Periodontal Epidemiology

Santosh Kumar Bangalore Balaram[1,2] Sushma Ravindra Galgali[3] Arvind Babu Rajendra Santosh[4]

[1]Private Practitioner, Kuwait City, Kuwait
[2]Department of Periodontics and Oral Implantology, MR Ambedkar Dental College and Hospital, Bengaluru, Karnataka, India
[3]Department of Periodontics, VS Dental College and Hospital, Bengaluru, Karnataka, India
[4]Faculty of Medical Sciences, School of Dentistry, University of the West Indies, Mona, Kingston, Jamaica

Address for correspondence Santosh Kumar Bangalore Balaram, BDS, MDS, FCOI, Private Practitioner, Kuwait City 35092, Kuwait (e-mail: drbbsantosh03@gmail.com).

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Abstract

The increased requirement on the information about nature, etiology, and pathogenesis of periodontal disease has demanded wide areas of research in periodontics. The growth observed in research conducted in periodontology had been observed in both basic and clinical research areas. Despite recent advances in periodontal research, many issues remain unresolved. The aim of this review article is focused on few important problems faced in periodontal research related to epidemiology, etiology, and pathogenesis of periodontal disease.

Keywords

- periodontal research
- epidemiology
- gingivitis
- periodontitis
- therapy

Introduction

Research is defined as "the study of materials and sources in order to establish facts or reach new conclusions."[1] The ability to correctly diagnose, assess, and treat periodontal disease has received considerable attention in the last decade. Periodontal research involves several nodes or levels. At various levels, investigators need to be able to study the etiological agents causing the disease, the reliability of markers of disease susceptibility, and markers of disease progression, and thereby diagnose the periodontium in terms of health versus disease. Lastly, we all face the challenge to substantiate the patient's beneficial aspects from research. Hence, it can be considered that the periodontal research has been developed along two related but separate pathways, that is, basic science research that focuses on etiology and pathogenesis of periodontal disease, whereas, clinical research focuses on developing and testing the diagnostic and therapeutic methods that could be used successfully to treat and prevent these diseases.[2]

The task of formulating research strategies at each of these levels can be tenuous. Hence, this review has been focused on understanding the various difficulties encountered in periodontal research related to periodontal epidemiology, etiology, and pathogenesis.

Problems in Periodontal Epidemiology

The core problems in periodontal epidemiology research that limit the interpretation and analysis of population data are as follows: (1) lack of structured study design, (2) accurate definition on the status of periodontal disease, that is, case definition, (3) disease detection methods, and (4) measurement criteria for case selection. Prevalence of periodontitis varies among various population groups; therefore, research on only one population cannot be considered representative for all the populations.

Epidemiological Studies Criteria for Case Definition of Periodontitis

Preshaw stated lack of uniformity in definition of periodontitis in epidemiological studies and suggested that establishing criteria on research that focus on periodontitis case is required.[3] Multiple disease indications are observed in periodontal disease such as probing depth of pocket (PD) and level of clinical attachment (CAL). The latter stated two indicators signify current status of pathology and level of tissue destruction. Further complications are observed due to values related to threshold variation in periodontal tissue destruction. The periodontal disease case definition criteria were proposed by Center for Disease Control (CDC) and American Academy of Periodontology in 2003.[4] Subsequently, Fifth European Workshop in Periodontology in

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2005 proposed on the diagnosis of periodontitis.[5] However, the proposed criteria focused on identifying risk factors of periodontitis and not over the epidemiological analysis of periodontitis across countries or age group. Thus, application of case definition criteria for periodontitis in epidemiological studies remains unclear.[6]

Methods for Disease Detection and Measurement

The methods that are available cannot assess periodontal disease as an active process instead of the current status. This is because the evidence collected from the assessment include (1) depth of periodontal pocket while probing, (2) level of attachment, and (3) bleeding on probing. This remains a major challenge in research on periodontal epidemiology due to poor correlation of tangible effect (true terminal point) for the cases, that is, tooth retention versus absence of discomfort. There is also scarcity on data assessing cause of trends or change, which is another challenging issue in periodontal epidemiology. Additionally, the therapeutic efficacy and preventive methods are difficult to assess only with clinical parameters. Prevention programs usually target the determinants of disease among population.[1]

