

**REVIEW ARTICLE****Critical issues in periodontal research****Manish Kumar¹, Vandana A. Pant², Vivek Govila³, Mona Sharma⁴**¹Post Graduate Student, Department of Periodontics, Babu Banarsi Das College of Dental Sciences, Lucknow, India²Professor, Department of Periodontics, Babu Banarsi Das College of Dental Sciences, Lucknow, India.³Professor & Head, Department of Periodontics, Babu Banarsi Das College of Dental Sciences, Lucknow, India⁴Reader, Department of Periodontics, Babu Banarsi Das College of Dental Sciences, Lucknow, India.**ARTICLE INFO***Article history:*Received 14th June 2015Accepted 9th Aug 2015**Keywords:**

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ABSTRACT

A significant recent development in periodontal research has been the convergence of basic and clinical research resulting in a logarithmic increase in the rate of progress. Scientific consensus has been reached in many areas. In most populations, moderate to severe periodontitis affects a relatively small segment of adults who are at high risk. The microbiological etiology is accepted and the identity of major pathogenic bacterial species is known. The mechanism through which resistant individual fend off the microbiological challenge are known, and the immune-inflammatory pathways activated by bacteria that underlie destruction of alveolar bone are reasonably well understood. The evidence shows that these pathways are held in common by all form of periodontitis. The better understanding of the pathogenesis has lead to host modulation, which helps in preventing the disease. Although bacteria are essential for disease to occur, they are insufficient; a susceptible host is also necessary. Host susceptibility, disease progression and response to treatment are determined predominantly by heredity and environmental and acquired risk factors. Some of these can be changed while others are immutable. Concept and procedure for treatment are generally scientifically based and appropriately applied. Preventive measures are widely practiced and applied in industrialized counties. Clearly, control of this ancient chronic disease is within the reach. Even after all these advances, there are still some issues associated with periodontics that remains unresolved and needs to be clarified. Enormous studies have been done regarding these critical issues since few decades but still stand tall and are yet to be clarified. So, the future of periodontal research will revolve around understanding and resolving these critical issues associated with it.

EPIDEMIOLOGY AND DISEASE PROGRESSION

The word epidemiology comes from the Greek words *epi*, meaning on or upon, *demos*, meaning people, and *logos*, meaning the study of. Epidemiology is defined as the study of distribution and determinants of health related states or events in specified populations, & the application of the study for control of the disease. Epidemiologic data can form the basis for selection and

implementation of strategies to prevent and treat periodontal diseases. Three broad strategies have been advanced -:

1) Population strategy: uses a community-wide approaching which health education and unfavorable behaviors are attempted to be changed.

2) Secondary prevention strategy: includes detecting and treating individuals with destructive periodontal diseases. Basically, health education is an integral part of this

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strategy, although it is more customized to the needs of the individual patient. Dental health education approaches to improve the oral hygiene of the individual patient, although successful in the short-term, have been shown to be relatively ineffective in making sustained changes in oral hygiene behaviors.

3) Identification of high risk groups for periodontitis: the early detection of active disease and identification of subjects and groups who are more likely to develop destructive periodontal diseases in the future are important elements of dental care systems planning.

From the studies done by (Loe et al 1978, Brown & Loe 1990, Salonen *et al.* 1991, Hugoson *et al.* 1998, Albandar *et al.* 1999, Schurch & Lang 2004, Susin *et al.* 2004)^{1,2,3,4,5,6,7} it appears that severe forms of periodontitis affect a minority of the subjects in the industrialized countries, at proportions usually not exceeding 10–15% of the population. The percentage of such subjects increases considerably with age and appears to reach its peak at the age of 50–60 years. The increased tooth loss occurring after this age appears to account for the subsequent decline in prevalence.

