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RESEARCH ARTICLE

A REVIEW ON MODELS OF PATHOGENESIS IN PERIODONTITIS.

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Abstract

Periodontitis is a complex disease in which disease expression involves intricate interactions of the biofilm with the host immune-inflammatory response and subsequent alterations in bone and connective tissue homeostasis. The past decade of basic research in periodontology has driven radical changes in our understanding and perceptions of the pathogenic processes that drive periodontal tissue destruction. The core elements of the classical model of disease pathogenesis (1997) remain pertinent today; however, our understanding of the dynamic interactions between the various microbial and host factors has changed significantly. This review article tries to draw these complex new learnings into a contemporary model of disease pathogenesis and attempts to highlight selected key steps in the evolution of our concepts of periodontal pathogenesis and to define how future models are likely to evolve based on the new technologies.

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Introduction:-

Chronic adult periodontitis is a bacterially induced chronic inflammatory disease that destroys the connective tissue and bone that support teeth. Concepts of the specific mechanisms involved in the disease have evolved with new technologies and knowledge. Histopathologic observations of diseased human tissues were used previously to speculate on the causes of periodontitis and to describe models of pathogenesis. Experimental evidence later emerged to implicate bacterial plaque deposits as the primary factor initiating periodontitis. At the same time, specific bacteria and immune-inflammatory mechanisms were differentially implicated in the disease. In the mid-1990s, early insights about complex diseases, such as periodontitis, led to new conceptual models of the pathogenesis of periodontitis. Those models included the bacterial activation of immune-inflammatory mechanisms, some of which targeted control of the bacterial challenge others that had adverse effects on bone and connective tissue remodeling. Such models also acknowledged that different environmental and genetic factors modified the clinical phenotype of periodontal disease. However, the models did not capture the dynamic nature of the biochemical processes, i.e., the innate differences among individuals and changes in environmental factors may accelerate biochemical changes or dampen that shift. With emerging genomic, proteomic, and metabolomic data and systems biology tools for interpreting data, it is now possible to begin describing the basic elements of a new model of pathogenesis. Such a model incorporates gene, protein, and metabolite data into dynamic biologic networks that include disease-initiating and -resolving mechanisms. This type of model has a multilevel framework in which the biochemical networks that are regulated by innate and environmental factors can be described and the

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interrelatedness of networks can be captured. New models in the next few years will be merely frameworks for integrating key knowledge as it becomes available from the “-omics” technologies. However, it is possible to describe some of the key elements of the new models and discuss distinctions between the new and older models. It is hoped that improved conceptual models of pathogenesis will assist in focusing new research and speed the translation of new data into practical applications. This study is an attempt to summarize the various models of pathogenesis and the current status in the field of periodontology.

Concepts In The Models Of Pathogenesis:-

Linear Model:-

The modern era of the pathogenesis, prevention, and treatment of periodontal diseases began in the mid- 1960s with human and animal experimental evidence demonstrating the critical role of bacteria in the initiation of gingivitis and periodontitis. This led to a clear concept of pathogenesis, i.e., bacteria cause periodontal disease (Fig. 1). This model implicated bacterial plaque deposits as the primary, direct factor in the development of periodontitis and resulted in the abandonment of former concepts that involved non-bacterial factors, such as trauma from occlusion, systemic conditions, and diet³. This tenet of the critical role of bacteria dramatically changed the prevention and treatment of periodontitis. However, several implicit statements were hidden within the simple concept, including, for example, the assumption that bacterial plaque mass was the causative factor and the bacterial products, such as collagenases, directly destroyed tissue.

Basic conceptual model - circa model (1980 model):-

A dynamic equilibrium between the periodontal microbiota and the host generally results in a clinical state of periodontal health, characterized by minimal inflammatory changes in the marginal gingival tissues. Maintenance of health is most easily achieved by controlling the resident mass of bacteria. In rare instances, control of specific microorganisms may be indicated. Lack of microbial control may lead to an imbalance between the microbiota and the host due to a markedly increased microbial mass and/or increased virulence of the micro-organisms present. Such alterations in the host-parasite equilibrium may result in transient episodes of tissue destruction and, in the long term, to cumulative damage to the periodontal tissues. During 1970's and early 1980's research and scientific discussions based on the simple concept of bacterial causation led to great advances in knowledge. 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^{12,15,17,19,22,23,25}. Finally, during this period, the initiation and progression of periodontitis was described in terms of distinctive histopathological characteristics that provided insights into the pathogenesis processes²⁶. The most important aspect of this model is that a distinction between the role of the microbial challenge and immune-inflammatory mechanisms in the pathogenesis of periodontal disease was apparent (Fig. 2).

