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ORIGINAL ARTICLE

Salivary Biomarkers in the Diagnosis of Periodontitis

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ABSTRACT

Periodontitis is caused by complex interactions among the host immune system and the subgingival microbiota, which causes damage to periodontal ligament attachment, and tooth loss. The impacts of periodontitis are highly significant. In the last few decades, periodontitis has enhanced the economic burden globally because it is associated with various other systemic diseases and the relative treatment is expensive. The prevalence of the periodontal disease varies in different countries of the world, with a higher prevalence reported in Asian countries. Traditional clinical methods for diagnosing and monitoring periodontitis are inadequate for anticipating patient sensitivity, disease activity, and treatment responses. Several disease-specific molecular biomarkers have been identified as a result of periodontitis immunopathogenesis studies and saliva mediator analyses. Assessments of these salivary biomarkers will yield more accurate diagnostic results, supporting the clinical management of patients. The discovery of these salivary biomarkers highlights salivary diagnostics by introducing quick, non-invasive, screening procedures. Finally, the development of sensitive and specific disease biomarkers will yield highly validated results and aid in the clinical management of periodontitis patients

Keywords: Periodontitis, Cytokines, Diagnosis, Salivary Markers

INTRODUCTION

Periodontitis is ranked as the world's sixth-most common chronic inflammatory oral disease. It is a multifactorial disorder caused by complex interactions between bacterial pathogens that adhere to the tooth surface. Gingivitis, chronic periodontitis, and aggressive periodontitis are the three major types of periodontal disease[1]. Periodontitis is an irreversible form that causes chronic gingival inflammation. Persistent bad breath, gum recession, impaired mastication, and painful jaws are common complaints seen in patients [2,3]. Systemic diseases like adverse pregnancy, cardiovascular disease, pulmonary disease, and diabetes mellitus have been linked to periodontal disease, but no causal relationships have been discovered [4]

Figure 1: A) Healthy Gums B) Gingivitis C) Periodontitis

Etiological Factors Associated with Periodontal Disease: Many etiological factors have been linked with Periodontal Disease among which some are modifiable, while others are not. Smokers have worse periodontal disease and more severe tooth loss than nonsmokers [5]. Tobacco use is another important modifiable risk factor for periodontitis, accounting for more than half of adolescent periodontitis in the United States.[6] [7]

Prevalence of Periodontal Disease: Periodontitis prevalence rises by age affecting approximately 10-15% of the adult population worldwide.[8,9] In Asia, however, the prevalence is estimated to be 15-20% of the adult population.[10] Adult Dental Health Survey (ADHS) reported approximately 9% of the UK population has advanced periodontitis, indicating the tendency toward more severity [11]. The periodontal disease National surveys in Pakistan are not frequently reported however, the World Health Organization (WHO) reported that 18% of the Pakistani population has periodontal problems, with 31% suffering from chronic periodontitis. People in Pakistan's rural areas are more likely to suffer from periodontal disease due to a lack of oral healthcare facilities and a lack of awareness caused by a low literacy rate.[12]

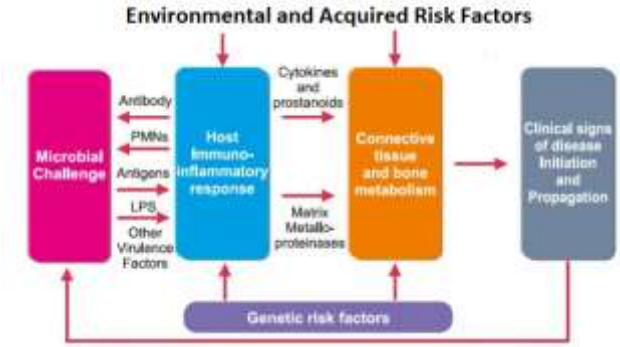

Figure 2: Environmental and Acquired Risk Factors associated with Pathogenesis of Periodontitis