Full versus Partial Mouth Recordings

Periodontal assessment can be done with either partial or full mouth recording. The advantage of partial mouth recording is quick and short examination, with minimal discomfort to participants, and it allows large number of people for examination with shorter period. In addition, partial assessment encourages both examiner and subjects to adhere with study protocols.[7] On the other hand, partial recording carries the risk for underestimation of periodontal destruction among less susceptible population or overestimate the frequency of periodontal disease when selective teeth are considered, that is, lower incisors and first molars.[8,9] In addition, partial recording carries the risk of bias while assessing attachment loss among larger population-based studies. Hence, correction factor should be identified while performing partial recording prior to the analysis of data; this will allow researchers to compare their results with other studies.[10]

Indices

Ideal requirements of an index are as follows:

1. It should be simple and easy to understand and apply.
2. It should be reliable and reproducible.
3. It should be objective in design.
4. It should have categories to help the examiner in decision making as to which category a condition will fit in.
5. It should have good specificity and sensitivity.
6. It should be able to measure small changes in both directions such as whether the condition improves or deteriorates.
7. It should not cause discomfort to the patient.

The main problem faced in using periodontal indices in epidemiological research is that it gives information on previous disease rather than the actual presence of disease.[11]

Errors Intrinsic to Periodontal Probing[6]

Probing pocket depth (PPD) and clinical attachment loss (CAL) are often the main outcome variables in periodontal (epidemiological and clinical) studies that are measured using a calibrated periodontal probe.

Periodontal probing measurements depend on the following factors:

1. Diameter of the probe tip.
2. Probing force.
3. Probe tine angulation.
4. Inflammation at the base of the pocket.
5. Experience of the examiner.
6. Presence of (overhanging) restorations.

Research has shown that automated or electronic probes improve consistency in PPD measurements than first-generation probes.[6]

Inter and Intraexaminer Consistency

Interexaminer and intraexaminer variability in measurements can cause bias in interpretation of the readings. Hence, examiner calibration is necessary as a part of epidemiological surveys. This can be achieved by examiner training and should lead to intra- and interexaminer agreements over scores in the range of 85 to 95%.[11] A measure of agreement between examiners is reported using a high value of Cohen's Kappa coefficient indicating a strong agreement between examiners' scoring.[12]

Limitations of using Kappa statistics:

1. A kappa score will not inform whether any disagreement is caused by just one examiner consistently scoring high or low.
2. The accuracy of kappa is influenced by the disease prevalence[13]

Analytical Difficulties

In periodontal research, especially between periodontal and systemic diseases, assessing confounding factors are of increasing importance. This can be dealt with in the design of prospective studies by randomization or in case of known confounders, by restriction of the study population based on the confounding variable. Failure to detect and quantify the key interaction effect in the data could lead to major errors in interpreting the exposure–disease relationship in the study.[14]

Problems in Statistical Analysis

Analysis of Larger Number of Species

Significant and statistical differences are likely to occur by chance among test groups. At α value of $p < 0.05$, one difference is likely to occur by chance in every 20 species.

Analysis of Diversity among Microbial Species Collected from Various Sites

Sparse arrays are the data extracted from microbiological studies that pick up 30 to 50 microbiological isolates that represent the sample from the site.

Statistical Treatment of Measurements Taken from Multiple Sites within the Same Mouth

The values recorded among various site within the same individual are correlated. Analysis that are conducted on the assumption of statistical independence is inappropriate. The results of such analysis are inflated type I error, that is, authors incorrectly claim, "statistically insignificant," in which there are no differences between the groups compared. However, this does not state that incorrect analysis will lead to incorrect conclusions. Hence, an appropriate "unit of analysis" should be considered while framing hypothesis. For example, when specific variables, such as gender, ethnicity, age, and systemic condition, influence the chance for developing periodontal disease, then the unit analysis described in the example is the subject.

Inappropriate Use of the t-test and "Bell-Shaped" Frequency Distribution

Periodontal research data are often skewed toward smaller values. Thus, periodontal researchers should rationalize the assumption by an appropriate statistical test ahead of applying *t*-test method.