Drawbacks: This model could not explain some clinical disease patterns or phenotypes which had characteristic bacteria and host responses. The extensive research through the mid-1980s led to critical refinements in the pathogenesis concept which stated that specific bacteria initiated the disease process by activating host responses, which were protective and destructive. The actual destruction of connective tissue and bone resulted primarily from activated tissue mechanisms, such as matrix metalloproteinases, interleukin-1, and prostaglandins²⁷.

Critical pathway model:-

In 1990 advances has led to the understanding the cellular and molecular interaction which resulted in periodontal disease progression. This led to critical pathway (Fig. 3) of pathogenesis by Offenbacher in 1996.¹

There was a growing appreciation during this period of the genetic variations in the development and severity of periodontal disease which accounted for 30% to 60% of variability which added further complexity to the earlier conceptual models. Genetic differences among individuals seemed to be a significant determinant of risk for periodontal disease and most importantly there were gene variations that altered host responses and modified the clinical severity of disease². With new knowledge of the various factors contributing to periodontal disease, the clinical phenotype is not simply the microbial challenge translated by a standard host response but also smoking and diabetes were shown to be powerful determinants of disease severity^{4,5}.

Non-linear model:-

The basic conceptual model of periodontitis was revised in 1997, in great part to acknowledge that various risk factors operated by modifying host responses led to changes in disease expression⁶. In this model, host immuno-inflammatory mechanisms are activated by bacterial products. Host derived enzymes such as matrix metalloproteinase as well as changes in osteoclast activity driven by cytokines and prostanoids cause most of the tissue destruction. The 1997 model was non-linear model.⁷ The model implied that there were a range of host responses and a range of clinical expressions of disease that were primarily determined by genetic and environmental factors that modified the host response (Fig. 4). Each combination of genetic variations and environmental factors may define a specific gene expression pattern⁸.

Although many of the concepts presented in the 1997 non-linear model of periodontal disease remain relevant today, there have been advances in knowledge about periodontal disease that may alter models of pathogenesis.

Periodontitis and other chronic diseases were acknowledged as “complex” in character. Complex biologic traits have molecular networks that display emergent properties as a result of contributions from genetic and environmental factors. The integrated behavior of the entire system can be studied using new simulation tools. Complex diseases that may be applicable to models of periodontal pathogenesis involve the roles of environmental factors such as smoking and diabetes, which may influence the biology through multiple mechanisms. To add further complexity to a conceptual model for periodontal disease, we must recognize that the modifying factors, such as a particular gene variant, may interact in a specific environmental context. Other advances in the general knowledge of chronic diseases included the use of genomic, proteomic, and metabolomic technologies to better explain the molecular networks that are involved in specific gene–environment interactions in selected tissues.

Multilevel hierarchical model :-

The 1997 conceptual model of the pathogenesis of periodontal disease is still relevant today; however, the framework is now based on a multilevel hierarchical organization, and the interactions are reflected in gene, protein, and metabolite expression patterns. In this model (Fig. 5) the top layer includes clinically observable parameters, such as smoking, whereas the levels below include tissue, cellular, and sub cellular layers, each divided into biologic networks. At the lower levels, the biologic expression of the immune inflammatory network and bone and connective tissue network are determined by the microbial factors and the specific combination of environmental factors and gene variations for that individual.

New Biological systems model:-

Building a systems biological model of periodontitis presents substantial requirements and challenges, but investigators have started to provide data on the entities and gene and protein expressions associated with certain components of the periodontal model. This model (Fig. 6) involves bacterial components, environmental factors such as smoking and diabetes⁹.

This provides a frame work for viewing the contributions and relative importance of all components that contribute to the clinical presentation of the periodontal disease and individual response, including cytokines and lipid mediators, produced by the host, as well as alterations in bone and connective tissue, can be clearly characterized by a specific pattern of gene, protein, and metabolite expression. The expressed proteins and metabolites provide feedback on the system to regulate the host response and bone and connective tissue, while helping to control the bacterial challenge.

The Keystone Pathogen Hypothesis:-

The “keystone pathogen” hypothesis holds that certain low-abundance microbial pathogens can orchestrate inflammatory disease by remodeling a normally benign microbiota into a dysbiotic one. In architecture, the keystone is the central supporting stone at the apex of an arch. The term “keystone” has been introduced in the ecological literature to characterize species whose effects on their communities are disproportionately large relative to their abundance and which are thought to form the “keystone” of the community’s structure.¹⁰

The quest to identify specific periodontal pathogens has led to significant progress, including the identification of a number of candidates, mostly gram-negative anaerobic bacteria that colonize subgingival tooth sites. Foremost amongst this group are three species which comprise the so-called “red complex”, are frequently isolated together, and are strongly associated with diseased sites in the mouth: *Porphyromonas gingivalis* (formerly known as

Bacteroides gingivalis)¹¹, *Treponema denticola* and *Tannerella forsythia*^{13,14}. Much research work has been directed towards understanding the pathogenic mechanisms and virulence determinants of these three bacterial species in the context of a conventional host-pathogen interaction, as exemplified by diseases with a single infective etiology¹³.

