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Pathogenesis of periodontal disease- historical thoughts, current concepts and future perspectives

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Abstract

Periodontal disease has been affecting humankind throughout time and geography. The understanding of its causation, and progression and treatment has evolved over centuries, with changing concepts reflecting the contemporary state of medical science and diagnostic aptitude. This review briefly summarizes the journey from the earliest recorded beliefs to the most recent hypothesis, with the aim to underscore the direction of scientific elucidation, and hence, foresee the probable future outlook. With such an overview, a better understanding of the evolving strategies of periodontal patient management can be aptly developed.

Keywords: Periodontal Disease, Pathogenesis

INTRODUCTION

Periodontal disease (PD) is one of the most common chronic inflammatory diseases affecting humans. Being the sixth most prevalent human disease globally, periodontitis has been estimated to affect more than 743 million individuals.[1,2] Despite its occurrence in humans throughout time and territory, an understanding of the etiology and pathogenesis of periodontal diseases (PD) has remained elusive, with the concepts continuously evolving since millennia. This review aims to summarize the historical transition of these concepts and briefly introduce the current trends and future prospects.

First concepts:

The earliest thoughts on gum disease were based on the generalizations with diseases elsewhere in the body, and accrued those diseases were caused by demons or as a divine punishment. Nothing but the supernatural could cause or cure this disease.

Early scientific thinking:

With the advent of a rational medical philosophy, the early physicians including Aristotle and Hippocrates, recognized the preventability of gum bleeding and prescribed numerous mechanical and chemical measures for the same. However, no significant elucidation was made regarding the cause of gum disease.[3]

Birth of causal hypotheses:

The earliest deliberations on the etiology of periodontal disease were divided into two broad schools of thought: localists and generalists.[4]

The localists hypothesized that the primary causes of periodontal disease were intra-oral and that intra-oral interventions can, by themselves, prevent and successfully treat periodontal disease. This school brought about the “domino theory” of disease causation (Fig 1). Prominent clinicians including Fauchard, Loe and Riggs belonged to this school of thought.[4]

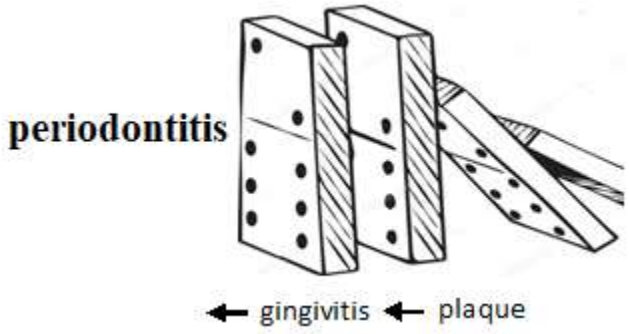

Fig.1: Domino theory of periodontal disease

The generalists believed that the primary causes of periodontal disease are remote from the oral cavity and cannot be cured unless these causes are pinpointed and intervened upon. Eminent scientist's miller and buchard belonged to this thought and related periodontal disease to diabetes, venereal diseases, mercury poisoning, rheumatoid arthritis, and gout, among other conditions.[4]

Over the subsequent decades, the coincident emergence of the germ theory of disease, coupled with the observed clinical effectiveness of oral hygiene based treatments, led to substantiation of the simplistic "plaque hypothesis" (Fig. 2).[5]

Fig.2: Simplistic Plaque hypothesis

Concept of the role of bacteria in periodontal disease pathogenesis:

As a breakthrough discovery, the presence of plaque was found to correlate with development of gum disease. However, when the mere presence of plaque could not concord with the development of periodontal disease, the quest for the identification of the specific "periodontal pathogens" led to various hypotheses regarding the causative role of bacteria.

1. **Traditional Non-specific plaque hypothesis:** originally put forward by Miller in 1890,[6] it purported that indigenous oral bacterium, in the absence of dental hygiene, colonized the subgingival area and initiated inflammatory diseases of the gums. Hence prevention should focus on removing all plaque from the tooth surface.
2. **Specific plaque hypothesis:**Loesche et. al. in 1973, [7]noticed that the antibiotic kanamycin was particularly effective against cariogenic species such as oral

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streptococci and reduced caries formation, and put forth the "Specific plaque hypothesis", which proposed that the use of antibiotics against specific bacterial species could cure and prevent caries. In 1976 [8], this postulation was extended to periodontal disease, which were proposed to be inflammations caused due to infection by specific periopathogens and therefore antibiotic treatment would be effective [9]. However, because the identity of these "specific" pathogens could not be clearly established, the specific plaque hypothesis in its original form could not gain much acceptance.

