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A REVIEW OF SALIVARY BIOMARKERS OF PERIODONTAL DISEASE

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ABSTRACT

Background: **Periodontal disease is a complex multifactorial disease resulting from the interplay amongst microbiota, host immune response (influenced by genetic make-up) and lifestyle factors. The chronic inflammatory nature of the disease results in the destruction of the component of the periodontium. The process of the disease is associated with inflammation, collagen degradation and, bone loss which correlate with clinical features of periodontal disease. The clinical diagnosis of periodontal disease entails clinical examination involving the evaluation of probing depth, bleeding on probing, and radiographic examination of alveolar bone loss but these examinations are not enough to determine the activity, progression and, evaluation of the efficacy of the periodontal disease treatment. Given the foregoing gap in the traditional method of diagnosing periodontal disease, research on the molecular disease, biomarkers became imperative. The aim of this review is to summarize the current knowledge of salivary biomarkers of periodontal disease and to evaluate their validity in predicting disease progression.**

Method: **This narrative overview of 46 articles bordering on biomarkers of periodontal disease was conducted between 2000 to 2023, and assessed in Google Scholars, PubMed/Medline, Science Direct Database using keyword combined with Boolean operators. This was done following literature search; articles title, abstract evaluation and full-text reading studies.**

Results: **The present review comprised of 46 studies were included (observational studies; reviews articles; and experimental studies), focusing on the detection of periodontal disease using non-traditional method; saliva as a medium for detection of periodontal disease biomarkers.**

Conclusion: **Saliva is considered as anon-invasive and easier to collect medium for the detection of biomarkers as it contains virtually all the molecules found in other diagnostic media; serum and blood. This review highlights recent advances in salivary biomarkers as proteomics, genomics, and microbial biomarkers and potential clinical applications as well as available Point of Care (POC) diagnostics that aid easy diagnosis and prognosis.**

Keywords: Biomarkers, Saliva, Periodontal disease

INTRODUCTION

Periodontal disease is a chronic microbial and inflammatory process characterized by the presence of pathogenic bacteria, impaired host immune response, and destruction of the components of the periodontium. In affected tissues, biochemical signaling involves three biological phases (inflammation, connective tissue degradation, and alveolar bone turnover).

Periodontitis is a public health issue and one of the six complications of diabetes worldwide, with an overall prevalence of 11.2% and affecting around 743 million individuals. There has been an increase in periodontal disease globally of 57.3% from 1990 to 2010.[1] Epidemiological studies have shown that the highest prevalence of periodontitis is in elderly populations (82%), followed by other adults (73%) and adolescents (59%).On the other hand, paucity of epidemiological data on epidemiology of periodontal diseases in Africa persist. People in lower socio-economic groups are unequally affected by periodontal disease.

Research emanating from the World Health Organization showed that children and teenagers experience gingivitis, a form of periodontal disease unlike severe periodontitis in adults persons of about 5-20%.[2] The relationship of periodontitis to certain systemic disease such as diabetes, atherosclerosis,

cancers, and Alzheimer has been proffered; as the effect of periodontitis is not limited to the periodontium. On account of the slow and innocuous progression of periodontal disease its harmful effect to the periodontal ligament, cementum, alveolar bone and gingiva can result in tooth loss and its associated effects on the quality of life of the patient. Early diagnosis of gingivitis may prevent its progression to periodontitis following treatment.[1]

Innate immunity helps to maintain oral health through physiological barriers (skin and mucous membranes) and other mechanisms (polymorphonuclear leukocyte surveillance and physiologic immune surveillance) through the toll like receptors, dendritic cells, macrophages, PMN cells, NK cells, complement system and cytokines. The numerous salivary defense mechanisms include locally and systemically produced cytokines, immunoglobulins, lysozymes, mucins, and an array of antimicrobial proteins(AMP); which serve as major components of the innate defense mechanism Circulating molecules such as interleukin (IL)-1â, C-reactive proteins, human macrophage inflammatory protein (MIP)-1á, matrix metalloproteinase (MMP)-8 and -9, osteoprotegerin (OPG), tumor necrosis factor (TNF)-á, receptor activator of nuclear factor-kappa B ligand (RANKL), and many others are somewhat elevated in the whole saliva of periodontitis patients, thus making them supposed biomarkers of the disease.[3,4,5]

Traditionally, periodontal diagnostic methods include assessment of clinical parameters and radiographs. The application of the clinical method in diagnostic though beneficial and reliable is froth with being expensive concerning time, cost, and professional expertise required. But with advanced diagnostic method using serum and salivary molecules periodontal diseases is relatively easily diagnosed.

