ISSN: 0976-3031

*Available Online at http://www.recentscientific.com*

**CODEN: IJRSFP (USA)**

*International Journal of Recent Scientific Research*
*Vol. 9, Issue, 2(B), pp. 23855-23859, February, 2018*

**International Journal of Recent Scientific Research**

**DOI: 10.24327/IJRSR**

**Review Article**

# CONCEPTUAL EVOLUTION IN THE PATHOGENESIS OF PERIODONTAL DISEASE: PAST, PRESENT AND FUTURE

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**DOI: http://dx.doi.org/10.24327/ijrsr.2018.0902.1549**

**ARTICLE INFO**

***Article History:***

Received 18th November, 2017
Received in revised form 10th December, 2017
Accepted 06th January, 2018
Published online 28th February, 2018

***Key Words:***

Pathogenesis, Periodontal disease, models

**ABSTRACT**

Chronic periodontitis is a multifactorial disease. Advanced mechanisms regarding the pathogenesis of periodontal disease have been developed due to the introduction of new technologies and expanding knowledge in the field of microbiology and genetics. The older models developed in the progression of periodontal disease could not identify innate and environmental differences amongst individuals that could alter the disease progression. Today, the emerging data about genomics, proteomics, and metabolomics can help us to develop new models which incorporate data about genes and proteins. New models in the next few years will just be a scaffold in order to integrate our knowledge available from the ''-omics'' technologies.



## INTRODUCTION

Periodontal disease (PD) is one of the most common chronic inflammatory diseases affecting humans. It is of multi-factorial origin where host, environment and bacterial factors interplay to initiate immune- inflammatory response that causes most of the soft and hard tissue destruction. Our knowledge regarding the pathogenesis of periodontal disease still remains unclear.[1]

A landmark study was performed by Loe *et al* in 1970 in order to study the initiation and progression of periodontal disease. It was conducted on Sri Lankan tea workers who were could not access any dental treatment or plaque control methods like tooth brushing. They concluded that age was directly related to attachment loss[2].The classical model of periodontal disease pathogenesis, developed by Page & Kornman in 1997, gives a skeleton to understand the complex relationships between the bacteria and the host response[3]. New discoveries in fields of microbiology and immunology have led to a shift from this classical paradigm. It is now known that though a pathogenic biofilm is required for the disease, but in itself, it is insufficient to cause the disease. Disease results from interactions between the biofilm and the hostresponse[4].Periodontitis is a multifactorial disease with multiple causes, which include genetics, epigenetic influences. The ultimate clinical expression of the disease is hence an interplay of a number of factors like microbial challenge, host response and disease modifiers[5].

Changes in our perception regarding the progression of periodontal disease have led to the development of different models of pathogenesis of periodontitis.

This article highlights key steps in the evolution of our concepts of period ontalpathogenesis

### *Early concepts of the pathogenesis of periodontal disease*

| Model | Concept of pathogenesis |
|---|---|
| Linear model- 1960's (Loe *et al*)[6] (FIGURE-1) | • Bacteria play a key role in the initiation of gingivitis and periodontitis<br>• Plaque accumulation by bacteria acts as a primary source for disease development<br>• Drawback- innate differences among individuals and environmental factors were not taken into consideration |
| Basic conceptual model - Circa model 1970s and early 1980s[7] (FIGURE 2) | • Role of Gram-negative, anaerobic bacteria<br>• Protective and destructive roles of the immune response<br>• Polymorphonuclear neutrophils (PMNs) in periodontal disease.<br>• Histopathological features of periodontal disease were described<br>• Drawback-No explanation to some clinical disease patterns |
| Late 1980's[8] | • Destruction of connective tissue and bone by mediators such as matrix metalloproteinases, interleukin-1, and prostaglandins. |

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| | |
|---|---|
| Critical pathway model- Offenbacher 1996[9] (Figure 3) | • Includes both bacterial etiologyand the host response and attempts to define the critical regulatory nodes which determine disease outcome<br>• Molecular and cellular pathogenesis is essential for disease manifestation.<br>• Many factors may be involved in inflammation, but only few may be critical to theprocess, and may be only a handful will be associatedwith attachment or bone loss<br>• Hostimmune-inflammatory mechanisms are activated bybacterial products. |
| Non-linear model- Page and Kornman 1997[10] (Figure 4) | • Expression of immunoglobulinsas and PMNs to control the microbial challenge.<br>• Disease severity is not directly proportional to the plaque levels.<br>• Range of host responses and different clinical expression of the disease could take place.<br>• Role of risk factors like environmental and acquired risk factors such as genetics in altering the host response leading to more periodontal destruction. |