3. **Mixed anaerobic infections:** This theory was a contemporary thought of the specific plaque hypothesis. It was proposed by van Steenburgen et al in 1984[10], that obligatory anaerobes, in synergy with facultative anaerobes, caused periodontal disease. Interestingly, they postulated "synergy" between microorganisms as a mechanism for disease initiation, much before the concept was revisited in 2012.

4. **Updated Non-specific plaque hypothesis:** Theilade in 1986 updated the NSPH, focusing particularly on periodontal disease [11]. It stated that all bacteria in plaque contribute to the virulence of the microflora by having a role in either colonization, evasion of the defense mechanism, and/or provocation of inflammation and tissue destruction. Nevertheless,it was observed that some indigenous subgingival bacteria can be more virulent than others and that plaque composition changes from health to disease, with differences in the microbial composition leading to differences in pathogenic potential of plaque.

5. **Red complexhypothesis:**The milestone discovery of "socransky complexes", particularly the association of the red complex with overt periodontal disease, reverted the focus of research to "specific pathogens", the presence of which could indicate/predict periodontal destruction [12]. However, this hypothesis was ambiguous as to the mechanisms by which these pathogens could consistently coexist exclusively in the diseased sites and as compared to the healthy ones.

6. **Ecological plaque hypothesis:**In 1994, Philip D. Marsh proposed a hypothesis that combined key concepts of the earlier hypotheses.According to his "Ecological Plaque Hypothesis" (EPH), disease is the result of an imbalance in the total microflora due to ecological stress, resulting in an enrichment of some "oral pathogens" or disease-related micro-organisms [13]. In 2003, this hypothesis was extrapolated to the "ecological catastrophe hypothesis" [14], which related the changes in microbial composition to changes in ecological factors such as the presence of nutrients and essential cofactors, pH and redox potential. In accordance, preventive strategies were suggested to focus on diet modification to prevent the "ecological change" that would result in selection of harmful species. However, like the other hypotheses, the traditional EPH did not address the role of genetic factors of the host that significantly contribute to the composition of dental plaque and to susceptibility to disease[15].

Contemporary hypotheses:

1. **Keystone pathogen hypothesis:** The concept of keystone species is derived from basic ecological studies. Certain species have an effect on their environment that is disproportional relative to their overall abundance [16,17,18]. George Hajishengallis and colleagues applied this concept to oral microbiology by proposing "The Keystone-Pathogen Hypothesis" (KPH) [19]. The KPH indicates that certain low-abundance microbial pathogens can cause inflammatory disease by increasing the quantity of the normal microbiota and by changing its composition.
   Evidence was found of three major KPH mechanisms of P. gingivalis that could impair

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the above-mentioned host defenses: (1) Toll-like receptor (TLR) response manipulation, (2) interleukin 8 (IL-8) subversion and (3) the corruption of the complement system ([18,20,21,22]).

Though highly plausible, the KPH relies highly on the activity of P. gingivalis, though other, yet unidentified species might be equally or even more active in the process that leads from periodontal health to disease. Besides, the "keystone pathogenesis" itself has yet to be demonstrated in humans [23].

