Periodontal Inflammation and Infections: Systemic Implications
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Abstract
The emergence of PERIOMEDICINE made it explicit that a bidirectional link exists between periodontal diseases and systemic health. For more than 3000 years now, this association is being investigated. Starting from the proposal of Focal infection theory, numerous paradigm shifts have been witnessed in the periodontal science. Enormous numbers of research studies supporting the bidirectional link are documented in the literature. However similar amount of evidence against it also exists. This article gives and insight into the various forms of evidence in literature that have been documented to prove an association or causal link or otherwise between periodontal disease and systemic implication.

Key Words: Evidence, Focal infection, Periodontitis, Systemic Health.

Introduction
“Take care of your teeth and they’ll take care of you.”

This dictum is of unknown origin, yet the relation between oral health and general health has been inquisitive for more than 3000 years. Hippocrates, the father of medicine advocated teeth extraction as means to cure arthritis. [1]

The rise and decline of the Focal Infection Theory
In the late 19th century, it was only after the acceptance of the germ theory and principles of Bacteriology, that the role of infections as etiological agents of diseases was being recognized. Willoughby D Miller attributed oral diseases to infections and general diseases to oral diseases. [2,3,4] British surgeon William Hunter accused oral sepsis to either be the origin or deleterious catalyst of certain grave diseases. This idea gradually crystallized into the Focal Infection Theory which stated that “circumscribed foci of bacteria, localized to various parts of the body can result in myriad systemic diseases”. [5,6]

The era of focal infection began with the proselytising efforts of its most visible proponent Frank Billings, claiming to cure infections of distant organs by extraction of teeth and tonsillectomies. Though pus within the bodily compartment was considered a systemic threat, its drainage into the mouth was interpreted to be inconsequential systemically.[8,9] One school of thought concluded that dissemination of infection from the focus was prevented by the immune response – but failure of the immune components was considered in dissemination leading to systemic disease. Exclusion of focal infections was considered a rational form of therapy and unresolved cases were attributed to unrecognized foci in the internal organs. Moreover a number of poorly understood diseases were explained by the focal infection theory including psychiatric diseases. This lead to a boom in tooth extractions and tonsillectomies to such an extent that one contemporary quoted “If the craze for violent removal goes on, it will come to pass that we will have a gutless, glandless, and toothless, and I am not sure we may not have, thanks to false psychology and surgery, a witless race”. [10]

At the turn of the century, with the dawn of Bacteriology, it appeared that most, if not all diseases might be infectious in origin. In time it became clear that the theory of focal infection carried this concept to an extreme. The elegance of this theory was easy application; but, it resulted in meagre cure rates, occasional deterioration of disease and inconsistencies in experimental results. Ultimately, it was demonstrated that the science on which the theory was based was flawed. [10]

Re-emergence of focal infection theory
But in the recent years, there has been immense interest in possible associations between periodontal disease and various systemic conditions. This has lead authors to adopt a cautious approach, some seeking intervention to determine causality. The inability of Epidemiology to confirm causality has been emphasized, categorizing the phenomena as a progressive invasion of local tissues distinguishing it from the former Focal Infection Theory. Others have found the scientific evidence of the theory to be slim but have conceded that it may be established by evolving science. Yet, select authors affirm the return of a modest focal theory.

Periodontal health
The oral ecosystem serves as a habitat for about more than 1014 microbes. These pose a constant threat to the defence mechanism. Moreover, the unique anatomy of the tooth which is partly exposed to the oral environment and partly rooted to the connective tissue presents as a vulnerable entity. The imbalance between the host factors and the microbial community initiates
the disease. The influence of systemic disease on the pathogenesis of periodontal destruction and vice-versa has been a topic of debate for years together necessitating the need to establish directionality. [11]

**Periodontal health and systemic health**

Modest associations between periodontitis and some, though not all, of the diseases and conditions reviewed, is supported by published evidence. [12,13,14] Ample mechanisms have been implicated in literature signifying the bidirectional relationship between periodontitis and a range of systemic conditions establishing a causal link. Amongst these, the theory of three mechanisms put forward by The den Van Velzen al was awarded much credibility. The theory corroborated that systemic effects could be attributed to metastatic infections, spread of bacterial toxins and immune mediated injury. [15] The above-mentioned concept was reinforced by Van Dyke, who emphasized that periodontal disease causes inflammation and the resultant bacteraemia can metastasize to different organs with production of inflammatory mediators and activation of adaptive immunity having far reaching influence on systemic health. [16] Yet, there exists a lacuna in establishing a definitive link to correlate these mechanisms aforesaid for pathogenesis of various diseases. [17-33]

**Definition of disease state**

There is a striking heterogeneity in the definition of Periodontitis across and within each disease condition. Moreover, not all studies met a stringent threshold for periodontitis. [17,21-26] Hence it is difficult to compare and identify size of any associations between periodontal disease and systemic diseases. In this context, the presence or absence of associations depend on the definitions adopted. Hence there is a need to conclude a consensus on the threshold to be used to define periodontitis as well as systemic diseases. [17]

