presence of an oral microbiota specifically associated with systemic diseases seems to be, to some extent, a clinical biomarker, although further studies are needed to confirm these associations (Pisano 2023)

Periodontitis is initiated by the accumulation of a dental plaque biofilm at and below the gingival margin, which becomes increasingly dysbiotic. This results in dysregulation of the host immune-inflammatory response, which further drives the dysbiosis and results in the destruction of periodontal tissues (Herrera *et al*., 2022).

Moreover, epidemiologic evidence indicates that periodontitis is more frequent in patients with uncontrolled diabetes mellitus than in healthy controls, suggesting that it could be considered the “sixth complication” of diabetes. Diabetes mellitus and periodontitis are two extraordinarily prevalent chronic diseases that share several comorbidities (Darby 2022).

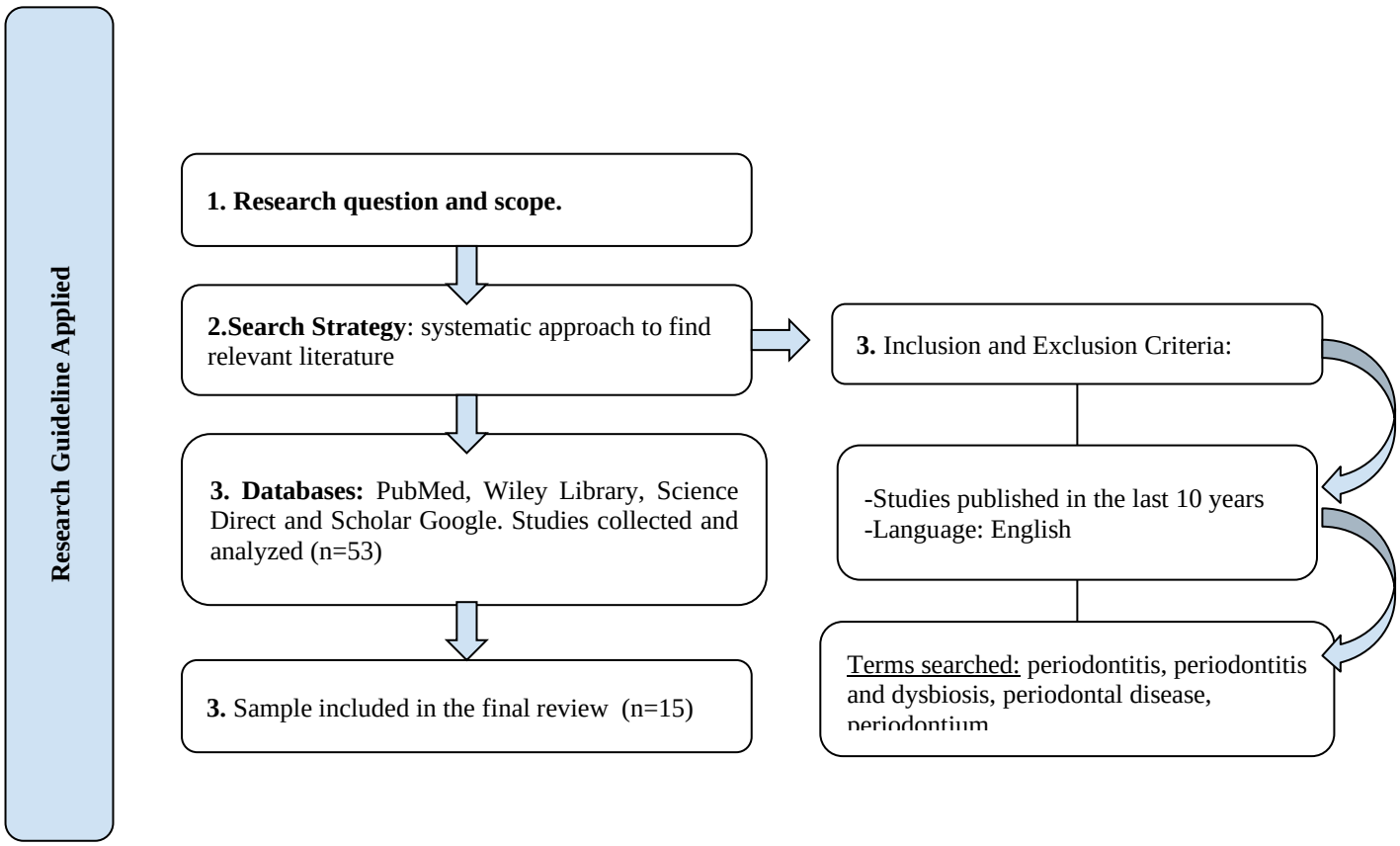
3. METHODOLOGY

A literature review can be defined as a systematic method of collecting and synthesizing previous research (Jesus *et al*., 2024). A well-executed review as a research strategy lays a robust groundwork for advancing learning and fostering theoretical development. The use of the integrative review method aims to critically review the existing database, potentially reconceptualize, and expand the theoretical framework of the specific topic as it develops (Jesus *et al.*, 2024).

To elaborate a qualitative study, the previous data selection was conducted using methodological methods to facilitate and filter the content. To sustain an integrative literature review, (N= 53) articles

published in English from the databases (PubMed, Wiley Library, Science Direct and Scholar Google) were analyzed. After the review, only 15 articles published in the last 10 years were included. The process to formulate the final study followed the steps described in flowchart 1, respectively:

Flowchart 1. Description of the methodology applied.



Source: elaborated by the authors (2024)

4. RESULTS AND DISCUSSIONS

The normal microbiota of the oral cavity is associated with oral pathologies, some of which are involved with periodontal disease. PD is caused by the sessile and planktonic microbiota found within the saliva and dental plaque. The migration of these microorganisms leads to inflammation of the gingiva.

This inflammation leads to an increased flow of gingival crevicular fluid, an inflammatory exudate found in the periodontal pocket between the tooth and the marginal gingiva (Morrison *et al*., 2023). To achieve additional knowledge regarding these facts, it is important to understand the following issues:

