

Models of Pathogens in Periodontitis

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Abstract

Periodontitis is a long-lasting inflammatory disease influenced by various factors, including microbial biofilm, the immune response of the host, genetics, and environmental elements. Different models have been suggested to clarify its development, starting from simple plaque-based theories to more intricate nonlinear and systems-oriented ideas. The Page and Schroeder model outlined the histopathological changes, while subsequent models incorporated host vulnerability and risk factors. Newer ideas like the key-stone pathogen, polymicrobial dysbiosis, and immunomicrobial models portray periodontitis as a cycle involving chronic inflammation, microbial imbalance, and tissue damage. Contemporary biological systems approaches could enhance personalized diagnosis and treatment. Grasping these models is crucial for improving periodontal care.

Keywords: Periodontitis; Microbial Biofilm; Page and Schroeder Model; Periodontal Care

Introduction

Periodontitis is a multifaceted disease characterized by complex interactions among various factors, all of which contribute to its dynamic progression. Pathogenesis models serve to integrate current scientific data, facilitating a more comprehensive understanding of the disease. Different models explaining the pathogenesis of periodontal disease have been suggested, each reflecting the prevailing understanding of the disease at the time [1]. This study aims to provide an overview of the various models of pathogenesis and highlight the current developments in the field of periodontology [2]. Various models of periodontal disease pathogenesis have been proposed based on the prevailing concepts of the disease at that point of time. This study is an attempt to summarize the various models of pathogenesis and the current status in the field of periodontology.

Models of pathogenesis

Linear model (1960s)

The linear model suggested that bacterial deposits play a primary and critical role in the pathogenesis of periodontal disease. With the introduction of this model, earlier theories emphasizing non bacterial factors such as trauma from occlusion and systemic influences were largely dismissed [1].



Figure 1

Page and Schroeder’s model (1976) [3]

Roy page and Hubert Schroeder were the first to highlight the histological events underlying the pathogenesis of human periodontitis in a landmark article that later became a citation classic. Their work introduced the first systematic model explaining the sequential host response leading to periodontitis. They described four types of histopathologic lesions: the initial, early and established lesions, which represent progressive stages of gingivitis, and the advanced lesion, characterized by bone loss and the clinical manifestation of periodontitis. This model also demonstrated a clear progression in the predominant immune cells- from neutrophils in the initial lesion, to macrophages and T cells in the early lesion, and finally to B cells and plasma cells in the established and advanced lesions. For the first time, this provided a rational and structured frame work for understanding the pathogenesis of human periodontitis [1].

Circa model (1980)

A dynamic balance between the periodontal microbiota and the host typically maintains a clinical state of periodontal health, marked by minimal inflammatory changes in the marginal gingiva. This equilibrium is most effectively sustained through control of the resident bacterial mass, although in rare cases targeting specific microorganisms maybe necessary. Failure to regulate microbial growth can disrupt the host-micro balance, either through excessive bacterial accumulation or increased microbial virulence. Such disturbances may cause transient episodes of tissue destruction and overtime, cumulative periodontal damage.

Drawback: This model failed to account for certain clinical disease patterns or phenotype that exhibited characteristic bacterial profiles and host response [2].

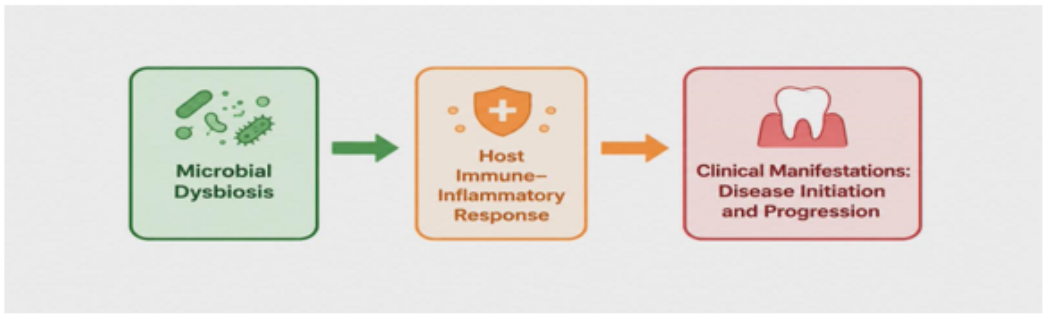


Figure 2

Critical pathway model (1996)