Pathogenesis of Periodontal Disease: Microbial Role: Chronic periodontitis pathogenesis is accelerated by dental plaque, resulting in inflammation and disease propagation. A single person's microbial biofilm contained approximately 150 species, and dental plaque contained up to 800 colonies of different species. Aggregatibacter actinomycetemcomitans species have been linked to aggressive forms of periodontal disease. Other species, such as Porphyromonas gingivalis, have been linked to severe or progressive periodontitis.[13]

Immunopathogenesis: Bacterial pathogens via intrinsic and secreted MAMPs activate host local tissue cells and immune cells. Periodontium is supported by an ecological balance of commensal (nonpathogenic) microflora and neutrophils. Disturbance in the ecological balance of pathogenic microflora such as

Porphyromonas gingivalis, and Tannerella causes the activation of intrinsic periodontal cells. A release of pro-inflammatory cytokines activates neutrophils (particularly IL-1β and IL-8) and osteoclasts (in response to RANKL).[14] Increased levels of MMP-8, MMP-9, and -glucuronides indicate increased local activity of neutrophils in the periodontium. TNF-, IL-12, IL-17, and IL-18 are proinflammatory cytokines and the balance of these proinflammatory cytokines is important factor of disease progression. This proinflammatory response results in periodontal tissue destruction—a specific feature involves loss of connective tissues of the gingival lamina propria and periodontal ligament leading to compromised tooth function.[15]

Saliva as Diagnostic Medium: Traditionally, periodontal disease diagnostic methods rely on clinical examination and radiographic evaluations. Recent years have paved the way for saliva to play a potential role in salivary diagnostics.[16] Although blood is the main salivary composition that changes as a result of active transport and secretion processes in the salivary glands. Saliva has gained widespread acceptance as a potential tool for diagnosis and therapeutic intervention. The main advantage using saliva as a diagnostic medium is that it can be acquired over noninvasive procedures.[17]

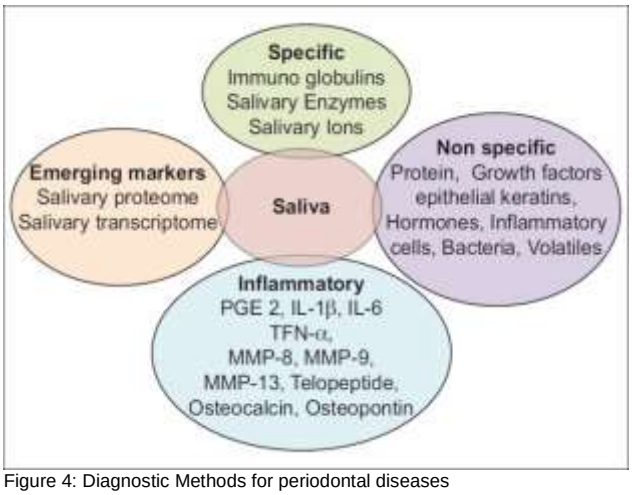

Figure 4: Diagnostic Methods for periodontal diseases

Diagnosis of Periodontitis Using Salivary Biomarkers: Cytokines in Periodontitis: Many salivary inflammatory biomarkers, including IL-1, IL-6, IL-8, MMP-8, TIMP-1, macrophage inflammatory protein (MIP-1), prostaglandin E2, and TNF-, have been linked to periodontitis and gingivitis in studies. Salivary IL-1 levels are much higher in patients, making IL-1 an established biomarker for periodontitis.[18-20] However, the IL-6 role in saliva is debatable and no significant link between salivary IL-6 and periodontitis is reported. The salivary levels of GM-CSF, IL-2, IL-3, IL-4, IL-5, IL-10, IL-12, and IFN-, on the other hand, showed no significant associations with periodontitis. Whereas the salivary levels of Toll-like receptor-4, Toll-like receptor-2, IL-18, uric acid, aspartate transaminase, CCL3 (MIP-1), and procalcitonin have been linked to periodontitis. Furthermore, these biomarkers showed positive correlations with clinical periodontal parameters such as probing pocket depth, clinical attachment loss, and gingival index. As a result, assessing their levels in saliva may be useful in the diagnosis [21,22].