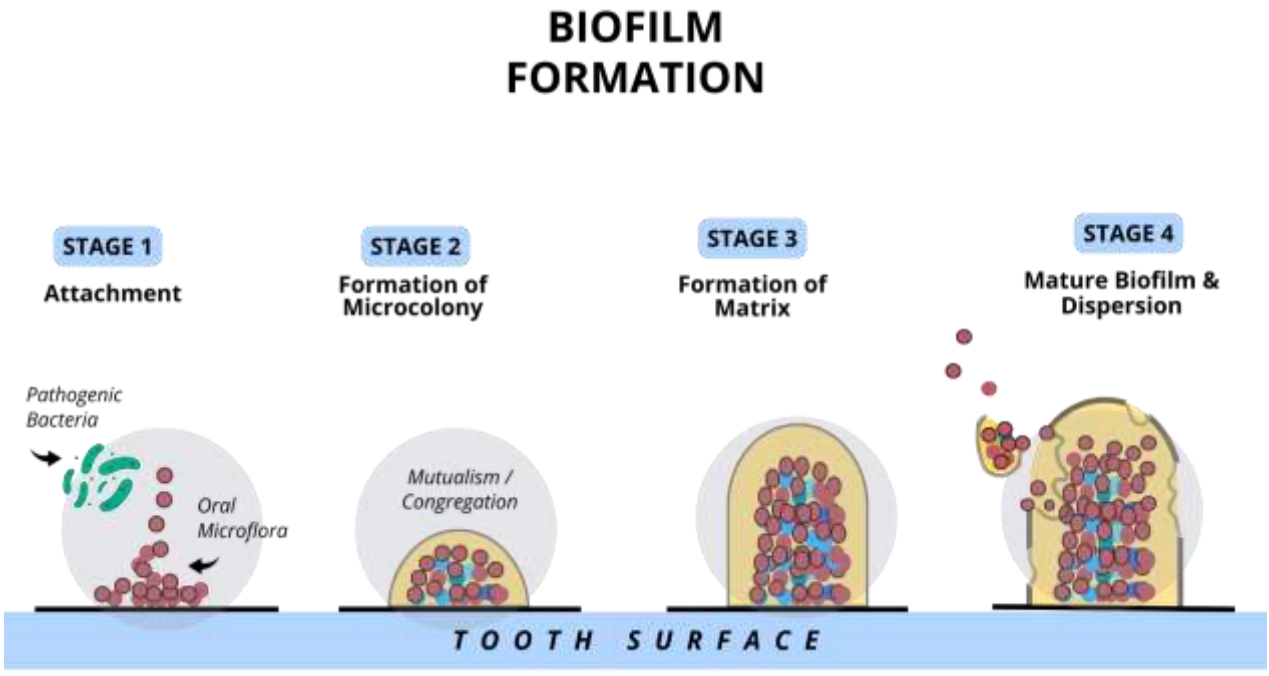
4.1. ORAL BIOFILM

Biofilms are groups of microorganisms that attach to and multiply on a solid surface, commonly with a fluid bathing the microbes. The microorganisms that are not attached but are free-floating in an aqueous environment are termed planktonic cells and are highly organized aggregates of microorganisms in an extracellular matrix, frequently self-produced (Bacali *et al*., 2022). Bacteria in biofilms have cell-to-cell contact, a synergistic lifestyle and a set of unique characteristics different from the free-living cells; Morrison *et al*., 2023).

The oral microbiome forms a biofilm that covers the structures, containing a high number of microbes influenced by the composition and surface characteristics they accumulate onto. The self-produced extracellular polymeric matrix of the biofilm is mainly composed of polysaccharides, proteins, lipids and extracellular DNA (Bacali *et al.*, 2022; Herrera *et al*., 2022).