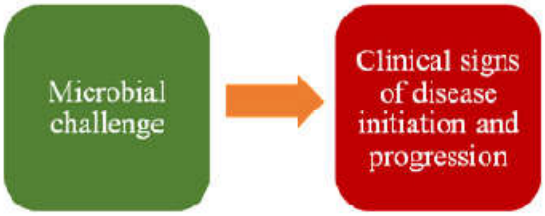


**Figure 1** Early linear model – Key role of bacteria in disease progression. AdaptedfromKenneth S. Kornman Mapping the Pathogenesis of Periodontitis: A New Look J Periodontol 2008; 79:1560-8.


**Figure 2** Circa 1980s model (IvanyiL ,Lehner T , 1980 ) – role of host immune response .Adapted from Kenneth S. Kornman Mapping the Pathogenesis ofPeriodontitis: A New Look J Periodontol 2008; 79:1560-8.

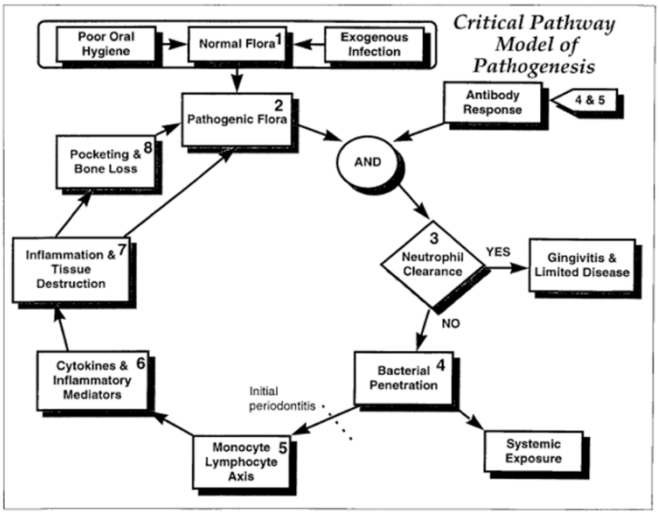


**Figure 3** Critical pathway model (Offenbacher, 1996). Adapted from Offenbacher S. Periodontal Diseases: Pathogenesis. Ann Periodontol 1996;1:821-878.

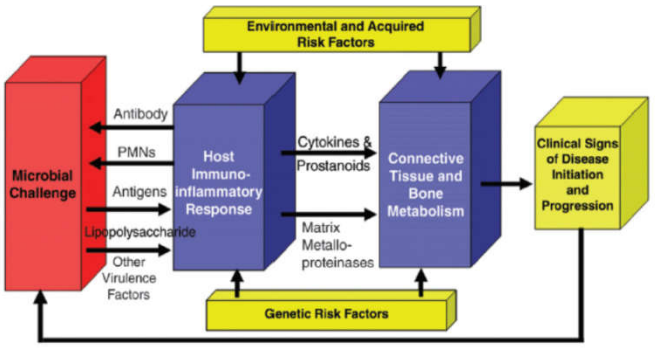


**Figure 4** Non- linear model, 1997. Adapted from Kenneth S. Kornman Mapping the Pathogenesis of Periodontitis: A New Look J Periodontol 2008; 79:1560-8.

## *Early Models of Disease Progression*

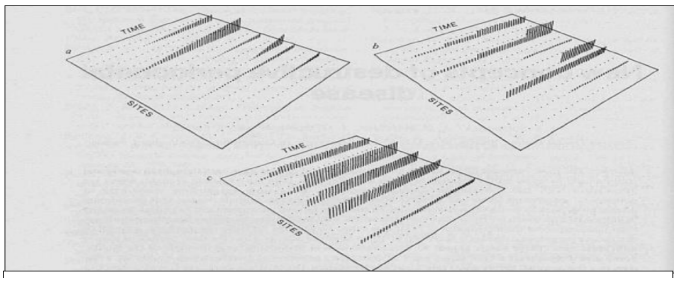


**Figure 5** Sites on the X axis are plotted against time on the Y axis and activity is shown on the Z axis. Some sites show progressive attachment loss over time, while others show no destruction. The time of onset and extent of destruction varies site to site. B. Random burst model- Activity is depicted as occurring at random at any site, some sites show no activity, while others show one or several bursts of activity. C. Asynchronous multiple burst model, several sites show repeated bursts of activity over a finite period of time, followed by prolonged periods of inactivity, occasional bursts may occur infrequently at certain sites at later time periods, other sites show no periodontal disease activity at any time, the difference between B and C is that majority of destructive periodontal disease activity occurs within a few years of an individual's life. Adapted from Socransky S, Haffajee A, Goodson J, LindheJ.New concepts of destructive periodontal disease. Journal of Clinical Periodontology. 1984; 11(1):21-32.