By 1990, advances in research had clarified the cellular and molecular interactions underlying periodontal disease progression. This work paved the way for Offenbacher’s 1996 [10] proposal of a critical pathogenic pathway [2]. Since a simple linear model based solely on the bacteria-host response relationship could not adequately explain the variability and site specificity of periodontal disease among individuals, nonlinear models of pathogenesis were developed. These models incorporated the influence of additional factors and disease modifiers that alter disease patterns, severity and susceptibility. The critical pathway model was the first nonlinear approach proposed to explain such association. The term “critical path” denotes the essential cellular and molecular steps in pathogenesis that are indispensable for the progression of the disease [1].

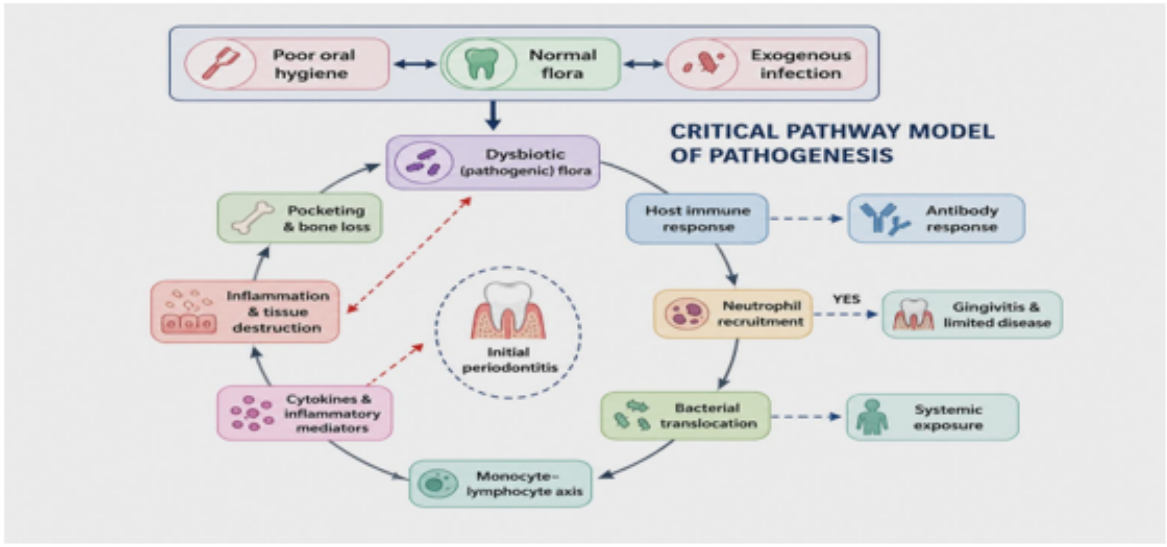


Figure 3

Classical model (1997)

The classical model explains the pathogenesis of periodontitis as the result of interactions between bacteria and host immune response, further influenced by environmental and acquired risk factors including genetic predisposition. As a non linear frame work it accounts for the diverse clinical manifestation of the disease by considering the combined effects of microbial challenges and modifying factors [1].