Biofilm formation starts from the salivary pellicle that favors bacterial adhesion, colonization, proliferation and then co-aggregation, followed by the biofilm maturation in a complex microbial community (**Figure 1** demonstrates how the biofilm forms on the surface of teeth through the interaction between the oral microbiome and pathogenic bacteria). According to the type of biofilm, bacterial gene expression changes can also occur (Bacali *et al.*, 2022).

Figure 1. Stages of the biofilm formation, expressing the process the bacterial adhesion–colonization–proliferation, co-aggregation and biofilm maturation in a microbial community.



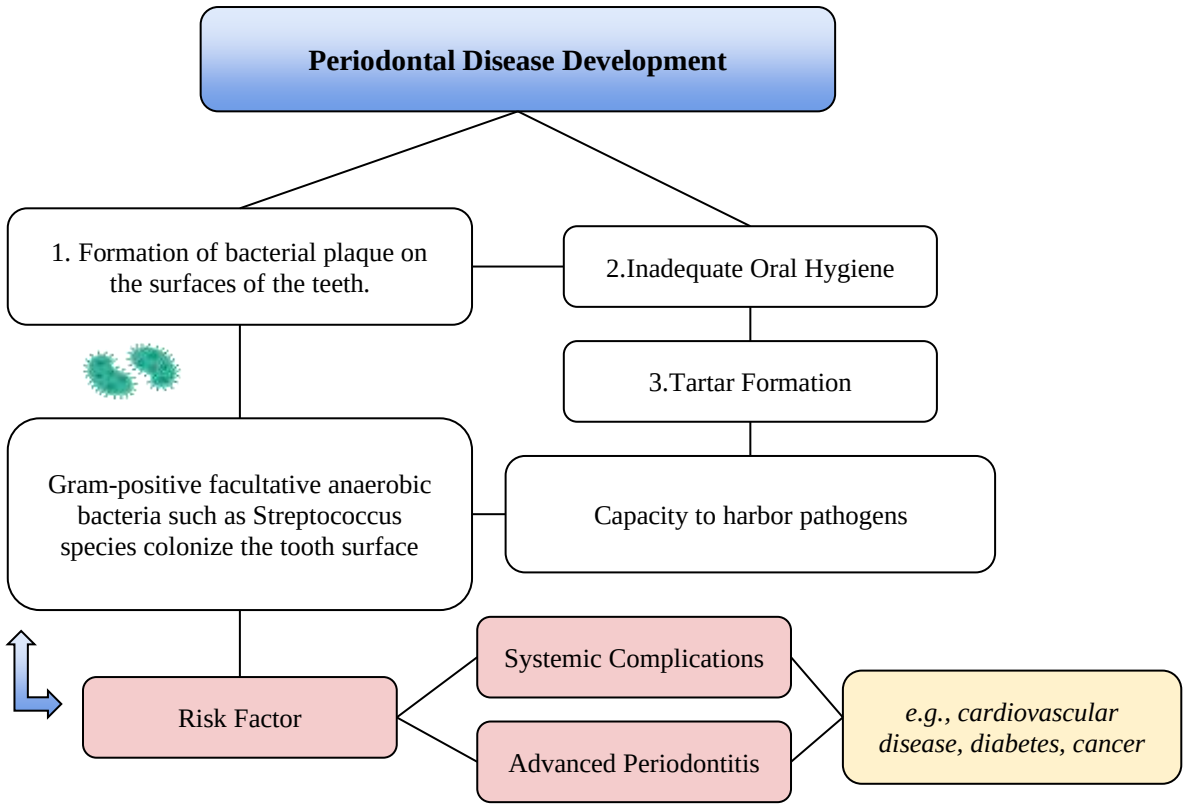
Source: elaborated by the authors (2024).