**Table 1** Adapted from Socransky S, Haffajee A, Goodson J, Lindhe J. New concepts of destructive periodontal disease. Journal of Clinical Periodontology. 1984; 11(1):21-32.

| Model | Mechanism |
|---|---|
| Epidemiologic model (Cohen et al, 1988) | Consistent with continuous disease aging process that depends only on the duration of the process |
| Brownian motion or stochastic model (Manji et al, 1989) | Random periods of sharp bursts and/ or remission can occur, but the underlying disease activity remains constant |
| Random walking model (Manji et al, 1989) | Similar to Brownian motion when observed at regular intervals |
| Fractural model (Landini et al, 1989) | Multifactorial model; simulates disease advancing with age in bursts and remission |

## *Advances in knowledge of the pathogenesis of periodontitis*

The 1997 non-linear model revealed path breaking concepts regarding the pathogenesis of periodontal disease. However, some of these concepts have become obsolete in the recent scenario leading to development of advanced models for

progression of periodontal disease. Various factors like genetics, epigenetics, smoking, lifestyle factors and systemic history of an individual have been established to influence the progression of the periodontal disease [11]

***Multilevel hierarchical model***[12]

This model depicts a graded system to express the various interactions which occur between the gene, protein and metabolite. The top most layer is generally represented by the clinical expression of the disease which is a result of the interaction of the lower levels of this hierarchical organisation which include the tissue and the cellular level(Figure 6)

Each level of this framework can be represented as a separate biological component of the system. Different elements can be studied to understand the summative effect on the biological system. For example, if the pathogens that cause the disease due to activation of immune response are considered to be inputs then production of different inflammatory mediators and cytokines can be considered as the output. Risk factors like smoking can also be considered as an input.

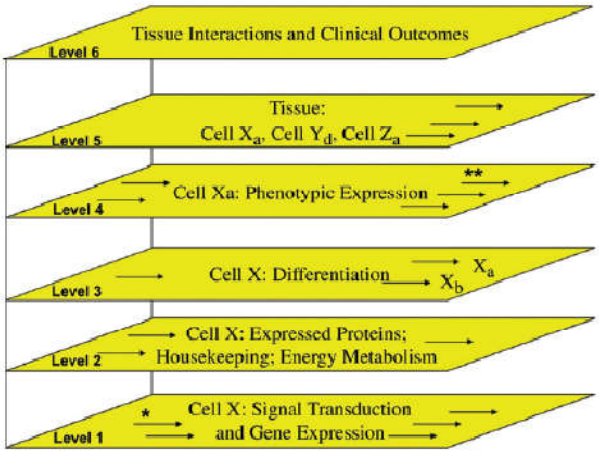


**Figure 6** Level 1 – denotes the elements that may act as input to cell x and inturn control the process of gene expression. This input may originate from the environment of the subject. The genes which are expressed at this level may further play a role in energy metabolism (Level 2), cell differentiation (Level 3), or phenotypic expression (Level 4) .Level 5 may therefore have a mix of various cell types and their differentiation states. These tissue interactions finally contribute to the clinical phenotype of the disease. Adapted from Kenneth S. Kornman Mapping the Pathogenesis of Periodontitis: A New Look J Periodontol 2008; 79:1560-8.

***Biologic system model (Kornman 2008)***[13-14]

This model highlights that periodontal disease could be multifactorial and various elements like bacteria, environmental factors , genetics may play an important role in the progression of the disease.All these factors combined together determine the clinical expression of the disease which is either healthy or disease. The goal in the future would be to identify how different sets of environmental and genetic conditions could lead to different clinical patterns.(Figure 7)

***Biologic system model (Offenbacher S Barros SP and Beck JD 2008)***[13]

This model outlines the role of different components which may lead to the clinical presentation of a disease. If periodontal disease is taken into consideration, the factors playing a key role will be on a person level, a genetic/epigenetic level, the biologic phenotype and the clinical phenotype. (Figure 8)