The hypothesis, in which periodontal pathogens transform the normally symbiotic microbiota into a dysbiotic state that leads to a breakdown in the normal homeostatic relationship with the host, came from evidence that *P. gingivalis* has evolved sophisticated strategies to evade or subvert components of the host immune system (e.g., Toll-like receptors and complement) rather than act directly as a proinflammatory bacterium^{16, 18}. Accordingly, it was hypothesized that *P. gingivalis* impairs innate immunity in ways that alter the growth and development of the entire biofilm, triggering a destructive change in the normally homeostatic host-microbial interplay in the periodontium. In other words, *P. gingivalis* could be a keystone pathogen of the disease provoking periodontal microbiota.

The keystone hypothesis was supported by a recent study in the mouse model. This study showed that, at very low colonization levels (<0.01% of the total bacterial count), *P. gingivalis* induces periodontitis accompanied by significant alterations in the number and community organization of the oral commensal bacteria.²⁰ These alterations occur soon after *P. gingivalis* colonization and precede the onset of inflammatory bone loss, suggesting that the dysbiosis is probably the cause of the disease. The obligatory participation of the commensal microbiota in disease pathogenesis was shown by the failure of *P. gingivalis* alone to cause periodontitis in germ-free mice, despite its ability to colonize this host.²⁰

Keystone pathogen-induced dysbiotic disease (Fig. 7):-

Despite its low-level colonization of the periodontium, *P. gingivalis* causes inflammatory periodontitis through dysbiosis, *i.e.*, an unbalancing of the relative abundance of individual components of the microbiota compared with their abundances in health. This activity requires the bacterium's gingipain, a C5 convertase-like enzyme which cleaves C5 generating high levels of C5a locally. C5a-induced activation of C5aR triggers inflammation but is also critically involved in a subversive crosstalk (with TLR2) that impairs leukocyte killing. The ability of *P. gingivalis* to orchestrate inflammatory disease via community-wide effects, while being a minor constituent of this community, qualifies it as a keystone pathogen. This process is reversible since C5aR blockade promotes the clearance of *P. gingivalis* and negates its dysbiotic effects.

P. gingivalis subverts complement and impairs host defense leading to overgrowth of oral commensal bacteria, which cause complement-dependent inflammation. Inflammatory tissue destruction is favorable to further bacterial growth as it provides a nutrient-rich gingival inflammatory exudate (degraded host proteins and hemin, a source of essential iron). These environmental changes are better exploited by and thus favor proteolytic and asaccharolytic bacteria, leading to compositional changes in the bacterial community. Inflammatory bone resorption, moreover, provides the dysbiotic microbiota with new niches for colonization. These alterations collectively lead to and sustain periodontal disease.

Polymicrobial synergy and dysbiosis model:-

Recent advances based on independent metagenomic and mechanistic approaches collectively suggest that the pathogenesis of periodontitis involves polymicrobial synergy and dysbiosis (the 'PSD model').²¹ The dysbiosis of the periodontal microbiota signifies a change in the relative abundance of individual components of the bacterial community compared to their abundance in health, leading to alterations in the host-microbe crosstalk sufficient to mediate destructive inflammation and bone loss (Fig. 8).

Synergism among periodontal bacteria:-

The synergistic pathogenicity of periodontal organisms in animal models has been recognized for some time and nutrient transfer among *P. gingivalis* and other species such as *T. denticola* is well defined.^{11,13} Indeed, co-culture of *P. gingivalis* with *T. denticola* induces an alteration in *P. gingivalis* hemin uptake strategies and changes in the abundance of enzymes involved in glutamate and glycine catabolism²¹. *P. gingivalis* can provide a source of free glycine and isobutyric acid for *T. denticola* growth, while *T. denticola* produces succinic acid which enhances growth of *P. gingivalis*.^{20,21} *S. gordonii* and *A. actinomycetemcomitans* interact on a number of levels. *S. gordonii* produce lactate as an end product of metabolism, and *A. actinomycetemcomitans* displays resource partitioning to favor lactate as a carbon source even in the presence of alternative carbon sources such as glucose or fructose.

Interactions between bacterial communities and epithelial cells:-

A consortia of *P. gingivalis* and *Fusobacterium nucleatum* invade gingival epithelial cells in higher number than either organism alone. *F. alocis* and *P. gingivalis* also exhibit synergistic infection of epithelial cells, and dual species invasion elicits a distinct pattern of host cell responses.