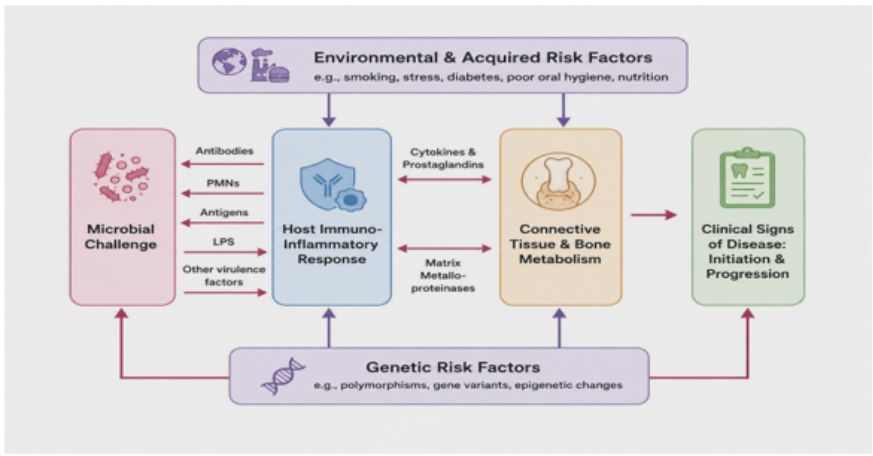


Figure 4

Multilevel hierarchical model (2008)

The 1997 conceptual model of periodontal disease pathogenesis remains relevant today; however, it has evolved into a multilevel hierarchical frame work in which interactions are reflected through gene, protein and metabolite expression patterns [2]. This model is structured around a multilevel hierarchical organization composed of functional modules, each defined by specific cellular and molecular inputs and outputs. The hierarchy extends from subcellular and cellular biological networks to tissue level interactions represented at the top layer. The interplay of factors within and between these modules determines the system’s overall behaviour, which ultimately manifest as clinical outcomes [1].

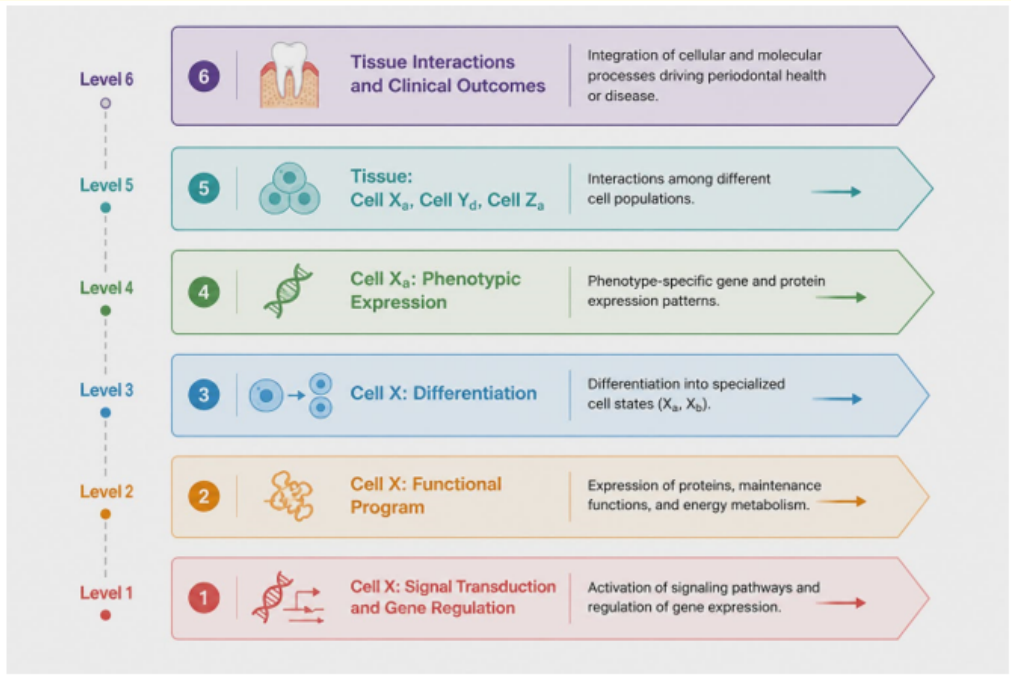


Figure 5

Biological system model (2008)

The biologic system model integrates all factors contributing to the final clinical phenotype within a stacked Venn diagram, illustrating the overlaps and interactions among these elements. The clinical phenotype can be further divided into underlying subclinical components. At the outermost level are subject-specific exposures, which include characteristics of the biofilm, coexisting health condition and environmental influences. These exposures interact with the individual’s genetic background which in turn shapes the biologic phenotype defined by cellular and molecular process, including inflammatory biomarkers. Together, these interconnected layers ultimately determine the expression of the clinical phenotype [1].