Thus, these studies demonstrated a decrease in prevalence but the methodology used in the study could also be decisive. So this issue is yet to be resolved and Resolution of this issue is critical, since changes in the prevalence of disease impact individual and group practices, manpower needs, third-party carriers and governmental and other public health programs. The results of several studies have required modification of existing ideas about progression of tissue destruction in individuals who have periodontitis. Beginning in the 1980s, several longitudinal studies were performed on untreated patients. Disease progression was observed not to be linear and continuous as previously thought, but

rather episodic, site-specific and infrequent. Indeed, in patients with early to moderate as well in those with advanced diseases, only roughly 3-10 % of sites worsened over a period of years, and most deteriorating sites occurred in small proportion of patients. These were unexpected results which mandated a major change in our concept of the nature of periodontal disease. The observation demonstrated that in most periodontitis patients at any given point in time, 90 % or more of the periodontal sites are inactive. On the other hand, in a small population of patients (roughly 5 %) who have enhanced susceptibility, disease progression occurs frequently and at multiple periodontal sites. Identification of determinants of disease resistance and susceptibility is at forefront of current periodontal research. Using traditional methods of periodontal diagnosis including assessment of pocket depth, attachment level, bleeding and radiographic manifestations of alveolar bone loss, we are unable to distinguish between disease-active and disease-inactive sites and between highly susceptible and resistant individuals. Our inability to make these distinctions is central critical issues in periodontics today. A second unresolved critical issue is to determine the identity and characteristics of this group. Differences in the prevalence of periodontitis between countries and across continents have been demonstrated (Baelum and Albendar 1996)⁸, but no consistent patterns across racial/ethnic groups have been documented when covariates such as age and oral hygiene are accounted for (Burt and Eklund, 1999)⁹. This is especially true in the United States, where the populations heterogeneous and consists of many subgroups differing in race and ethnicity, age, and educational and socioeconomic status. There is evidence that severe periodontitis is much higher in American Blacks, especially older males, than

in Caucasians(Hughes TJ et al, 1982)¹⁰, and that individuals in the lower socioeconomic and educational groups are significantly at greater risk for severe periodontitis. However, race/ethnicity is usually a social construct that determines an array of opportunities related to access, status and resources(Baelum et al, 1986 and Michalowicz BS et al, 1991)^{11,12}. As a result, race/ethnicity and socioeconomic status (SES) are strongly intertwined, suggesting that the observed racial/ethnic effect may be partially attributed confounding by SES due to the unequal meaning of SES indicators across racial/ethnic groups. Thus this issue is yet to be resolved and studies aimed at identification of high-risk groups and sub-populations are badly needed. A third important critical issue is to determine the validity of the concept that good oral hygiene equates to periodontal health, while poor or no oral hygiene results in a high prevalence of severe periodontitis. Clearly, studies such as that suggest a more complex relationship between oral hygiene and periodontal status than has previously been suspected (Baelum et al, 1986)¹¹. Data seem to support the idea that bacteria are essential for periodontitis to develop, but bacteria alone are insufficient; there must be a susceptible host. (Michalowicz et al)¹² performed studies on twins raised separately or together in an attempt to assess the role of heredity in susceptibility. They reported that roughly half of the variance related to susceptibility to severe periodontitis could be accounted for by genetics alone, without consideration of bacteria. Thus while Numerous observation reported over several decades demonstrates a relatively strong association between accumulation of microbial deposits and periodontal deterioration, clearly the relationship is complex and there is not a 1 to 1 correlation. This issue remains unresolved.

MICROBIOLOGY AND ETIOLOGY

By the end of the 1960's, there was consensus that periodontitis in humans is an infectious disease process (Haffajee AD and Socransky SS, 1994)¹³. Initially, microbial plaque of any composition was considered to be the cause of periodontitis, but this idea was replaced by the specific plaque hypothesis(LoescheWJ, 1976)¹⁴ which suggested that specific microbial species are responsible for the disease.

According to R.C. PAGE Bacterial species associated with periodontitis -:

Very Strongly/Strongly Associated

- Actinobacillus actinomycetemcomitans
- Porphyromonas gingivalis
- Bacteriodes forsythus
- Prevotella intermedia
- Campylobacter rectus
- Eubacterium notadum
- Treponema species

Moderately Associated

- Streptococcus intermedius
- Prevotella nigrescens
- Peptostreptococcus micros
- Fusobacterium nucleatum
- Eubacterium species
- Eikenella corrodens

An obvious critical issue is whether a dozen or more microbial species are in fact involved in a meaningful way in the etiology of human periodontitis. If so, periodontitis is unique among human infectious diseases. There appear to be other possible options to account for the observations. There may be only one or, at most, two species essential for the initiation of periodontitis, while

the other species may be innocent bystanders, or may participate in propagation of lesions once initiated. Under such conditions, the subgingival flora could present a picture typical of mixed infections where in fact only one or two species are essential. If that were the case, strategies for prevention and control could be quite different from approaches used for a mixed infection involving a dozen or more species.