Manipulation of host immunity:-

P. gingivalis and certain other periodontitis-associated bacteria can suppress complement activation through the action of specific proteolytic enzymes. The gingipains of *P. gingivalis*, interpain A of *Prevotella intermedia*, and karilysin of *Tannerella forsythia* can all block complement activation by degrading the central complement component C3, or upstream components of the complement cascade such as the pattern-recognition molecules mannose-binding lectin and ficolins.

According to the PSD model, if a keystone pathogen is a conductor in the orchestra, the pathobionts are its musicians. Dysbiosis is crucially dependent, not on the particular microbial roster rather on the specific gene combinations or collective virulence activity within the dysbiotic microbial community. Polymicrobial synergy and dysbiosis drive periodontitis in a susceptible host. Dysbiosis involves specialized accessory and keystone pathogens and pathobionts. Microbial immune subversion is central to the persistence of dysbiotic communities. The dysbiotic microbiota sustains itself by feasting on the “inflammatory spoils.”

Contemporary model- Chapple 2015:-

Contemporary model of periodontitis pathogenesis is based upon a circular relationship between the periodontal biofilm and the inflammatory immune response (Fig. 9). Implicit in the model is that the transition from health to gingivitis, and ultimately to periodontitis, is associated with evolution of a health-promoting biofilm, to one of incipient dysbiosis and then to one of frank dysbiosis, and at the same time the host's inflammatory response transits from being proportionate and pro-resolving, to proportionate/nonresolving and then to disproportionate/nonresolving.²⁴ Unlike the classical paradigm of a pathogenic microflora inducing inflammation, we now recognize that inflammation also contributes to the biofilm structure and function and there is a need for metagenomic studies to start defining what functional characteristics of the biofilm render it pathogenic as opposed to health promoting. At the same time, pathogenic roles for viruses are emerging, either as priming agents of host immune cells or as co-infectors alongside bacteria, conspiring together to deregulate host-defence systems. It is also becoming clear that the hosts' periodontal armamentarium against dysbiosis includes diverse cell types, epithelial cells, dendritic cells, natural killer cells, T- and B-lymphocytes and neutrophils, all of which carefully orchestrate an appropriate response to the biofilm and its components. There are likely to be a multitude of pathways to dysregulation of local host immunity within the periodontium that may arise when such a complex series of highly coordinated signalling events is necessary to maintain tissue homeostasis. The key features of immune disruption in periodontitis include excessive inflammation that fails to resolve and becomes chronic and self-destructive in nature, generating an environment that favours pathogenic bacteria. Future research needs to identify ways of restoring a balance between the inflammatory immune response and the biofilm, resolving the chronic inflammatory lesion and re-establishing a symbiotic relationship within the biofilm and between the biofilm and the host.

Conclusion:-

Over the past few years a number of models describing the pathogenesis of periodontal disease have been presented based on existing knowledge at that time.

The more recently explored biologic systems approach to modeling holds promise for revolutionizing conceptual models of the past by providing a comprehensive view of the disease process as a complex regulatory network.

Genomic, proteomic, and metabolomic data related to periodontal diseases are being collected. When these data are combined with knowledge of even a limited set of environmental and genetic factors contributing to periodontitis, we should be able to build more robust models of the pathogenesis of periodontal diseases.