Pathogenesis model (2012)

This model highlights the role of keystone pathogens in the pathogenesis of periodontal disease. These pathogens represent a small subset low-abundance microbes that exert an influence on the microbial community far greater than their numerical presence. Efforts to

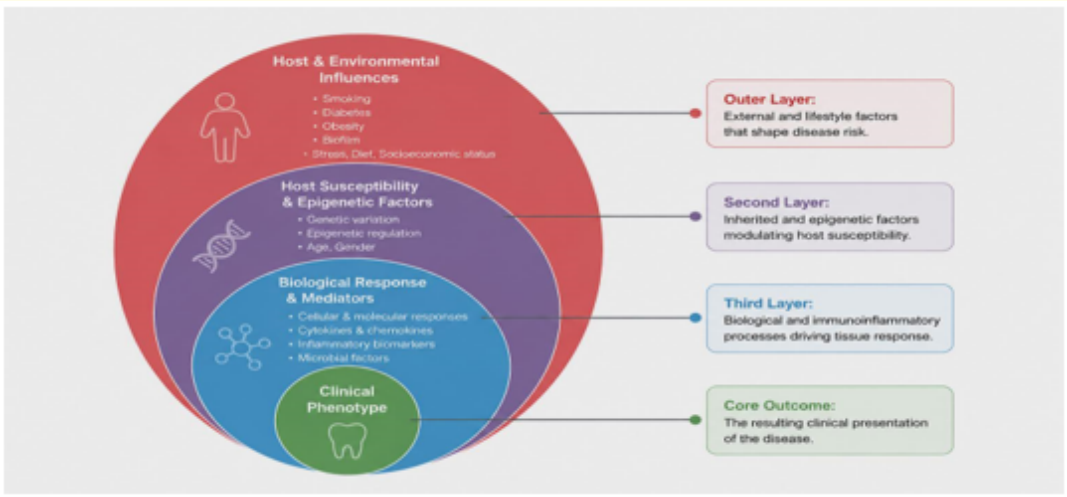


Figure 6

identify such keystone pathogens in periodontal disease are ongoing, with *Porphyromonas gingivalis* emerging as a strong candidate due to its ability to convert commensal microbes into dysbiotic ones. This transformation is achieved both through direct, host independent modulation of gene expression and through indirect effects mediated by host immune modulation. *P. gingivalis* has been termed the “master of subversion” because of its sophisticated strategies to evade and manipulate the innate immune system. Specifically, it impairs host defence by blocking toll like receptor for (TLR-4) activation, while simultaneously promoting a deceptive crosstalk between TLR-2 and the complement system, thereby neutralizing phagocytic activity. Additionally, *P. gingivalis* induces TLR-2 inside out signalling, leading to CR3 mediated ineffective phagocytosis and suppression of interleukin-12 production. It also paralyzes neutrophil chemotaxis by inhibiting interleukin-8 further undermining the immune response [1].