In the mouth, there are several niches and local microenvironments inhabited by different microbial communities, such as supra and subgingival plaque on teeth, gingival sulcus, hard palate, tongue, sublingual area and cheek oral zone. In the oral cavity, most habitats were dominated by *Streptococcus*, but these were followed in abundance by *Haemophilus* in the buccal mucosa, *Actinomyces* in the supragingival plaque and *Prevotella* in the subgingival plaque. In saliva, the main species found were *Streptococcus*, *Prevotella*, *Veillonella*, *Neisseria* and *Haemophilus* (Bacali *et al*., 2022).

Other non-bacterial components of the healthy oral microbiota are fungi such as *Candida* spp., *Cladosporium*, *Saccharomyces*, *Aspergillus*, *Fusarium*, *Cryptococcus* spp. and others. Viruses such as herpesviruses, retroviruses and papillomaviruses are commonly found in the oral microbiota. Viruses such as Epstein–Barr virus, herpes simplex virus, HIV or hepatitis C viruses serve as reservoirs for pathogenic gene functions (Bacali *et al*., 2022; Herrera *et al*., 2022).

Periodontitis begins with the formation of dental biofilm (bacterial plaque) on the surfaces of the teeth. If oral hygiene is inadequate, this biofilm can turn into tartar and harbor periodontal pathogens (**flowchart 2**). Bacterial adhesion to the tooth surface, biofilm maturation and plaque formation lead to periodontal disease (Herrera *et al*., 2022).

Flowchart 2. Periodontitis evolution process after the biofilm formation.