A second critical issue is whether periodontal infections are a consequence of overgrowth of commensal periodontal microflora or exogenous infections. If infection is a consequence of overgrowth of members of the commensal flora present in most or all individuals, then transmission may not be a critical issue, and attention should be focused on determining factors that account for and permit overgrowth to occur at some sites in some individuals but not in others. In contrast, if the bacteria must be acquired for infection to occur, then transmission is a key issue. This question is far from resolution. There is strong evidence that putative periodontal pathogens can be found at periodontally normal sites in patients with periodontitis (Socransky et al., 1991)¹⁵ and at sites in periodontally normal individuals (McNabb et al., 1992)¹⁶. These observations support the idea that, with sufficiently sensitive techniques, pathogenic species can be found commonly in periodontally normal individuals. On the other hand, there is also strong evidence that *Actinobacillus* and *P. gingivalis* are transmitted among family members (Alaluusua et al., 1993; Petit et al., 1993a,b)^{17,18}, and between spouses (Van Steenberg et al., 1993)¹⁹.

Another critical issue is the unresolved question of the relationship between the presence of a "pathogenic" flora and disease status. As noted above, it is now clear that,

when sufficiently sensitive techniques for detection are used, putative pathogens can be found commonly in periodontally normal individuals (McNabb et al., 1992)¹⁶ and at healthy sites in mouths of periodontally diseased individuals (Socransky et al., 1991; Haffajee and Socransky, 1994)^{15,13}. Clearly, there is not a one-to-one correlation between the presence of detectable amounts of various periodontal pathogens and active disease. Nevertheless, the issue is complex and unresolved. (Haffajee and Socransky 1994)¹³ have shown that thresholds exist below which periodontal sites, even though colonized by a given pathogen, are disease inactive, but above which disease activity is observed. The threshold for disease activity for *P. gingivalis* appears to be about 5×10^5 , and that for *A. actinomycetemcomitans* just over 10^4 bacterial counts. Threshold values for a given pathogen may not be independent of other species, since certain combinations are known to be more pathogenic than the individual species alone (Simonson et al., 1992; Snyder and Boyer, 1992)^{20,21}. Furthermore, it is now clear that various strains of periodontopathic bacteria such as *P. gingivalis* differ greatly with regard to virulence and pathogenicity (Marsh et al., 1989; Shah et al., 1989;)^{23,22}

An additional critical issue in the area of microbiology is the role that environment and ecology play in bacterial gene expression, genetic change, and virulence. Isolates of *P. gingivalis* differ greatly one from the other (Marsh et al., 1989; 1989; Shah et al., 1989; Smalley et al., 1989)^{23,22,24}, and a very small number of clonal types may account for the observed pathogenicity (Socransky and Haffajee 1991, 1992)^{15,25}. There is evidence that local environmental factors may be major determinants of virulence. For example, the concentration of iron is a major determinant of the production of certain cell-envelope proteins that may be important virulence

factors (Bramanti et al., 1993)²⁶. Whether a pocket bleeds may be important in this regard. Other factors such as temperature, pH, and the concentration of ions such as calcium and magnesium may also participate in regulation of gene expression. Interactions among and between species are also known to occur. For example, species such as *Streptococcus sanguis* and *A. actinomycetemcomitans* are known to be antagonistic. Hydrogen peroxide produced by *S. sanguis* inhibits growth of *A. actinomycetemcomitans* (Hillman and Socransky, 1987;)²⁷, while *A. actinomycetemcomitans* suppresses growth of *S. sanguis* through a bacteriocin (Hammond et al., 1987)²⁸. There are other examples where one species produces nutrients that are essential for the growth of other species. Most aspects of the role of environmental factors remain obscure.