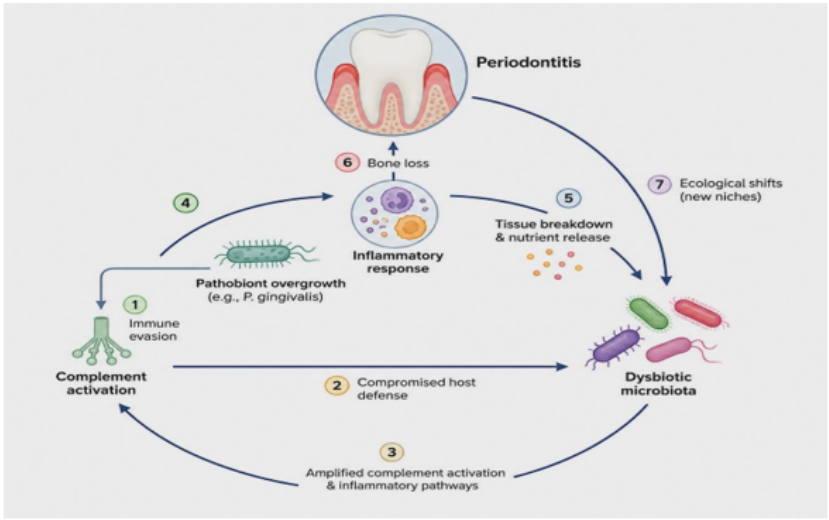


Figure 7

Polymicrobial synergy and dysbiosis model (2012)

The core principle of this model suggests that periodontitis arises from a synergistic and dysbiotic microbial community composed of native organisms acting together. These microbial consortia display collective properties that exceed the capabilities of their individual members. Each constituent plays a specific role that contributes to the overall pathogenic potential of the community. The colonizing bacteria organize themselves into a structurally stable network, supported by syntrophic nutritional interactions and chemical signalling, resulting in a physically and physiologically integrated ecosystem.

Recent advancements derived from independent metagenomic and mechanistic studies collectively indicate that the pathogenesis of periodontitis is driven by polymicrobial synergy and dysbiosis (the “PSD model”). This dysbiosis within the periodontal microbiota reflects an alteration in the relative abundance of specific bacterial species compared to their proportions in a healthy state. Such microbial imbalance disrupts the normal host–microbe interactions, ultimately triggering destructive inflammation and bone resorption [1].

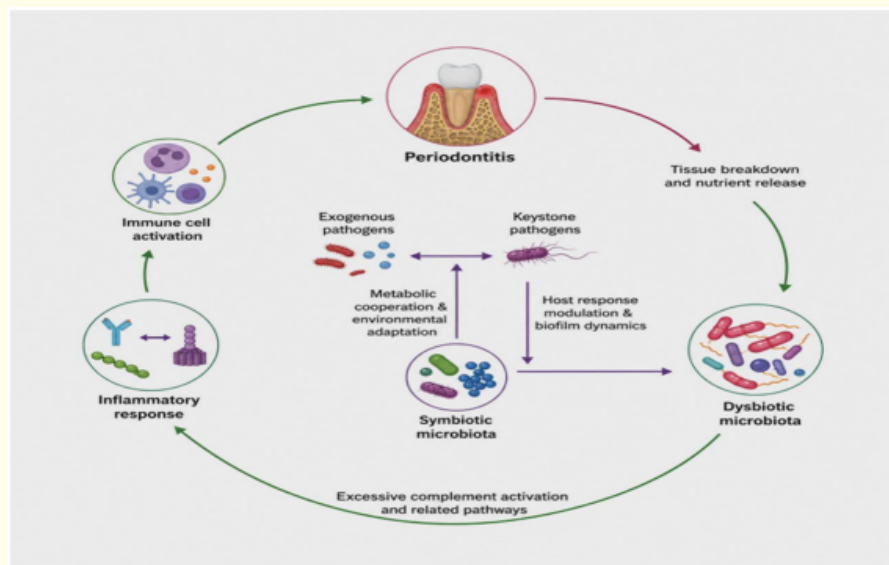


Figure 8

Generic multicasuality model (Heaton and Dietrich 2012)

Periodontal disease is a multifactorial condition resulting from the simultaneous interaction of several causal components. The five major contributing factors include genetic and epigenetic influences, lifestyle factors (such as smoking, stress, and diet), environmental factors (bacterial biofilms), systemic diseases like diabetes, and other unidentified factors. Their relative contributions are represented in a pie chart. It is suggested that the influence of these factors differs among individual patients with periodontitis. In younger patients with aggressive periodontitis, genetic factors play a comparatively greater role than in adults with chronic periodontitis. In contrast, lifestyle and environmental factors contribute more significantly to chronic periodontitis than to aggressive periodontitis [1].