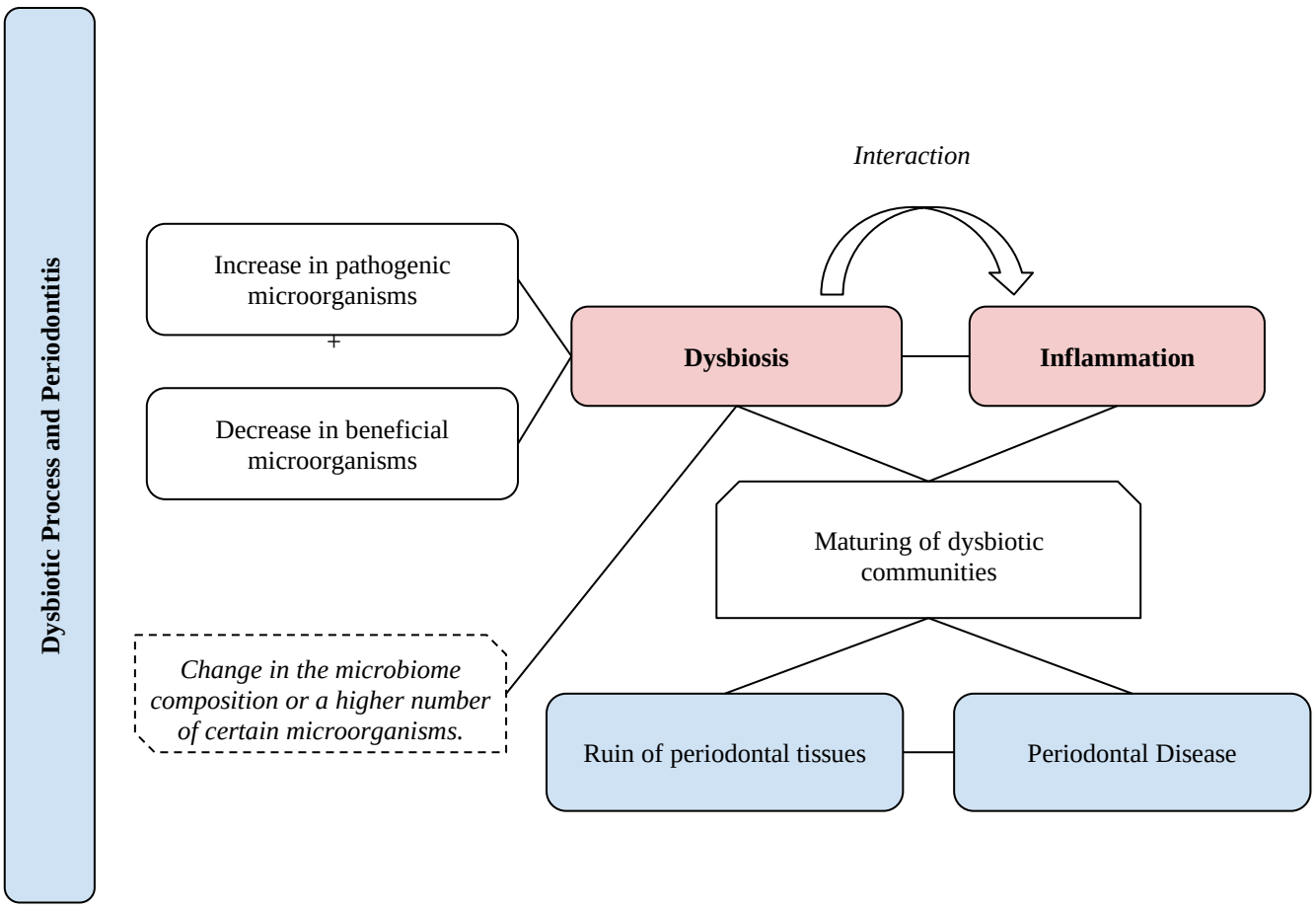
Source: elaborated by the authors (2024).

4.2. DYSBIOSIS

In periodontitis, dysbiosis occurs, where there is an increase in pathogenic microorganisms and a decrease in beneficial microorganisms (**Flowchart 3**). Bacteria such as *Porphyromonas gingivalis*, *Tannerella forsythia*, and *Treponema denticola* are often associated with periodontitis (Morrison *et al*., 2023). Studies have demonstrated a relationship between dysbiosis and inflammation, where inflammation fuels the maturing of dysbiotic communities and this dysbiosis aggravates inflammation guiding to the ruin of periodontal tissues (Bezerra *et al.*, 2022; Morrison *et al*., 2023).

The polymicrobial synergy and dysbiosis theory (PSD) proposes that a synergistic polymicrobial community is responsible for initiating disease as several factors within this community lead to a dysregulation of the host inflammatory response (Bezerra *et al.*, 2022).

Flowchart 3. How the dysbiosis and inflammation lead to periodontitis.



Source: elaborated by the authors (2024).

The dysbiosis of oral microbiota induces diseases and disorders in various physiological systems, including cardiovascular, respiratory, digestive, excretory, reproductive, immune, and neurological systems, leading to various diseases and even cancer (Ray, Pattnaik 2023).