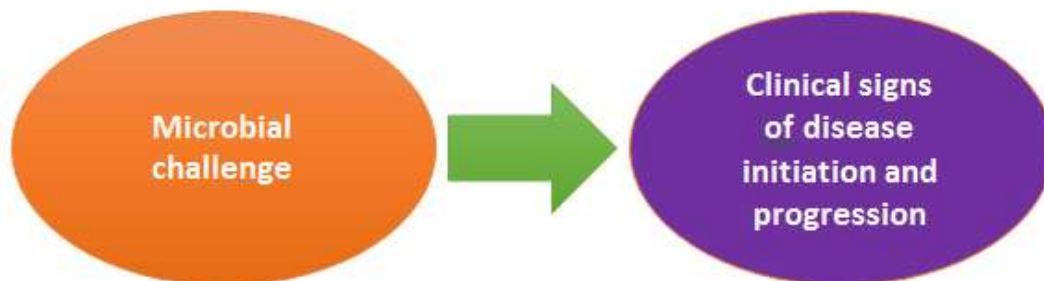


Fig. 1:- Linear model



Fig. 2:- Circa model

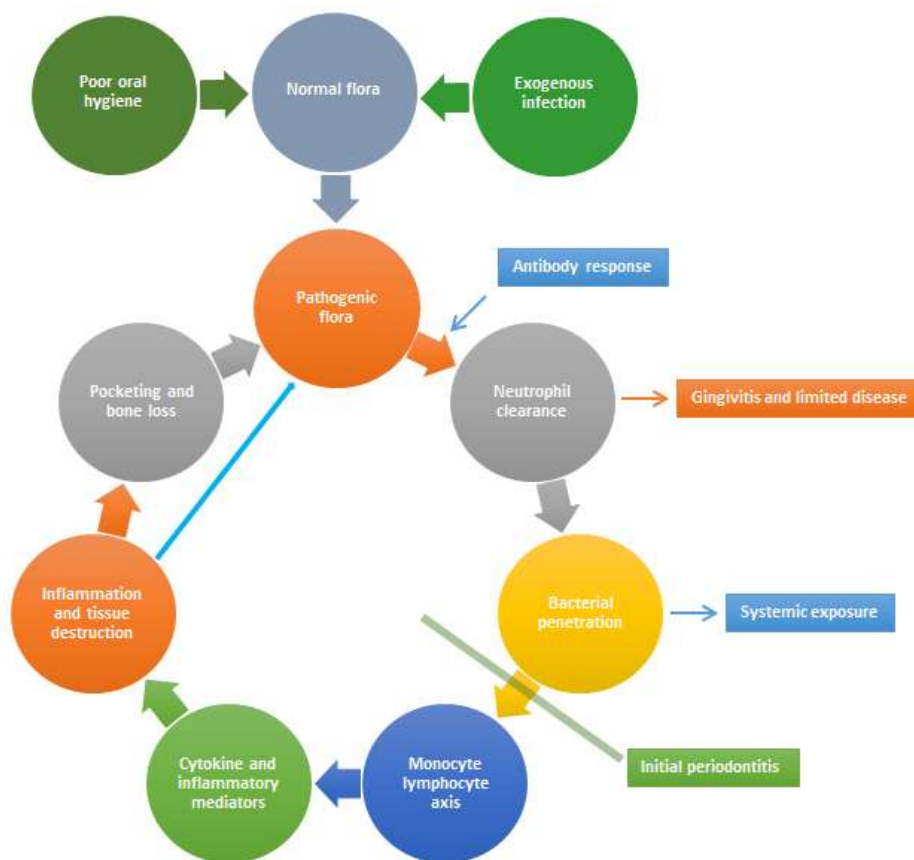


Fig. 3:- Critical pathway model