**Study Designs**

There is a need for a paradigm shift from using cross sectional studies to longitudinal studies. This may enable the observation of disease progression and treatment results. [17,21,25,28,30]

**Use of surrogate measures**

Epidemiological studies predominantly did not use clinical measurements but rather surrogate measures of disease producing intriguing results. The examination of evidence based surrogate markers, do not justify the definite disease event. Studies should rather aim to analyse health outcomes. [25,27-28,31]

**Test of hypotheses**

In a vast majority of studies, identification of association is followed by suggestion of hypotheses which can be tested. The difficulties posed by the future study designs to investigate the hypotheses should not be underestimated. [24]

**Concept of causation**

The concept of causation is difficult and any given disease can be caused by more than a single mechanism and every causal mechanism involves the combined action of many component causes. The association of periodontitis with certain systemic disease cannot offer explanation or understanding of the disease. The associations in many cases may be weak but a causal link cannot be totally dismissed. The principles of disease causation and causal theory are beyond the scope of discussion. [17]

**Role of shared risk factors**

According to the risk factor hypothesis, periodontal diseases share a series of common risk factors with a range of systemic conditions. These may be accountable for the increased risk of systemic complications. These factors present the issue of confounding and bias. [18,24,26,29]

**Applying the Bradford Hill criteria**

Scientific studies reveal an association between a given factor and a health effect. This cannot be inferred to indicate that the factor causes the specific disease. Researchers are suggesting the application of the Bradford Hill (1965) criteria to establish the strength of evidence for complex conditions for infective aetiology. [17]

This necessitates the evaluation of the body of existing proof for the following:

(a) Statistical strength of association
(b) Consistency
(c) Specificity
(d) Temporal relationship
(e) Biological gradient or dose response relationship
(f) Biological plausibility
(g) Coherence
(h) Experimental reversibility
(i) Analogy / other precedents

**Evolving dynamics of systemic diseases**

With the advent of predictive, preventive and personalized medicine, it has become even more relevant to integrate these concepts with periodontics. [34]

**Prevention**

The known methods by which periodontal disease can be prevented are more efficient than those available for
any other chronic diseases. Periodontal disease prevention employs uncomplicated procedures. But taking into consideration the high prevalence of the disease, it can be concluded that it is hardly being used. The approach of prevention has to be embraced. Neglect is the principle cause of periodontal disease. Neglect of oral health is the primitive cause; neglect of systemic health can be merely contributory. [35]

**Prediction**

Patients with systemic diseases should be placed at a higher risk for periodontal health deterioration and vice-versa. Though the relation between periodontal pathologies and systemic disorders is complex, status of deteriorating periodontal health can be an early indicator as well as a risk factor for a variety of multifactorial diseases. This includes pre-term birth, a spectrum of vascular pathologies, stroke, heart and lung disease, diabetes mellitus with co-morbidities, some types of cancer, neurological disorders and several mental disorders such as depression, anxiety, anorexia, bulimia, Alzheimer’s disease and so on. [34]

**Personalization**

The patient in question and the wide range of other systemic contributory factors should be comprehensively analysed. Applying the concept of individual medicine - the great strength of individualized treatment is to offer a holistic and integrative approach comprising of curative, rehabilitative and preventive examination as well as treatment methods tailored for the individual. The multidimensional interaction of risk factors - both internal and external including genetic background, age, gender, environmental risk factors, lifestyle, culture and beliefs as well as social status in the overall predisposition of individuals to disease is recognized. Other aspects like development of disease, course of the disease and response to therapeutic intervention is to be considered. The fact that this varies from individual to individual is to be highlighted. [34]

**Conclusion**

There is a need to use concrete and community agreed case definitions of periodontal disease status. The systematic implementation of the same is essential to decipher the relationship of periodontitis and systemic diseases. Moreover these associations are uncertain since periodontal disease is a heterogeneous mix of conditions. This issue is exaggerated by the ill-defined systemic outcomes in the target disease. A clear cut and narrower definition of diseases may enable identification of profound relationships. Shared genetic susceptibility and cross genetic susceptibility have been considered in correlating certain diseases though there is lack of substantial evidence to support this notion. This is significant as individual variation in disease experience observed clinically can be influenced by a range of factors - genetic, epigenetic and environmental.

Moreover the systemic virulence potential of one’s oral micro biome and immune response may be a completely different issue in assessing the nature of the challenge. Hence one size fits all intervention should be replaced by a more customized approach. In order to understand the associations of systemic diseases and periodontal diseases, well designed observational studies should be an integral component of future research. Longitudinal studies to assess the risk would be valuable. Further research is essential for the translation of basic research into clinical studies and practice. Such focused research modalities could go a long way in unravelling the dogma that plaques this dubious association between periodontal disease and various systemic infections.

**References**