Inferences from Negative (Nonsignificant) Results

Conventional statistical testing methods for hypothesis does not allow null hypothesis. Clinical or biological differences might be present while comparing two or more groups with smaller size, but differences might not be detected by statistical hypothesis test. Thus, statistical inferences can be drawn from a negative result when 90 to 95% confidence interval is employed.

Use of Randomization

Randomization should be employed when one member of a pair of sites is measured by a random table or computerized random number generator. Lawrence et al stated that assignments done irregularly or according to the day identified in the week are not random assignment.[15]

Problems Associated with Etiology and Microbiology

Relationship between pathogenic organisms and status of disease continuous to be debatable. Although, bacteria are essential for the establishment of disease; a susceptible host is also important. Evidently, studies demonstrated that major determinants of disease resistance, susceptibility, severity, and progression are genetic, epigenetic, environmental, and acquired risks.[2]

Environment and ecology also play an important role in bacterial gene expression, genetic change, and virulence. Local environmental factors may also be major determinants of virulence. The question "whether periodontal infections are a consequence of overgrowth of commensal periodontal microflora or exogenous infections" is yet to be answered. However, to simplify, problems associated with search for etiological agent of periodontal disease can be classified as technical, conceptual problems, characterization, and identification problems, and problems associated with the nature of periodontal diseases.[16]

Technical Difficulties

►**Fig. 1** shows the technical difficulties; they are as follows:

1. **Sampling**: Too large a sample causes dilution of pathogens by noncontributory "contaminating species" while small sample may miss the pathogen entirely. Site and time also play a very important role, such as, whether the sample collected is from an active site or remitted site. In addition, the peak of disease activity may be missed during research investigation due to need for measuring alterations between time intervals. Sampling devices in investigation of pocket are larger than periodontal pockets. The diameter of periodontal pocket is 100 to 300 µm, whereas diameter of device is 300 to 1,200 µm. Hence, developing suitable dimension of sampling devices is essential. These attempts are hampered by the absence of a "primary" or "gold standard."
2. **Dispersion**: Sampling procedure followed in culture studies requires dispersing sampling environment without the loss of cellular viability. Gentle dispersion of sample may not remove tightly adhered microbial species in clumps, whereas vigorous dispersion method may remove the microbes with robust cell walls. Thus, dispersion may cause artifacts in final analysis.

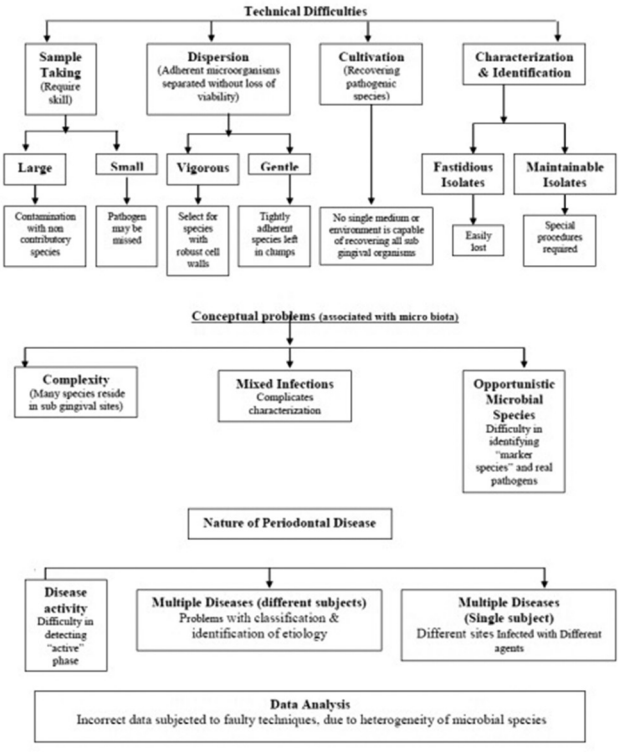

Fig. 1 Technical difficulties in periodontal research.

3. **Cultivation**: None of the media have the potential of recovering all microorganisms that are isolated from subgingival environment (plaque/calculus).
4. **Characterization and identification**: Few microbial isolates are meticulous and may lose their viability duringmicrobial characterization. However, recent research methods are able to differentiate cultivable pathogens from nonpathogens.