Bone Biomarkers in Periodontitis: Chemokines such as RANKL, Osteoprotegerin (OPG), Osteocalcin, and Osteonectin regulate bone metabolism. The molecular interactions between bone metabolism and inflammation causes alveolar bone loss.[23] Because RANKL promotes bone resorption and is activated by cytokines such as IL-1 and IL-6, the ratio of RANKL to its natural antagonist Osteoprotegerin (OPG) is an important factor in determining bone cell resorption and turnover. Chronic periodontitis patients had significantly higher levels of sRANKL and lower levels of OPG when compared to healthy controls. [24] Osteocalcin-a calcium-binding protein found in bone is the mineralized tissues' most abundant noncollagenous protein. Osteocalcin levels in saliva were found to be significantly correlated with clinical attachment loss can be used as a critical diagnostic marker for periodontitis. Previous literature supported the theory that Osteocalcin has significant diagnostic potential, and can also be used as a prognostic marker to predict the likely outcome of the disease. In patients with chronic periodontitis, salivary concentrations of bone biomarkers Osteonectin and osteopontin were found to be positively correlated with alveolar bone loss and other clinical periodontal parameters.[25]

Systemic Inflammatory Markers in Periodontitis: Calprotectin is thought to be an important indicator of systemic inflammation. Calprotectin levels are elevated in periodontitis patients' saliva. Similarly, periodontitis is associated with decreased levels of C-reactive protein (CRP) in saliva. Salivary C3 and C4 levels have also been linked to periodontitis. C3 levels in saliva were lower in healthy controls.[26] Lactate dehydrogenase, aspartate aminotransferase, and alanine aminotransferase are specific markers of cellular damage. The significant association between salivary levels of all these mediators and periodontitis exists in the literature. Salivary levels of β -Glucuronidase are a marker of neutrophil influx into GCF, and salivary levels of this enzyme correlate positively with periodontitis severity. Salivary glutathione peroxidase, which is a marker of neutrophil antioxidant capacity, also significantly higher in periodontitis.[27]

Growth Factors in Periodontitis: Growth factors play a variety of roles in immune responses, and elevated levels of TGF-, epidermal growth factor, and vascular endothelial growth factor have been found in periodontitis patients. However, only a few studies have found a link between salivary hepatocyte growth factor and periodontitis. HGF is secreted by gingival fibroblasts and is influenced by cytokines and bacterial byproducts.[28] epithelial apical migration in periodontitis is also mediated by HGF.

Matrix Metalloproteinases (MMPs): MMP synthesis and secretion are altered in periodontal disease, MMP-8 and MMP-9 levels elevate in periodontal disease. Several studies have reported matrix metalloproteinase 8 (MMP8)/neutrophil collagenase as a diagnostic biomarker of periodontal disease.[29] Surprisingly, TIMP-1 levels in saliva are higher in healthy people than in periodontitis patients. However, salivary MMP-1 (fibroblast collagenase), MMP-3 (stromelysin-1), or MMP-14 (a membrane-type MMP) are not reported to be linked to periodontitis. Periodontitis patients have significantly higher levels of MMP-2 and MMP-9 than controls.[30]

CONCLUSION

Salivary biomarkers have the potential diagnostic role in periodontitis. Based on the accuracy and efficacy of these biomarkers, dental practitioners can not only detect periodontitis early, but also develop an effective treatment strategy. The discovery of these salivary biomarkers highlights salivary diagnostics by introducing quick, non-invasive, screening procedures. Finally, the development of sensitive and specific disease biomarkers will yield highly validated results and aid in the clinical management of periodontitis patients.

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