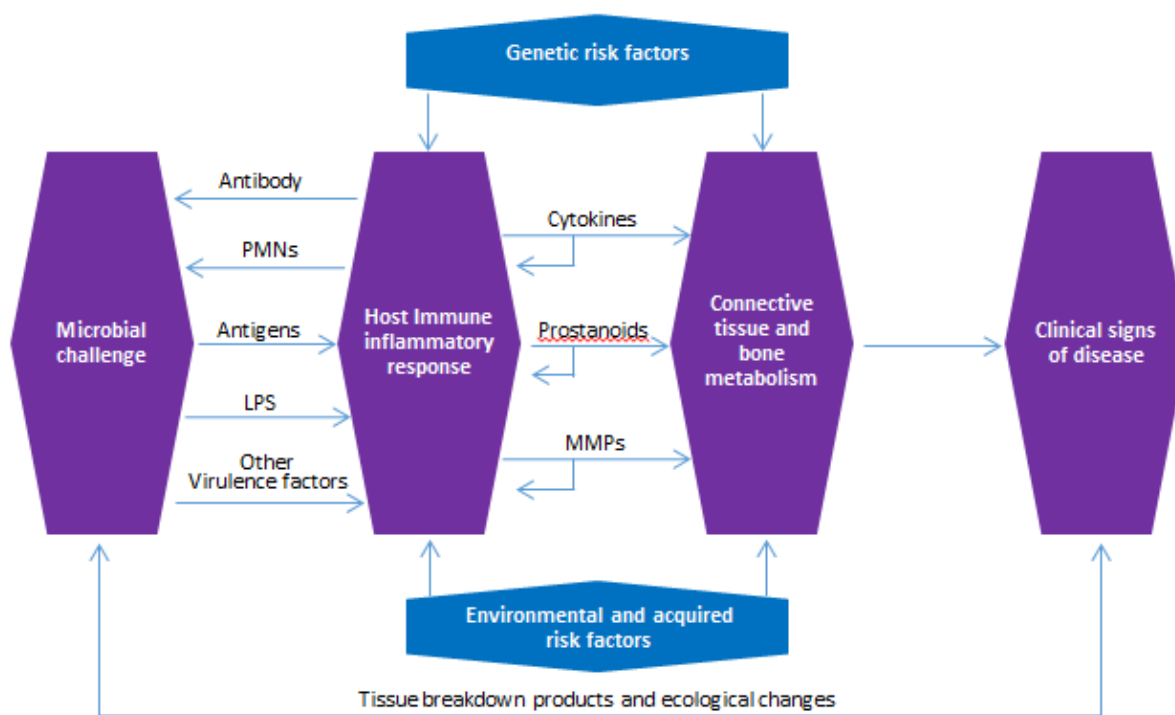


Fig. 4:- Non- linear model

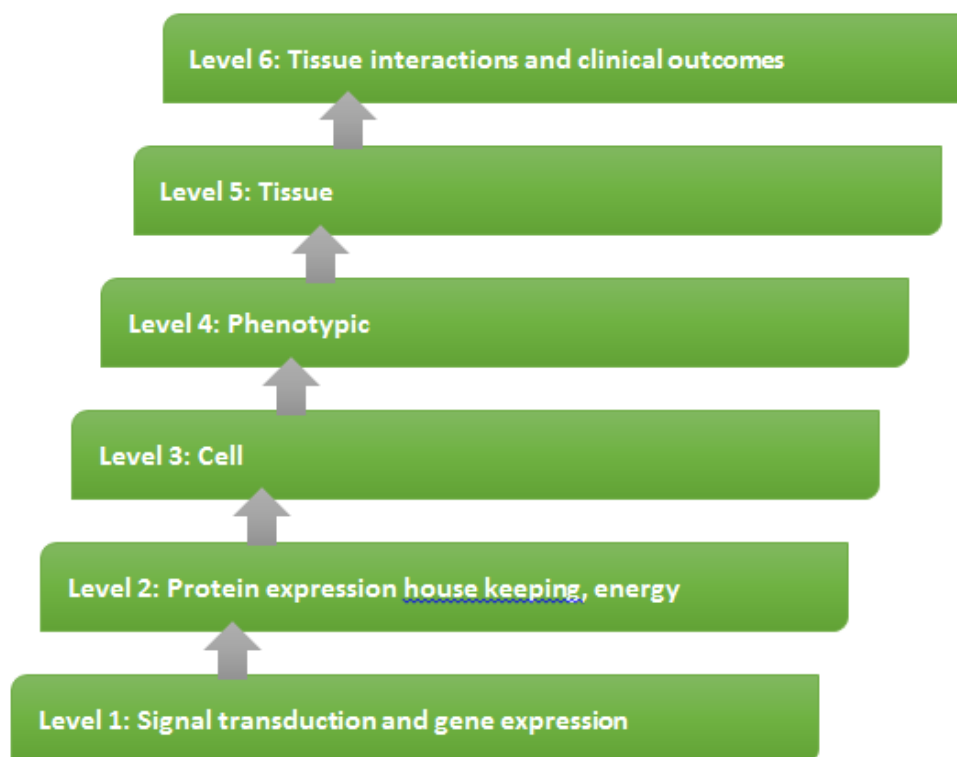


Fig. 5:- Multilevel hierarchical model