    - **Conceptual problems**: One of the challenges in characterization and identification is due to complex microbial population from subgingival environment that consists of polymicrobial nature and presence of opportunistic microbial pathogens. Opportunistic species are confounding and takes an advantage of the presence of true pathogens.
    - **Challenges associated with periodontal diseases**: Advancement of periodontal disease are identified with periods of exacerbation and remission. Challenges associated with identification of active phase of disease could obstruct the identification of periodontal pathogens. The periodontal pathogens are observed even at remission phase of disease. Hence, identification of periodontal pathogens at inactive sites act as confounding comparison for active sites. However, the levels of periodontal pathogens at inactive sites might be lower.
        - **Multiple periodontal diseases in different subjects**: Diverse appearance of periodontal disease may be observed in longitudinal progression of disease, where dramatic change in response is identified following periodontal therapy. In addition, microbiological- and/or immunological - laboratory investigations show major variations in host response and microbiological population among individuals or
        - **The Possibility of multiple diseases within a subject**: Differences observed in clinical symptoms in different parts of the mouth may be explained by differences in levels of the pathogen or the stage of the destructive process. Thus, sampling provides a series of "replicates" of the same disease process.

Some Key Issues that Need to Be Explored Regarding the Clinical Implications of Periodontal Microbiology

1. Does the presence of pathogen alone or the number of pathogens play a key role in relation to the disease? Mere presence of pathogens reduces the specificity (i.e., presence of pathogen means periodontitis) of microbial examination as it has been shown that several pathogens have been detected in periodontitis-free patients also by the high sensitivity of microbial tests. Also, they are not found at a significant proportion at diseased sites.[17,18] In other words, even though a microbiological analysis is positive, the patient may not have disease. This undermines the reliability and usefulness of microbiological tests. Resolution of this issue is made difficult by the clonal structure of some of the species. More than 50 genetically distinct clones of *Porphyromonas gingivalis* are known to exist.[19] Little information exists about clonal virulence; some clones may be virulent and others avirulent. No single clone or group of clones can account for periodontitis.
2. Is the understanding of the etiology more complicated? The threshold level for periopathogens between health and disease is unknown and subject dependent.
3. Is there a large intrastrain variation in genetic information? Information on the genotype level is needed before the pathogenicity of the strain can be estimated. The critical issue here is whether environment and ecology play a role in bacterial gene expression, genetic changes, and virulence. 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 virulent factors.[20] Other factors such as temperature, pH, and the concentration of ions such as calcium and magnesium may also participate in the regulation of gene expression.
4. Besides bacteria, does the quality of host response play an essential role in the etiology of disease? If yes, can it be estimated correctly?
5. Another critical issue is whether periopathogens are endogenous species or exogenous? This has a significant impact on the treatment strategies. For endogenous species (i.e, if the infection is a consequence of overgrowth of commensal bacteria), the endpoint of a therapy would be reduction of the species, whereas for exogenous species (i.e., infection occurring by transmission among the family members), the endpoint would be eradication and prevention of reinfection.
6. Is there a suitable model to demonstrate microbial plaque as a biofilm? Biofilms are communities of bacteria evolved to permit survival of the whole community. They have numerous microenvironments with differing pH, oxygen tension, and electrical potential, and they have primitive circulatory system through which waste are eliminated and nutrition is provided. Properties of biofilms differ from that of planktonic state such as cell-to-cell communication (quorum sensing), antibiotic resistance, and resistance to phagocytosis. Of all the areas of periodontal microbiology, the need for a better understanding of the pathophysiology of biofilms is the most urgent.[20]

Other Risk Factors for Periodontal Disease

Susceptibility for periodontitis varies greatly among individuals. In a given population, most individuals manifest low susceptibility while a minority (usually ~5–15%) is more highly susceptible. In addition, disease severity, rates of progression, and the extent of response to preventive and treatment measures vary enormously among patients. Published reports state that major determinants of disease

resistance, susceptibility, severity, and progression are influenced by genetic, environmental, and acquired risks.[2]