A change in the microbiome composition or a higher number of certain microorganisms, called dysbiosis, can be associated with certain oral or systemic diseases (Bacali et al., 2022). Several host factors can negatively influence the composition of the oral microbiome to a dysbiotic state, altering the balance between the host microbiome toward a harmful relationship (Bezerra *et al.*, 2022).

In vitro studies have shown that the availability of products derived from inflammatory tissue breakdown, such as amino acids, iron, etc., drives the outgrowth of pathogens which perpetuate the dysbiotic environment in the periodontal pocket (Bezerra *et al.*, 2022; Herrera *et al*., 2022).

4.3. IMMUNE RESPONSE

Pathogenic microorganisms in dental biofilm produce toxins and enzymes that trigger an inflammatory response in the host. Persistent inflammation can lead to the destruction of periodontal tissues, including the periodontal ligament and alveolar bone. The disease involves complex interactions among specific bacterial pathogens, destructive host immune responses, and environmental risk factors (Ebersole et al., 2017; Kwon, Lamster, Levin 2021; Herrera *et al*., 2022).

The host response to biofilm accumulation can be a double-edged sword. It can be protective, maintaining a symbiosis between the host response and the biofilm, and preserving tissue homeostasis without periodontal tissue destruction. However, it can also be dangerous. A dysregulated inflammatory response causes the tissue destruction seen in periodontitis, and upon detection, the immune system activates various immune cells, including neutrophils, macrophages, and dendritic cells (Ebersole et al., 2017; Bezerra *et al.*, 2022).

A dysregulated immune response can cause a shift in biofilm composition, allowing more pathogenic bacteria to thrive. This triggers a host immune response, creating a feedback loop of tissue destruction and maintaining a dysbiotic microbial community. Chronic inflammation further damages tissues, including the periodontal ligament and alveolar bone (Kwon, Lamster, Levin 2021; Bezerra et al., 2022).

As the disease progresses, the interactions between the polymicrobial community and the host immune response become a continuous cycle that perpetuates the dysbiosis leading to the tissue damage observed in periodontitis (Bezerra *et al.*, 2022). Although it is without question that specific groups of oral

bacteria that populate dental plaque play a role in periodontitis, it is now thought that once this disease has been triggered, other factors play an equal, and possibly more important role (Ebersole et al., 2017).

The innate immune system cells, when protecting the host from microbial invasion, mount a response that includes upregulation of proinflammatory cytokines, matrix metalloproteinases and reactive oxygen species, contributing to the tissue damage and loss of teeth commonly associated with periodontitis (Sczepanik *et al*., 2020).

The host response to the bacterial stimulus varies amongst individuals and this variation is due to a wide variety of determinants that play a role in the regulation of the immune response (Bezerra *et al*., 2022). Conclusively, the detection of pathogens, activations of immune cells, inflammation and tissue response leads to the resolution or chronicity of periodontal disease (Ebersole et al., 2017; Sczepanik *et al*., 2020).

4.4. RISK FACTORS

Pathogenic microorganisms in dental biofilm produce toxins and enzymes that trigger an inflammatory response in the host. Persistent inflammation can lead to the destruction of periodontal tissues, including the periodontal ligament and alveolar bone. The disease involves complex interactions among specific bacterial pathogens, destructive host immune responses, and environmental risk factors. (Bacali *et al*., 2022; Baima *et al*., 2022; Darby 2022; Morrison *et al*., 2023)

Other more generalized diseases that have been correlated with oral disease include rheumatoid arthritis, endocarditis, bacteremia, cardiovascular disease, pulmonary disease, liver disease, and cancer (gastrointestinal, pancreatic, and breast) (Bacali *et al*., 2022; Morrison *et al*., 2023).

In concordance with Bacali *et al*., (2022), variations in sex hormones may influence the subgingival microbiome and periodontal disease. Likewise, the author affirms that the ecosystem's composition and characteristics are associated with several factors such as dental materials of restorations, crowns, bridges and implants and also prosthetic devices, systemic diseases, or medications (Curtis et al., 2021; Darby 2022).