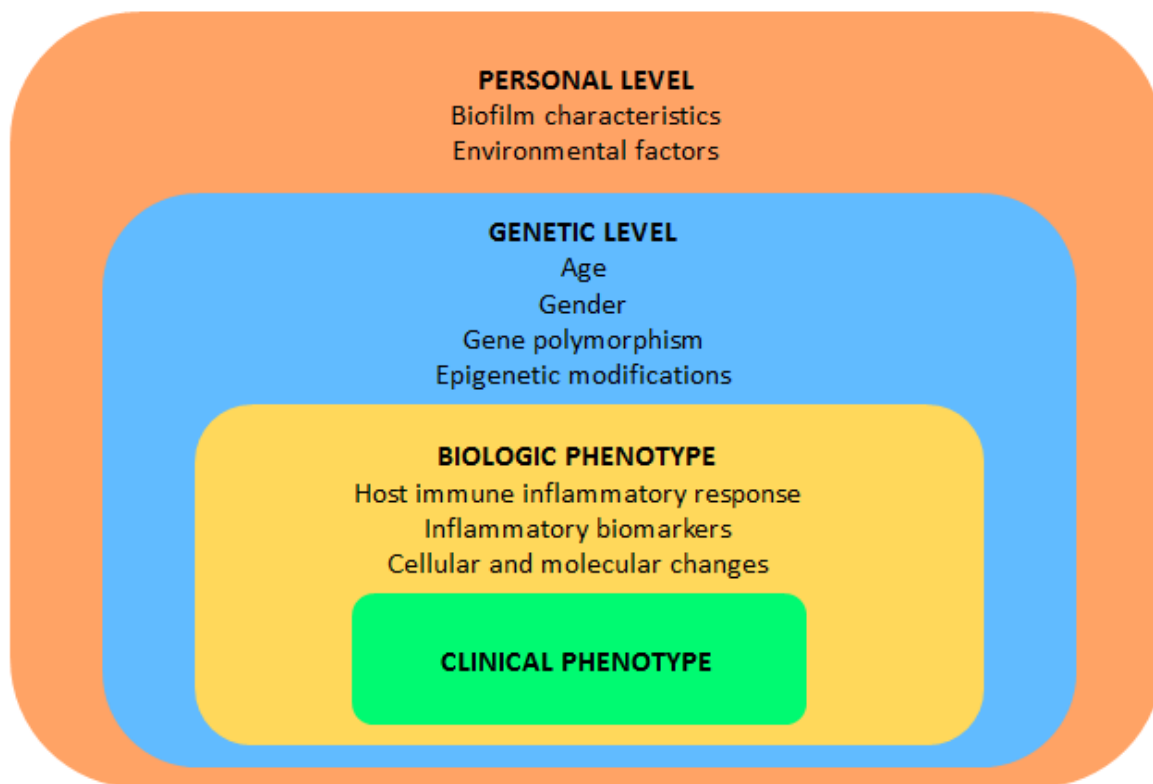


Fig. 6:- Biological systems model

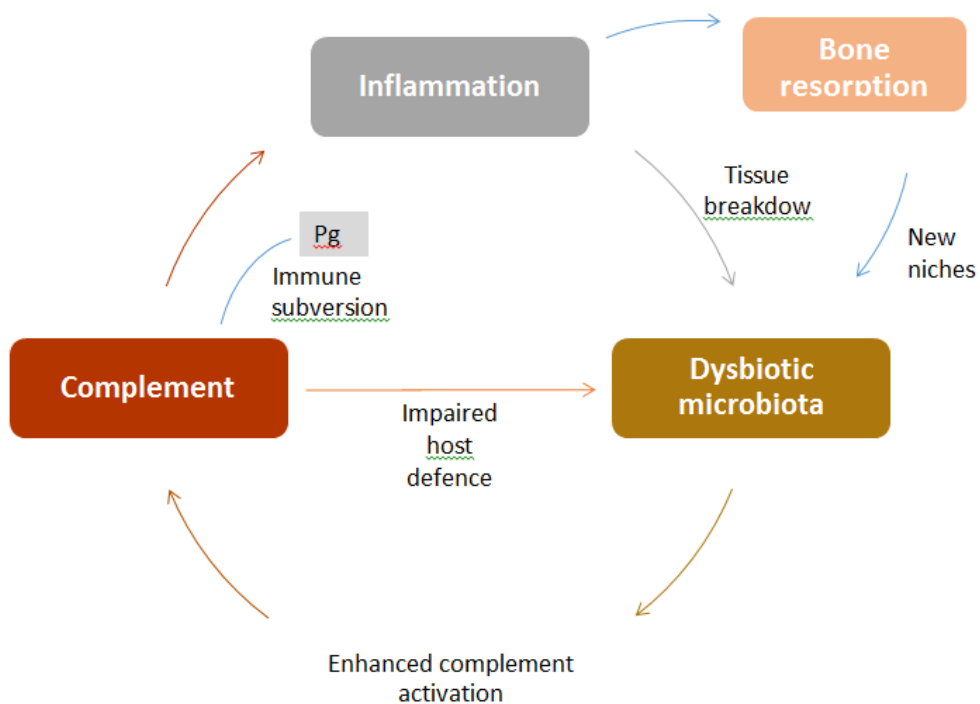


Fig. 7:- *P. gingivalis* induced dysbiosis and periodontal disease.