An important problem related to research in hereditary periodontitis is that whatever the cause of the disease, the symptoms are similar, like deepening of the pocket, loss of attachment, and alveolar bone loss. It is likely that overlapping of clinical phenotypes exit between different forms of periodontitis. Heterogeneity in case definitions is one of the major problems encountered in the interpretation of various studies in relation to genetic risk factors for periodontitis. Another problem is that many studies have investigated putative genetic risk factors without considering other established risk factors for periodontitis, as covariates. Further, the vast majority of studies have not considered the infectious components (gene–environment interruption).[16,21]

Age, ethnicity, stress, smoking, diabetes, genetics, poor host response, poor oral hygiene practices, low socioeconomic status, low education poor dental visits, human immunodeficiency (HIV) infection, and osteoporosis, are considered as risk factors and indicators for development of periodontal diseases.[21] Hence, dental surgeons and periodontists should identify these status risk factors among their patients and assess the future development or occurrence of periodontal disease. It is worth to state that measurement of plaque and calculus alone does not assist dental surgeons/periodontist to predict the future development of periodontal diseases.[22,23]

Studies that considered the subgingival identification of *Aggregatibacter actinomycetemcomitans*, *P. gingivalis*, and *Tannerella forsythia* suggested moderate degree of predictability of periodontal diseases.[24,25] McGuire and Nunn stated that identification of interleukin-1 (IL-1) genotype status in nonsmokers revealed a better approach in studying baseline clinical indicators for periodontal disease.[26] This is because smoking and genetic predisposition play a major role in development of periodontal diseases. IL-1 genotype is identified as a reliable tool in predictive model studies for periodontal disease and tooth loss due to periodontal damage.

Multiple reports have related psychological stress to progressive periodontitis. The association is positive in study models such as case-control studies, cross-sectional studies, or longitudinal studies.[27-29] It is understood that psychological stress is associated with multiple systemic diseases. Saying that, there is also a relation of systemic diseases with periodontitis. Thus, periodontitis is a multifactorial disease and understanding host response is very essential in combination with assessment of local and general risk factors of patients for diagnosis, management, and prevention of periodontitis.

Development of Risk for Systemic Diseases due to Periodontal Disease

The risk association of periodontal infections for development of systemic diseases received greater research and clinical attention. In addition to periodontal infections, other chronic inflammatory medical conditions share common risk factors: age, sex, ethnicity, genetics, smoking, stress, or obesity. Umino and Nagao, in 1993, reported that cardiac diseases are most frequently seen in patients with periodontitis.[30] A study reported that individuals with periodontitis had 25% increased risk for developing coronary heart disease (CHD) than individuals without periodontitis.[31] In addition, men younger than 50 years with periodontitis are 70% more likely to develop CHD than those who do not have periodontitis. Periodontal infections induce low-level bacteremia, increased white blood cell (WBC) counts, elevated endotoxins, and endotoxins-mediated loss of endothelial integrity, platelet function, and blood coagulation.[32]

Offencbacher et al in 1996, stated that periodontal infections act as a risk factor for preterm low birth weight (PLBW).[33] The study measured the attributable risk and concluded that 18% of PLBW cases were probably resulting from periodontal infections. The results of data support the published findings from experimental studies.[34-36]

Systematic reviews and meta-analysis have shown a link between periodontal disease as a risk factor for coronary artery disease, obesity, and adverse pregnancy outcome (low birth weight and PLBW). Moreover, there is evidence of periodontal treatment on the improved glycemic status of the diabetic patients.[37-40]

But due to several confounding factors and application of various types of inferential statistics, the clinical significance of the profound results in the epidemiological studies need to be carefully assessed. However, legitimate concerns have arisen about the nature of these relationships. Further, experimental study designs are in need to confirm the cause and effect relationship between the periodontal disease and systemic diseases.