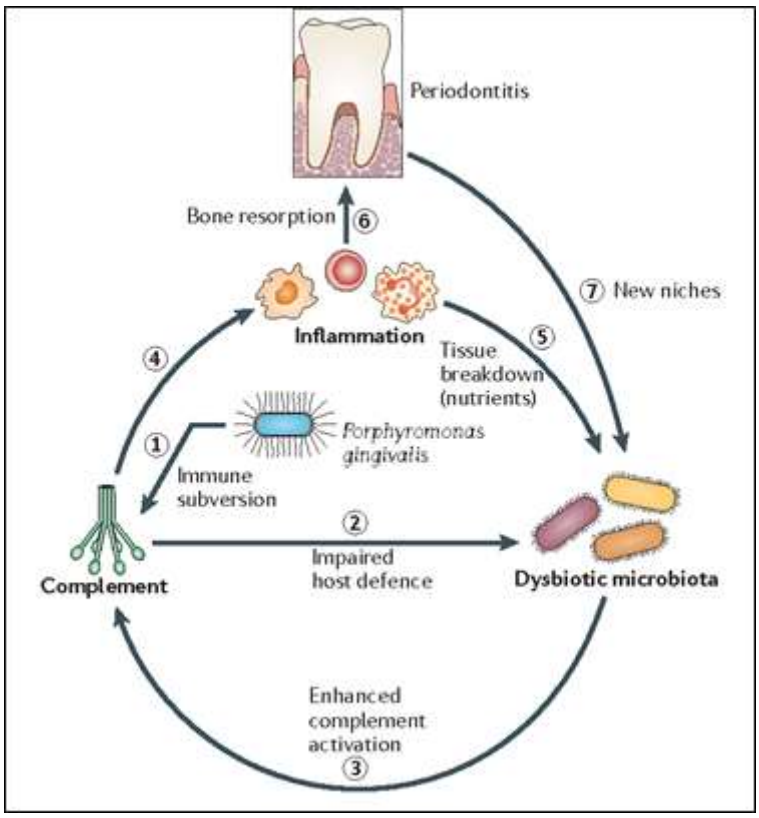

Fig.3: Keystone Pathogen hypothesis 19

2. **Polymicrobial synergy and dysbiosis:** This concept put forth by Hajishingalis aims to address these loopholes in the KPH. This model highlights the importance of bacteria other than the classical "red complex" species that could have similar keystone roles in periodontitis [24]. It states that in periodontitis, polymicrobial synergy can lead to dysbiosis. It recognised the role of host system, since different members or different gene combinations can result in a disease-provoking microbiota. The conclusion is that the transition to periodontitis requires a dysbiotic microbiota and a susceptible host [25]. The PSD-model is currently the most extensive, however it is modeled only for periodontitis.

Models of periodontal pathogenesis:

Coincident to the discovery of microbes as being causally associated with periodontal disease, were also the observations, that their oral hygiene status alone could not predict the development of disease in all individuals. Therefore, the paradigms of periodontal pathogenesis also evolved, as an active involvement of host response became more apparent, in contrast to the previous belief of a passive "host-parasite" relationship. Simultaneously, the models of periodontal disease pathogenesis also changed over time, as briefly described below:

Early models of pathogenesis

1. **Linear model:** proposed by Loe et.al.[26] implicated bacterial plaque deposits as the primary, direct factor in the development of periodontitis.

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2. **Circa model:** During 1970's and early 1980's specific Gram-negative, anaerobic, or microaerophilic bacteria were implicated in the causation of periodontitis, and the protective and destructive roles of the immune-inflammatory responses and the critical role of polymorphonuclear Neutrophils (PMNs) in contributing to periodontal damage were described. [27-29] A recognition of the host response as an active process was a highlight of this model.
3. **Critical pathway model:**Offenbacher in 1996 [30] proposed this model, based on the new knowledge of the various genetic and environmental factors contributing to periodontal disease,which were recognized to be powerful determinants of disease severity. however, the degree of influence of pathogen versus host factors was not elucidated.

Contemporary models:

1. **Non-linear model:** In this model, proposed by Page &Kornmann in 1997 [29], host immuno-inflammatory mechanisms were thought be activated by bacterial products, which in turn, stimulated the damage to connective tissue and bone and shaped the clinical presentation of disease. However, a "non-linear" nature of interaction was proposed to exist between the host response elements (antibodies, PMNs Inflammatory mediators) and the pathogens, which could inter-regulate each other, as well as the clinical presentation of disease. The model also took into consideration that the range of host responses and range of clinical expressions of disease, were primarily determined by genetic and environmental factors that modified the host response. Though quite inclusive of the contemporary knowledge, the model was simplistic in the face of the current evidence on the molecular and genetic level.
2. **Multilevel hierarchical model:**Kornmann in 2008 [31], further refined the nonlinear model to include advancements in proteomic research, and proposed this model, which reflected the interactions at gene, protein, and metabolite level. A hierarchy of interactions and manifestations was put forth, from signal transduction and gene level (Level 1) to the tissue and clinical phenotype (Level 6) .
3. **Biologic system model:**Simultaneous to the previous model, Offenbacher in 2008 [32], proposed this model as a simplistic integration of the various interactions that occur at different levels (i.e, environmental, genetic and cellular) to affect the clinical phenotype of periodontal disease.
4. **Contemporary model:** Contemporary model of periodontitis pathogenesis was proposed by Meyer and Chapple in 2015[33], and is based upon an inter-relationship between the periodontalbiofilm and the inflammatory immune response. Implicit in the model is that the transition from health togingivitis, and ultimately to periodontitis, is associated with evolution of a health-promoting biofilm, to one ofincipient dysbiosis and then to one of frank dysbiosis, and at the same time the host's inflammatory response transitsfrom being proportionate and pro-resolving, to proportionate/non-resolving and then todisproportionate/non-resolving. These categorizations reflect the current understanding of the ambivalence in the bacterial etiology, host response and environmental factors that permits their influence to shift to either side of the spectrum. Based on this model, antiinfective treatment, host modulation, as well as risk factor modification, have their specific niches in comprehensive patient management.
5. **Simple Random Effects Model:** This model, proposed by Dahlen et al. in 2020 [34], takes into account the highly variable and multilevel interactions (noise) between various factors that occur in the "symbiont-host parasite relationship" involving the host and periodontal pathogens. The model gives expression to the concept of periodontitis, as a process involves the tissues accumulating the effectively random noise of inflammatory provocations and factors promoting recovery within the biofilm, in contact with the tissues,