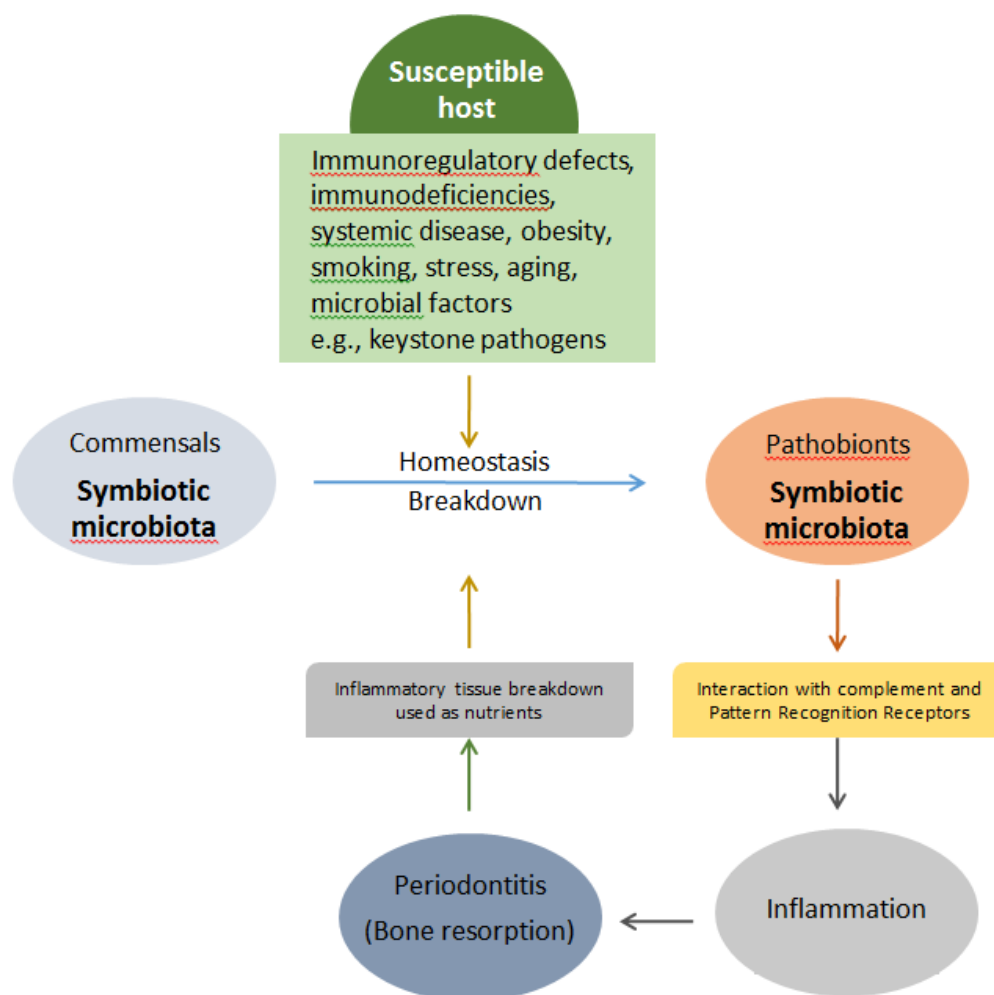


Fig. 8:- Polymicrobial synergy and dysbiosis in susceptible host causes periodontitis

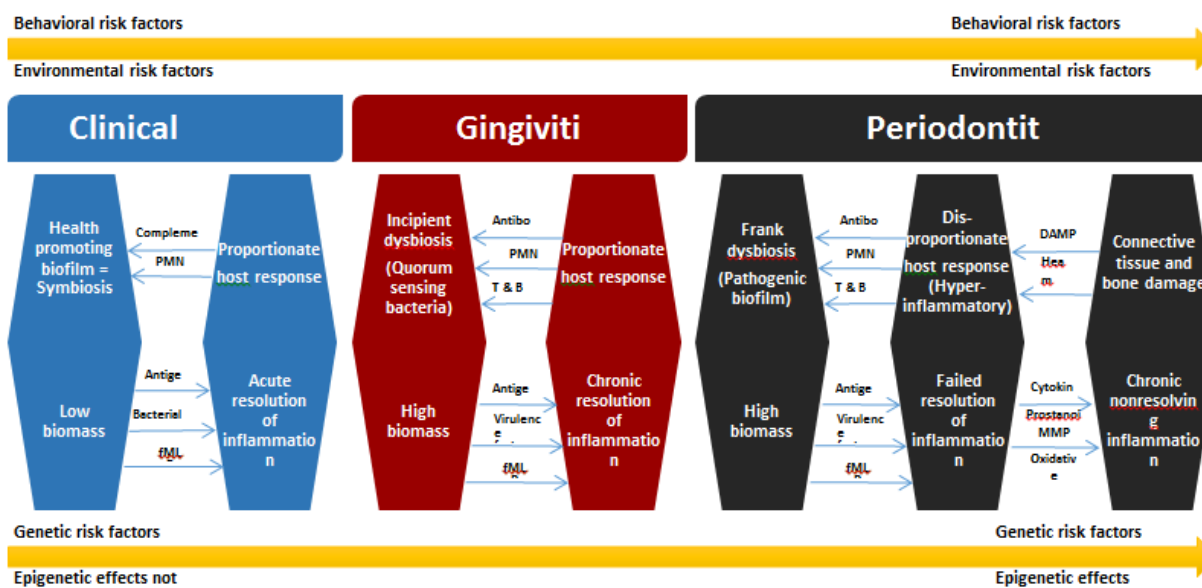


Fig. 9:- Contemporary model

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