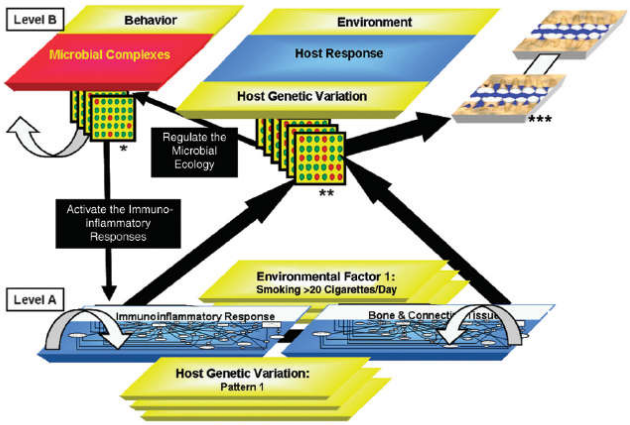


**Figure 7** Level A-denotes the mechanisms involved inimmunoinflammatory responses and in bone and connective tissue metabolism, and level B-clinical expression of the disease. Arrays (*) in level B depict the various mediators produced by different microbes which could lead to an immune response thereby influencing the homeostasis of the bone and connective tissue. Each individual may have different combinations of these genetic and environmental factors which may interact in level A. These interactions of the proteins and metabolites as well as expression of genes in level A can be assayed in tissue samples (**), which may lead to clinical signs of the disease (***).Adapted from Kenneth S. Kornman Mapping the Pathogenesis of Periodontitis: A New Look J Periodontol 2008; 79:1560-8.

The outermost element represents the exposure at a subject level, where factors like the infecting organism and the medical history, habit history of the individual play a role. This element might react with the next level component which is depicted by genetics .The level of biologic phenotypemainly includes the various biochemical markers which may be related to the clinical phenotype of the disease. Therefore, each individual has different predisposing factors and hence the presentation of the disease varies from person to person.

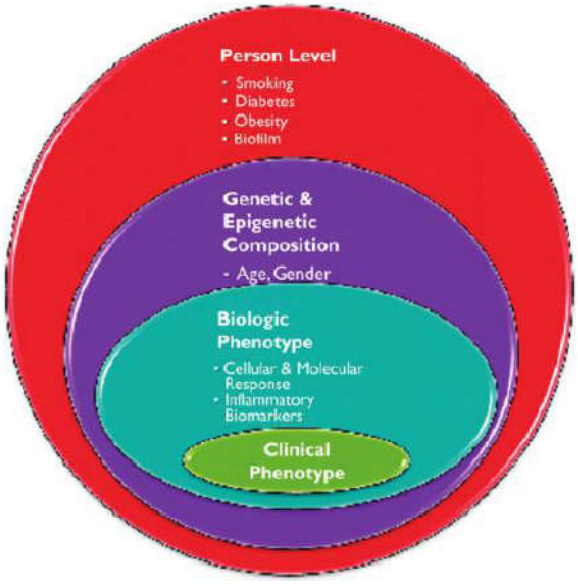


**Figure 8** Biologic system model. Adapted from Offenbacher S, Silvana P, Beck JD. Rethinking Periodontal Inflammation. J Periodontol 2008;79:1577-1584.

***Mathematical model (Papantonopoulos 2013)***[15]

This model hypothesises that periodontitis is a nonlinear chaotic disease. It helps in assessment of the rate at which the disease process occurs. To validate the model the authors used clinical and immunologic records from patients with periodontitis. They observedthat this data fits into 2 separate clinical entities – aggressive periodontitis and chronic periodontitis. The key point postulated in this model was that, the rate of the disease process depends crucially on the immune response of the host. (Figure 9)

The authors proved that the disease progression decreased if the level of the host immune response was increased. Patients with chronic and aggressive periodontitis show different immune response. The authors also hypothesised that factors like, genetics, smoking and nutrition may make the system more disordered and random.

Drawbacks- Systemic diseases which could be a causal factor for periodontitis were not taken into consideration. Moreover, localised and generalised forms of periodontitis were not distinguished as separate disease processes.