PATHOGENESIS AND HOST MODULATION

The first major milestone was publication by Ivanyi and Lehner (1970)²⁹ of a paper demonstrating that peripheral blood mononuclear cells from patients with periodontitis were sensitized to antigens of their infecting periodontal bacteria. This observation served as a catalyst for investigators worldwide to focus on the role of host defense mechanisms in the etiology of periodontitis. Enormous advances were made in the 1980's in our understanding of mechanisms of tissue destruction in chronic inflammatory diseases, including periodontitis. The mechanisms by which bone and the extracellular matrix of periodontal tissues are destroyed are reasonably well-understood. Macrophages and fibroblasts present in the inflamed gingival tissue become activated, probably by bacterial substances such as LPS, to produce and secrete prostaglandin E and interleukin-1, and these molecules mediate osteoclastic

destruction of the alveolar bone (Page, 1991)³⁰. These same cells, as well as keratinocytes of the pocket epithelium and blood neutrophils, are similarly activated to produce a family of enzymes known as the metalloproteinases, which collectively have the capacity to degrade and destroy the gingival tissue and periodontal ligament (Birkedal and Hansen, 1993)³¹. A very recent development has been the realization that fibroblasts can play a major role in destruction of the very tissues they produce and maintain. When fibroblasts are located in normal healthy gingiva, their genes for production of collagen and other extracellular matrix proteins and those for inhibitors of the activity of the metalloproteinases are turned on, while the genes for the metalloproteinases are turned off. Under these conditions, normal connective tissue is produced and maintained, and wound healing and tissue regeneration can occur. As periodontitis develops, the cells undergo a change in shape; the genes for collagen and other proteins normally produced are turned off, and the genes for metalloproteinases are activated, resulting in degradation. Following successful treatment by scaling and root planing, the reverse occurs and healing and regeneration can proceed (Page, 1991; Birkedal-Hansen, 1993)^{31,32}.

Additional milestones were identification and characterization of mediators of host response especially prostaglandin, cytokines and chemokines by many investigators and family of matrix metalloproteinases and their inhibitors, also by many investigators. The role these antibodies may play in pathogenesis remains to be clarified. In individuals who are susceptible to periodontitis, the microbial challenge overcomes the primary host defense mechanism, apical and lateral extension of the biofilms occurs, junctional epithelium

converts to ulcerated highly permeable pocket epithelium and inflammation worsens. The LPS complexed to lipid binding protein (LBP) binds to the CD14 receptor of tissue macrophages. The cells become activated to secrete large quantities of PGE2, TNF-alpha and matrix metalloproteinases (MMPs). IL-1 and TNF-alpha, in turn bind to receptors on resident fibroblast. As a result, gene for production of collagen and related molecules and tissue inhibitors of MMPs (TIMPs) are turned off and genes resulting in production of additional PGE2, IL-1, TNF-alpha and MMPs are turned on. Concentration of prostaglandins, cytokines and MMPs reach high levels and account for tissue destruction observed. The MMPs digest and destroys the collagenous matrix of the gingival tissue and periodontal and the prostaglandins, and to a lesser extent, IL-1 and TNF-alpha, mediate resorption of the alveolar bone to produce the clinical and radiographical changes recognized as periodontitis. To summarize periodontitis is characterized by high concentration of anti-inflammatory cytokines and TIMPs, while periodontal health is characterized by opposite.

The destructive pathway described above are held in common by all forms and all stages of severity of periodontitis. These pathways account for the pathological tissue alteration observed periodontitis and for clinical and radiographic manifestations of the disease. The destructive are activated and driven by microbial substances emanating from bacteria in subgingival biofilms. The bacteria, are therefore, essential for periodontitis to occur but, as noted below, they are insufficient to cause a disease; a susceptible host is required.