Revised model (2013)

The idea that inflammation can drive changes in microbial composition was first introduced through the ecological plaque hypothesis. The revised model emphasizes a paradigm shift — recognizing bacterial colonization as a secondary consequence of inflammation rather

than its primary cause in periodontal disease. In this framework, the host immune response is considered the central factor responsible for uncontrolled inflammation and subsequent tissue destruction. Gingivitis, therefore, arises as a nonspecific inflammatory reaction, which alters the local environment and promotes the proliferation of specific periodontal pathogens. When the host response is effective and supported by favorable genetic and environmental factors, the pathogenic process is contained. Conversely, an inadequate response leads to disease progression and the clinical manifestation of periodontitis [1].

Immunomicrobial pathogenesis model (2014)

This model is grounded in the concept that periodontitis arises from a disturbance in host-microbiome homeostasis. It highlights the mechanisms through which a dysbiotic microbial community provokes a dysregulated immune response, ultimately resulting in periodontal disease. In a susceptible host, this process disrupts the delicate balance between host and microbial communities, leading to an imbalanced and uncontrolled inflammatory response that results in collateral tissue damage. Furthermore, the model emphasizes the distinct contributions of both innate and adaptive immune mechanisms in the pathogenesis of periodontal disease. Particular attention is given to the emerging roles of neutrophils and novel T helper cell subsets (Th17 and Treg), alongside the traditional Th1 and Th2 pathways, with B cells contributing to osteoclastogenesis. This intricate interplay between host immunity and microbial factors establishes a self-perpetuating cycle that intensifies dysbiosis and accelerates tissue destruction.

Contemporary model (2015)

A healthy periodontium is maintained by a symbiotic biofilm that elicits a balanced and self-limiting host response. However, when this biofilm accumulates, it creates an environment conducive to the proliferation of specific bacterial species that, through quorum-sensing mechanisms, amplify the host response and promote inflammation. The contemporary model illustrates a progression from a health-associated biofilm to an incipient dysbiotic state, eventually culminating in frank dysbiosis. Correspondingly, the host inflammatory response evolves from being proportionate and resolving to proportionate but non-resolving, and finally to a disproportionate, non-resolving state.

Polymicrobial genetic dysbiotic model (Stein and Karydis)

The current understanding of periodontal disease pathogenesis has evolved into a polymicrobial genetic dysbiosis model, which better explains the complex nature of periodontal diseases. This model incorporates polymicrobial synergy within a specific environment, dysbiotic microbial gene expression, and host genetic susceptibility. Polymicrobial synergy refers to cooperative interactions among different bacteria, including mutual growth support and complex signaling mechanisms. In this process, diverse dysbiotic microbial communities collectively contribute the genes required for the initiation and progression of periodontal disease [1].

Revised Page and Schroder model (2017)

The Page and Schroeder model (1976) offered a histopathologic framework outlining the sequence of pathological events that culminate in the clinical manifestations of periodontal disease. Initially, the Page and Schroeder model limited the role of neutrophils to the early stages of periodontal lesion development, attributing to them only restricted functions. However, recent advancements have revealed their structural diversity and functional versatility, uncovering previously unrecognized roles in both innate and adaptive immunity. Remarkably, neutrophils have been found to modulate lymphocyte activity and contribute to RANKL-mediated bone resorption, highlighting their involvement not only in the initiation but also in the progression of periodontal disease. Following the Page and Schroeder model, the significance of innate immune components in guiding and shaping adaptive immune responses has become increasingly recognized.

Inverted model (2019)

The inverted model suggests that periodontitis represents a continuum of inflammation, tissue destruction, and microbial dysbiosis, influenced by factors such as smoking, systemic conditions, and genetic predisposition. In this framework, the initial inflammatory response always precedes the emergence of periodontal pathogens. As inflammation intensifies, it generates “inflammatory spoils” that serve as nutrients, promoting the selective growth of specific bacterial subsets, particularly proteolytic and a saccharolytic species. Contrary to the traditional view where a dysbiotic microbiota triggers inflammation, the inverted model emphasizes that inflammation itself drives the development of dysbiosis.