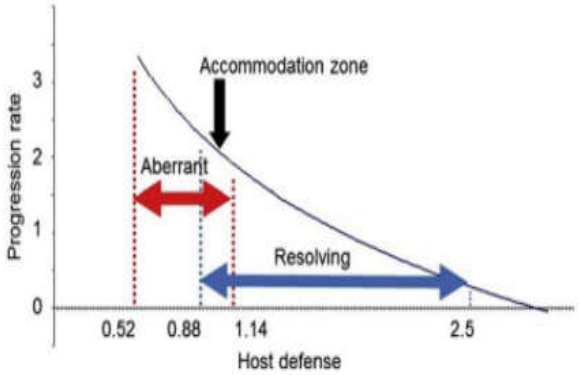


**Figure 9** Different areas of host immune response.-Aberrant zone (Red zone) : fast disease progression rate and resolving zone(blue zone): slow progression of disease. The two zones overlap to give the settlement oraccommodation zone. Host response of patients with aggressive periodontitis is localised more to the aberrant zone whereas host response for chronic periodontitis lies more in the resolving or settlement zone. Therefore the host response can fluctuate from blue to red zone analogous to a pendulum. Adapted from Papantonopoulos G, Takahashi K, Bountis T, Loos B. Mathematical Modeling Suggests That Periodontitis Behaves as a Non-Linear Chaotic Dynamical Process. Journal of Periodontology. 2013; 84(10):e29-e39.

***Contemporary model of host–microbe interactions*** *(Chapple 2015)*[16]

The periodontal health in an individual is determined by relationship between the microorganisms and the host response. A stable periodontium requires the presence of bacteria which promote health. A mutually beneficial relationship/ symbiotic relationship occurs between the two at this state, where the microbes derive their nutrients from the host and the peptides released by these organisms leads to a balanced host response.

Infrequent disturbance of this biofilm may lead to eventual accumulation of plaque leading to a host response which might be destructive in nature. This can lead to a strong inflammatory response which in turn increases the nourishment of certain pathogens like Porphyromonasgingivalis. This is termed as 'incipient dysbiosis' because in non-susceptible individuals it does not progress beyond gingivitis.

However, in susceptible patients, there can be an extremely strong host response which can lead to destruction of the periodontal apparatus. At this stage it is highly crucial to remove the pathogenic organisms and promote healthy microbes.

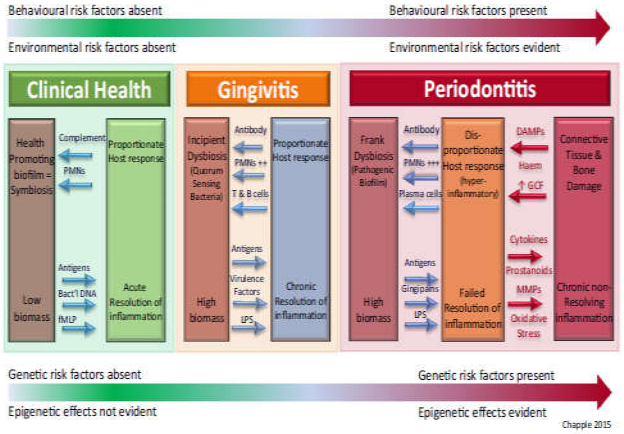


**Figure 10** Contemporary model- Adapted from MeyleJ, Chapple I. Molecular aspects of the pathogenesis of periodontitis. Periodontology 2000 2015; 69: 7–17

## SUMMARY AND CONCLUSION

Various models have been hypothesised in the past few years to describe the pathogenesis of periodontal disease. The following key points highlight the evolution of these models

1. Initial models made use of histopathological examination to reveal the progress of periodontitis in a linear fashion. This model highlighted the role of bacteria in initiation as well as progression of the disease process
2. Later, around 1970's experimental evidence was used to demonstrate the role of specific anaerobic bacteria in the disease process. These models also focused on the role of host response in the disease process.
3. In the mid-1990's, models emphasised the role of bacteria in activating the immune system and how the host response could act as a double edged sword. The host response could either help in eliminating the bacterial challenge or lead to destruction of the connective tissue and bone
4. Recently developed models focus on the role of risk factors and disease modifiers like genetics and environmental factors like smoking. Emphasis was also laid on the newly found data in the field of genomics and proteomics which helped in developing a multilevel system.
5. Biologic systems model was explained where the innate and environmental factors were recreated to monitor their role in the progression of the disease [15]

These advanced models of pathogenesis will aid in further research and may help in the extrapolation of this data to clinical scenarios.

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**How to cite this article:**

Ankita Khandelwal and Santhosh Shenoy.2018, Conceptual Evolution in The Pathogenesis of Periodontal Disease: Past, Present And Future. *Int J Recent Sci Res.* 9(2), pp. 23855-23859. DOI: http://dx.doi.org/10.24327/ijrsr.2018.0902.1549


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