HOST MODULATION

Host response modulation (or host modulation) is a term that has been introduced to the dental profession relatively recently. In the periodontal context, and in very simple terms, it means modifying or modulating destructive or damaging aspects of the inflammatory host response that develops in the periodontal tissues as a result of the chronic challenge presented by the subgingival bacterial plaque. Host response modulation is routinely practiced by our medical colleagues, who use host modulation strategies in the treatment of disorders such as rheumatoid arthritis and osteoporosis. And while the term host modulation has only recently started to be widely used in general dentistry, the concept was first introduced to the research community in the late 1980s and early 1990s³⁴.

Host modulation agents

Host modulatory therapy is a treatment concept that aims to reduce tissue destruction and stabilize the periodontium by down regulating or modifying destructive aspects and / or up regulating protective or regenerative components of the host response. Host modulatory therapies could include systemically or locally delivered pharmaceuticals that are prescribed as adjuncts to other forms of periodontal treatment. In periodontitis, the host is responsible for most of the tissue breakdown that occurs, leading to the clinical signs of disease. Host response modulators offer the potential for modulating or reducing this destruction by ameliorating excessive or pathologically elevated inflammatory processes to enhance opportunities for wound healing and periodontal stability. A variety of drug classes have been evaluated as host response

modulators, including the non-steroidal anti-inflammatory drugs, bisphosphonates, and tetracyclines.

DIAGNOSIS

Medical diagnosis has been defined as the process (or the conclusion reached through that process) of identifying a disease by its signs, symptoms, and the results of various biological assessments. Detection of disease as such, however, is not the only purpose of medical diagnosis.

Using traditional methods of periodontal diagnosis, including assessment of pocket depth, attachment level, bleeding, and radiographic manifestations of alveolar bone loss, we are unable to distinguish between disease-active and disease-inactive pockets. Our inability to make the distinction between diseased and healthy pockets is the central critical issue in periodontitis. Currently, there is a very large research effort aimed at development of diagnostic methods capable of detecting disease-active sites. These include tests aimed at detection of pathogenic bacterial species in the sub gingival microflora, as well as analysis of samples of gingival crevicular fluid for components that correlate with active tissue destruction. Several such diagnostic tests exist and are undergoing clinical trials. The availability of these tests will permit us, to focus on treatment of patients and sites known to be actively diseased, and to monitor the outcome of treatment accurately. An important aspect of diagnosis upon which investigations are currently focusing is assessment of risk. Risk factors are participants in the causation of disease, such as smoking and lung cancer, while risk indicators may be associated with a disease but have not been proven to be linked to causation. Consideration of periodontal diseases in terms of risk indicators and factors is a very interesting development. Evidence from variety of sources demonstrates that various genetic

influences and environmental and acquired risks are major determinants of disease resistance, susceptibility, severity and progression. Tobacco smoking and diabetes mellitus greatly outweigh all others environmental and acquired risk factors. Individuals who are heavy smokers are 4- fold more likely to develop severe periodontitis than those who are non smokers. Smoking appears to enhance susceptibility by suppressing specific antibody production and PMN phagocytosis and killing of bacteria, and thereby, decreasing the host defense against the microbiological challenge and enhancing the microbial challenge at the microbial host interface.

Risk factors and indicators (according to R.C.Page)

- Tobacco smoking
- Stress
- Advancing age
- Race, ethnicity
- Compromised host response
- Poor oral hygiene
- Heredity
- Low educational / socioeconomics
- Infrequent dental visit
- Past history of periodontitis

Genetic factors are major determinant of risk for periodontitis. Practitioners have long observed that some individual with excellent oral hygiene develop severe periodontitis and respond poorly to treatment, while others with poor oral hygiene and high level of plaque manifests little to no periodontal destruction. Heredity may, in part, account for this. Genetic factors are estimated to account for greater than 50 % of susceptibility for periodontitis. Several genetic traits that may enhance susceptibility have been identified for suspected. These are listed below-

Possible mechanism of genetically based susceptibility

- Abnormal phagocytic function
- Reduced capacity to produce IgG2
- hfe-gamma-r-2a receptor polymorphism
- TNF-alpha polymorphism
- Chromosome 9q32,33, COX-1 gene
- IL-1-beta gene family polymorphism