Inflammation mediated polymicrobial-emergence and dysbiotic exacerbation (IMPEDE) model (2020)

Building on earlier research on inflammation-driven dysbiosis, the “Inflammation-Mediated Polymicrobial Emergence and Dysbiotic Exacerbation” (IMPEDE) model provides a comprehensive perspective on how inflammation serves as the primary driver of plaque-associated periodontitis. This unifying model is designed to integrate with and complement the 2017 World Workshop Classification of Periodontitis, recognizing five stages (0–IV). Stage 0 represents health, followed by four progressive phases of disease: gingivitis (inflammation associated with commensal plaque overgrowth); initiation/early periodontitis (increased polymicrobial diversity and dysbiosis triggered by inflammation); inflammation-driven exacerbation of dysbiosis via a self-sustaining feedforward loop; and late-stage periodontitis.

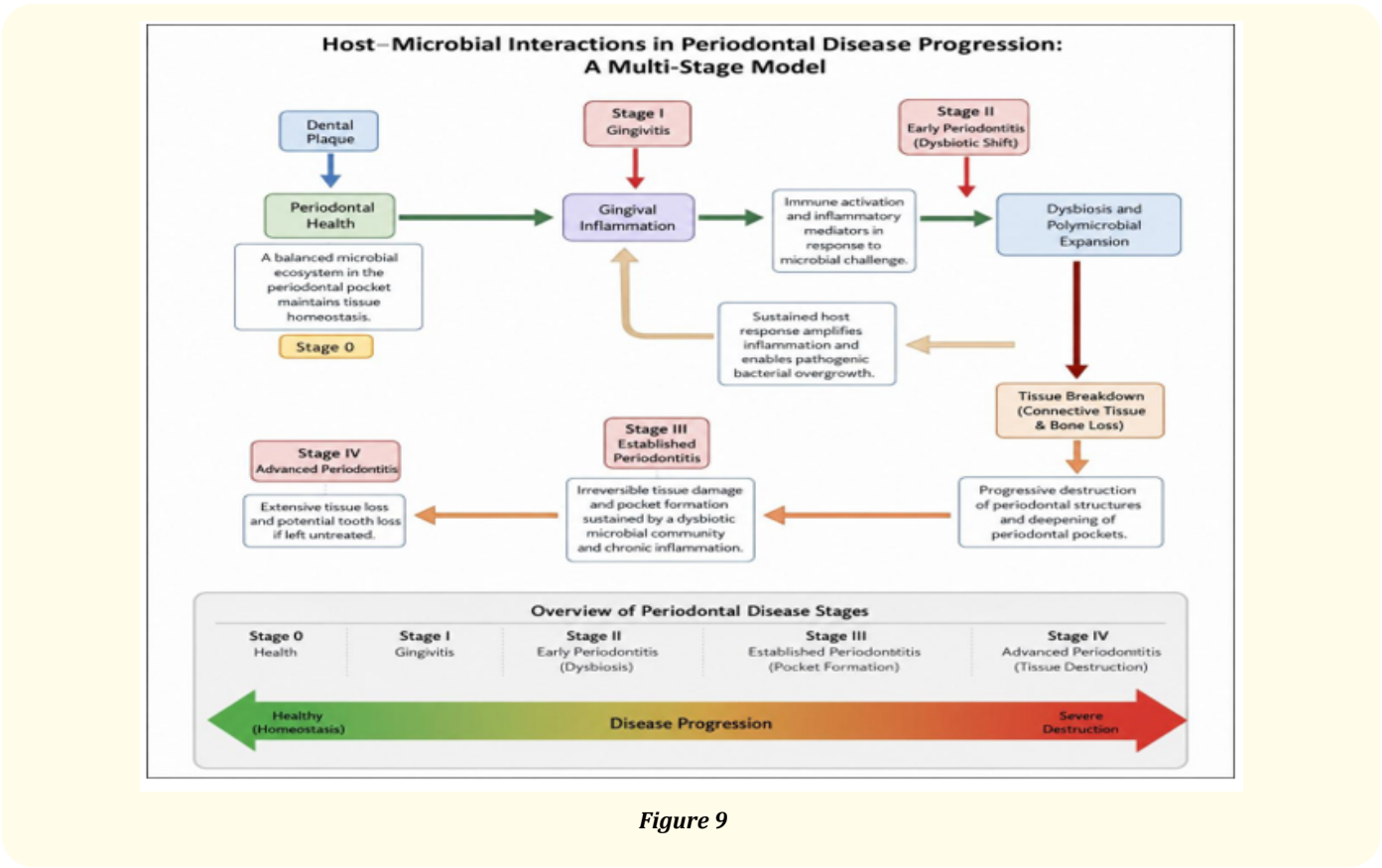


Figure 9

Models of periodontal disease progression

Disease progression is an essential component of periodontal disease pathogenesis. Therefore, understanding the various models of periodontal disease progression is important for timely diagnosis and appropriate treatment planning [1].

Continuous model

The continuous model describes chronic destructive periodontal disease as a slow, steady, and progressive process. Some periodontal sites may remain unchanged throughout life, while others begin to show attachment loss at different stages of an individual's life [1].

Random burst model

The random burst model suggests that periodontal destruction occurs in episodic bursts of activity. Attachment loss reflects the cumulative effect of repeated disease episodes. Activity may arise randomly at any site, with some sites remaining unaffected while others experience one or multiple bursts of breakdown [1].

Asynchronous multiple burst model

This model is an extension of the random burst model. It proposes that several sites may undergo periodontal breakdown within a relatively short period, followed by long phases of remission [1].

Stochastic model (Manji, 1989)

According to this model, periodontal disease progresses through sudden bursts of activity alternating with remission periods, despite an underlying stable disease tendency. The process is compared to Brownian motion, reflecting the cumulative and multifactorial nature of the disease [1].