Pathogenesis of Periodontal Disease

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 is converted to ulcerated highly permeable pocket epithelium, and inflammation worsens. Periodontitis is characterized by high concentration of the proinflammatory cytokines, prostaglandins and matrixmetalloproteinases (MMPs), and low concentration of the anti-inflammatory cytokines and tissue inhibitors of matrixmetalloproteinases (TIMPs), while periodontal health is characterized by the opposite. The destructive pathways are activated and are driven by microbial substances emanating from bacteria in the subgingival biofilms and calculus for initiating gingival and periodontal disease.[41] Recent advances in the area of research on pathogenesis are that patients with periodontitis mount a humoral immune response to the antigens of their infecting pathogens. The role of these antibodies whether they are protective or destructive in nature remains to be clarified. Advances in our understanding of pathogenesis of periodontitis have major implications for development of future therapies such as to control gene activation, anticytokine therapy, periodontal vaccines, and chemically modified tetracyclines to inhibit the activities of MMPs.[2,42] Reports on proteomic studies have shown that gingival crevicular fluid is characterized by variable protein in systemic

disease.[43] Another study mentioned that proteolytic enzymes identified in gingival crevicular fluid (GCF) are collagenase, elastase, and cathepsins and these are associated with periodontal tissue destruction with a potential to degrading damage to type I collage fibers and glycoproteins.[44] Another study demonstrated effects of periodontal disease based on the production of salivary salivary trefoil factor (TTF) 3 peptides.[45] Another study mentioned that salivary MMP-8 levels are indicated by the diabetic influence in periodontium.[46] A biochemical study on GCF validated the use of oxidative stress index as a marker for periodontal disease activity, and highlighted the role of oxidative stress-induced damage in the periodontium of diabetic individuals.[47] Another salivary study mentioned that higher levels of 8-hyroxydeoxyguanosine, malondialdehyde, and lower salivary antioxidant activities are related to periodontal inflammation due to increased oxygen radical activity.[48] Periodontal health and oral hygiene practices should be considered important as they contribute positively towards oral health-related quality of life.[49,50]

Periodontal disease is most common disease and constantly increasing worldwide. The need for classification of increasingly important for accuracy case definition and diagnostic criteria which will assist both clinicians and researchers for measuring and management of disease.[51] This article will not be complete without a mention on the recent World Workshop on the classification of periodontal and periodontal diseases and conditions published in 2017. The classification system of periodontal diseases and conditions show three main headings: (1) periodontal health, gingival diseases, and conditions; (2) periodontitis; and (3) other conditions affecting the periodontium. The periodontal health, gingival diseases, and conditions constituted (1) periodontal and gingival health, (2) dental biofilm-induced gingivitis; and (3) nondental biofilm-induced gingival diseases. Periodontitis constituted (1) necrotizing periodontal diseases, (2) periodontitis, and (3) periodontitis as a manifestation of systemic disease. Under the topic "other conditions affecting the periodontitis," five subheadings were noted: (1) systemic diseases or conditions affecting the periodontal supporting tissues, (2) periodontal abscess and endodontic–periodontal lesions, (3) mucogingival deformities and conditions, (4) traumatic occlusal forces, and (5) tooth- and prosthesis-related factors, whereas peri-implant diseases and conditions showed discussion of peri-implant health, peri-implant mucositis, peri-implantitis, and peri-implant soft and hard tissue deficiencies.[52] Dental anomalies that predispose to exposure of root surfaces also contribute to the development of gingival/periodontal disease.[53] The 2017 workshop also revisited definition and diagnostic criteria of aggressive periodontitis. The new classification of periodontal disease will emphasize the researchers on the case definition and selection for cohort studies, as well as it will also permit clinicians for more rapid diagnosis, and more consistent and better treatment outcomes.[54]

Conclusion

Emerging evidence from periodontology research is continuously growing with significant need in improvement of oral and overall health. The complexity in periodontal research should be addressed strategically with appropriate clinical and research methodologies to minimize knowledge and research gaps in basic, applied, and clinical research. Periodontal epidemiological research requires uniformity in designing and conducting research, and reporting data. The design of periodontal epidemiological research should reflect the advancements of epidemiological sciences and clinical approach in diagnosis, investigation, and management. The link between periodontal infections and systemic diseases requires attention to designing high-quality experimental/interventional randomized controlled clinical trials (RCTs) for confirmation of cause and effect. Risk prediction assessment of periodontal disease requires accuracy. Accurate risk assessment will facilitate dental practitioners in assessing development of periodontitis and reduce morbidity and clinical care costs.

Conflict of Interest

None declared.

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