THERAPY

Adjunctive antibiotic therapy has become the most commonly used treatment for individuals who do not respond to other more routine treatments, such as scaling and root planing or surgery. Antibiotics commonly used include the tetracyclines and various drugs of the penicillin class. There is now evidence that combined antibiotic therapy using metronidazole and amoxicillin is highly effective in treating refractory patients (Van Winkelhoff et al., 1993)³⁵. Chemotherapy is currently undergoing a major advance with the development of local delivery devices that are placed directly into the periodontal pocket, which can maintain extremely high local concentrations of drug for periods of up to one to two weeks. Future of pharmacological treatment of periodontitis appears to be exceptionally bright. Many new drugs can now be developed that affect production of inflammatory mediators and modulate the tissue destructive pathways. R.C. Page stated that among these may be drugs that reduce the concentration of the proinflammatory agents such as IL-1, TNF-alpha and PGE2 and inhibit MMP activity, and drugs that enhance the anti-inflammatory cytokines and lipoxins.

Another advancement has been the demonstration that alveolar bone and other attachment tissues of the periodontium destroyed by periodontal disease can in fact be regenerated, at least in some cases, using a

treatment designated "guided-tissue regeneration" (Gottlow et al., 1986)⁶⁶. This form of therapy involves thorough debridement of the diseased root surface and removal of granulation tissue from the affected site. The bone lesion is then covered by a permeable membrane that excludes gingival epithelial cells and fibroblasts from migrating into the wound site, and permits population by pluripotent cells from the viable periodontal ligament and bone marrow. These cells undergo differentiation and regenerate bone, cementum, and oriented and attached periodontal ligament fibers.

A second critical issue is our lack of understanding of why some patients fail to respond favorably to any form of periodontal therapy. Clearly such patients exist, and this fact is now acknowledged by the American Academy of Periodontology. At the present time, it is not possible to identify them prior to treatment, and no understanding of the reasons why they fail to respond favorably. This issue leads us to the next critical issue in periodontal therapy. A large number of questions remain unanswered in relation to the impact of osteoporosis and its treatment on the risk for periodontitis and the implications for periodontal therapy. Is osteoporosis a risk factor for periodontitis? Can we identify the signs of osteoporosis from dental radiographs? Do bisphosphonates have an impact on periodontal status? Should implants be placed in the osteoporotic patient, or in patients taking bisphosphonates? A common clinical scenario is that in which a patient with periodontitis presents with a mobile tooth that has lost much of its bony support. Should the tooth be preserved, or should it be extracted and place an implant? Many patients (and possibly many dentists) appear to feel that implants are a panacea, once an implant is placed, they can forget all their worries about their oral health. And sadly, evidence is emerging that many patients do just

that peri-implantitis is emerging as a huge problem⁷³. And what is the role of the dentist in all this? It is easy to place an implant but it is not at all easy to maintain an implant. And, presumably, the very patients who are susceptible to periodontitis and have teeth replaced by implants are the ones who are most likely, in turn, to be susceptible to peri implantitis. There is a large body of evidence in the scientific literature that provides clear information on the outcomes of conventional periodontal care and the maintenance of natural teeth. At present, we do not have the same level of evidence regarding the long term outcomes of implant therapy. Implants have been placed in patients in large numbers only over the last 15 years or so, and many of the longitudinal follow-up studies apply to implant systems that are no longer available. Whereas our knowledge of the pathogenesis of peri-implantitis is still fairly limited (certainly in comparison with periodontitis)⁷⁵, the prevalence of this condition is increasing at an alarming rate.

CONCLUSION

A significant recent development in periodontal research has been the convergence of basic and clinical research resulting in a logarithmic increase in the rate of progress. Scientific consensus has been reached in many areas. In most populations, moderate to severe periodontitis affects a relatively small segment of adults who are at high risk. The microbiological etiology is accepted and the identity of major pathogenic bacterial species is known. The mechanism through which resistant individual fend off the microbiological challenge are known, and the immune-inflammatory pathways activated by bacteria that underlie destruction of alveolar bone are reasonably well understood. The evidence shows that these pathways are held in common by all

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So to conclude, the future of periodontal research will revolve around understanding and resolving these critical issues associated with it.

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