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that over long periods of time, result in breakdown of the tissues and loss of attachment. The model predicts the occurrence of bursts and remissions in the progress of periodontitis. The model suggests that some degree of loss of attachment is likely to occur after 30–40 years of age, but that simple measures to disturb the biofilm regularly (oral hygiene) may reduce the probability of loss of attachment.

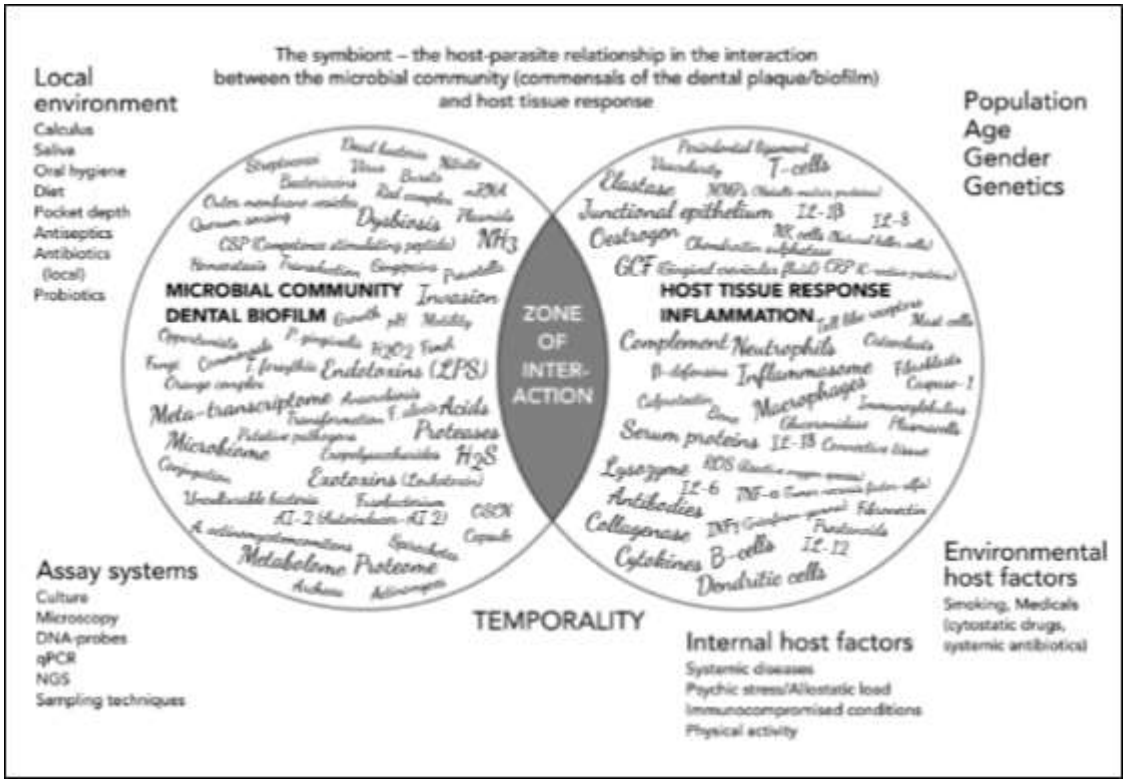

Fig.4: Simple Random Effects Model [34]

Future perspectives:

The advancement in technology for sequencing has allowed detailed analysis at the meta-genome and meta-transcriptome level. This will lead to unravelling of the mechanistic inter-relationships among bacteria, and with the host,that trigger the development of periodontal disease. Moreover, the discovery of other "keystone" species/strains, as well as non-bacterial micro-organisms will enable future studies to provide a more holistic view of the oral ecology and modify the contemporary hypotheses. Nonetheless, given the multifactorial nature of periodontal pathogenesis, the current "dysbiosis" model is most likely to be upheld, with newer host response components being accommodated in the already assigned levels of influence.

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