Mental health disorders are associated with more severe periodontal disease and, in some cases, poorer healing outcomes to nonsurgical periodontal therapy. They can result in behavior modification, such as poor oral hygiene practices, tobacco smoking, and alcohol abuse, which are also risk factors for periodontal disease and, therefore, may have a contributory effect (Darby 2022).

A combination of genetic, environmental and lifestyle factors, and more recently, epigenetic factors, can affect an individual's susceptibility to and severity of periodontal disease (Baima et al., 2022; Bezerra *et al*., 2022; Darby 2022)

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4.5. TREATMENT

Management of periodontal disease consists of control of the bacterial biofilm, the primary etiological factor, however, the progression of the disease is highly dependent on the inflammatory response triggered by the bacterial plaque (Bezerra *et al*., 2022). The treatment of periodontitis involves the mechanical removal of biofilm and tartar (through scaling and root planing), as well as interventions to restore a healthy oral microbiome. In some cases, the use of antibiotics or adjuvant antimicrobial therapies may be necessary.

Considerations of the patient's general health, the selected periodontal treatment plan, and the selected completed restorative procedures need to be considered. The influence of caries, fixed prosthodontics, partial dentures, shortened dental arch, and implant therapy can have unintended impacts on periodontal health in the elderly (Curtis et al., 2021)

Achieving adequate home care is an essential component of the prevention of periodontal disease, successful periodontal therapy and long-term retention of the dentition. Clinicians should educate patients about the importance of effectively removing dental biofilm at home. The importance of adequate home care should be reinforced frequently during the initial and subsequent phases of periodontal treatment (Bacali *et al.*, 2022).

Adverse periodontal outcomes in the elderly can be minimized by carefully assessing the patient's medical history, impact of medications, functional needs, properly finishing and contouring restorations to avoid plaque accumulation, and designing restorations to allow access for hygiene. Partial dentures can be a source of plaque accumulation leading to periodontal disease, caries, and recession around abutment teeth (Curtis et al., 2021).

Scaling and root planing are achieved. This phase of treatment should be delivered in conjunction with the correction of local contributing factors, extraction of hopeless teeth and treatment of active carious lesions. Periodontal re-evaluation, surgical therapy and resective periodontal surgery are approaches reported by specialists (Bacali *et al*., 2022; Morrison *et al.*, 2023).

Multiple coexisting changes, including xerostomia, altered wound healing, altered bone physiology, altered microbiome, and diminished plaque control, can add complexity to periodontal management (Curtis et al., 2021).

Although an adjunctive local and systemic antibiotic treatment temporarily increased the antibiotic resistance of subgingival microorganisms (Ardila *et al*., 2023); some effective dental approaches and educational environments during the treatment can be cited, as well:

1. **Mechanical removal of biofilm:** this concerns daily practices such as brushing and flossing, which are crucial for removing plaque and preventing accumulation.
2. **Professional dental cleaning:** Frequent visits to a dentist for professional cleaning aids to remove hardened plaque (tartar).
3. **Antimicrobial therapy:** This includes using mouthwashes with antibacterial agents.
4. **Lifestyle modifications:** Adopting a healthy diet low in sugars and quitting smoking can significantly improve gum health and reduce the progression of periodontitis.
5. **Regular dental check-ups:** Scheduled visits to the dentist allow for early detection of gum disease and timely intervention to prevent further damage.

Ultimately, it is understood that the oral microbiome has a considerable influence on the process and outcome of periodontal disease. Correspondingly, new studies are necessary to acquire new methods of treatment for the current professionals and patients (Abou-Arraj *et al.*, 2021; Herrera *et al*., 2022)

5. CONCLUSION

Discovering the oral microbiome and its relationship with periodontitis is essential for developing effective preventive and therapeutic strategies to maintain periodontal health. Careful diagnosis, elimination of the causes and reduction of modifiable risk factors are paramount for successful prevention and treatment of periodontitis. The alteration in the composition of oral microflora is an indicator of the initiation of diverse diseases, which might involve various physiological systems or even affect the psychology of an individual. Unquestionably, getting a better understanding of the steps of the immune response in periodontal disease is essential for developing targeted therapeutic strategies to modulate inflammation, enhance host defense mechanisms, and promote periodontal health.

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