Fractal model (Landini, 1991)

The fractal model interprets time-dependent periodontal events as noise and offers a theoretical explanation of the relationship between causes and effects in periodontal destruction. It emphasizes the multifactorial nature of periodontal disease and explains how minor changes in certain factors may lead to significant clinical outcomes [1].

Unification of burst and linear theories (Gilthorpe, 2003)

This model combines the principles of both the linear and burst theories by analyzing periodontal disease within a multilevel framework. A multilevel model is used for hierarchical data, where variations at each level are assessed independently. This approach provides a better understanding of the dynamic process of periodontal breakdown [1].

Mathematical model (Papantonopoulos, 2013)

This model considers periodontitis as a nonlinear chaotic process and measures disease progression quantitatively. Host response is compared to a clock pendulum swinging between an aberrant zone (rapid progression) and a resolving zone (minimal progression), with an overlap called the settlement zone. Aggressive periodontitis shifts toward the aberrant zone, while chronic periodontitis shifts toward the resolving or settlement zone.

Conclusion

Over the past few years, several models outlining the pathogenesis of periodontal disease have been proposed, each reflecting the understanding available at the time. More recently, a biologic systems approach has emerged, offering the potential to transform traditional conceptual models by portraying the disease as a complex, interconnected regulatory network. Periodontitis is no longer viewed as a straightforward bacterial infection or a linear host response to microbial dysbiosis. Instead, it represents a self-sustaining state of chronic inflammation, driven by the interplay between a dysbiotic microbiome, host factors, and environmental influences, ultimately resulting

in tissue destruction. Ongoing research is essential to uncover the regulatory pathways and molecular mediators at the host–pathogen interface, enabling the development of personalized preventive and therapeutic strategies tailored to an individual’s unique biology and risk profile.

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