What are Biomarkers

According to the National Institutes of Health (NIH), a biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to therapeutic intervention. Summarily, biomarkers are entities within the body capable of providing impartial information regarding the current physiologic state of a living organism.[4]

Biomarkers exist in a variety of different forms, including antibodies, microbes, DNA, RNA, lipids, and metabolites.

Sources - Biomarkers of Periodontal disease

Microorganisms and their products, inflammatory and immune products, enzymes released from host cells, connective tissue degradation products, and bone resorption products.

SALIVA AS A MEDIUM

Saliva is a body fluid like blood; contains numerous amounts of proteins and nucleic acids and other components that have diagnostic properties.[6]

Physiological, environmental, age, and sex-related issues tends to affect the volume and constituents of saliva as a medium for determining periodontal diseases, despite these challenges and limitations, opportunities in clinical periodontics exist about the identification, monitoring, and tracking of disease progression in patients through salivary diagnostics

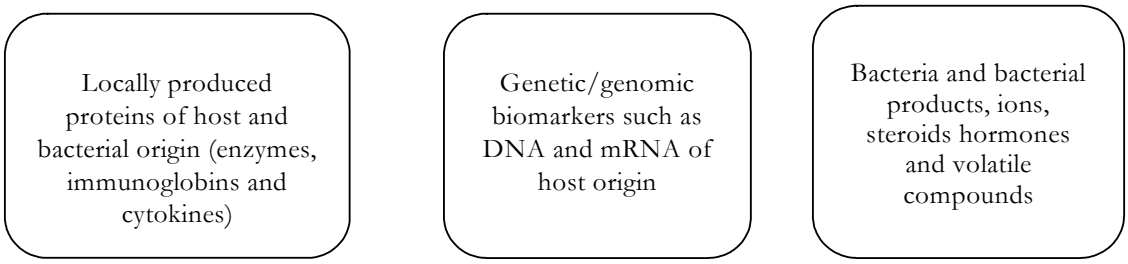
Technological advancement over the years has made it possible for salivary diagnostic to be demonstrated with point-of-care (POC) applications for multiple diseases-periodontal conditions.[5] More so, concerning periodontal disease, researchers have shown that gingival crevicular fluid (GCF) bio-markers that reveal local disease status, represent a technically difficult approach (that is, difficulty in accessing all tooth sites, salivary contamination, or bleeding from the sites) to implement clinically. Saliva is more readily available and easier to collect than GCF. And unlike, other bodily fluids, salivary diagnostics offer an easy, inexpensive, safe, and noninvasive approach for disease detection, and possess a high potential to revolutionize the next generation of diagnostics. There has been concern that although saliva contains diverse constituents with diagnostic signatures, their low concentration compared with levels in the blood may prevent salivary diagnostics from being clinically practical; however, with the development of new and highly sensitive techniques (e.g., molecular diagnostics, nanotechnology), the challenges of low concentrations of some molecules in the saliva is relatively insignificant.[6]

QUALITY OF SALIVA FOR DIAGNOSTIC

Several qualities cut out saliva as a good medium for diagnosis of diseases. Characteristics such as high sensitivity and specificity, high throughput, portability, safety of sampling (no needle), no special equipment, cost-effective, elimination of the risk of infection, and screening of large population.[7]

Driving force for Periodontal Biomarker

Research into biomarkers of periodontitis is enforced by majorly three objectives: to identify 'at risk' patients before periodontal tissue destruction occurs; to



Types of Salivary Biomarkers

determine disease activity and progression; and to build up our understanding of this complex disease to find new therapeutic target.[8]

SALIVARY PROTEOMIC BIOMARKERS

Specific salivary proteomic biomarkers have been identified for the three key features in the pathogenic processes of periodontal disease: Dental biofilm, Inflammation, Collagen degradation, and Bone turnover. Examples are: IL-1β, TNFα, IgA, Aspartate aminotransferase, Metalloprotienase-8,9,13,C-reactive protein, Cathepsin-B, Osteocalcin, ICTP etc.[11]

DENTAL BIOFILM

Immunoglobulins (Ig)

The predominant immunoglobulin in the saliva is secretory IgA (sIgA), which is derived from plasma cells in the salivary glands. A lesser amount of IgG and IgM are also found in saliva. Immunoglobulins (Igs) influence oral microbiota as they interfere in adherence and bacterial metabolism. Higher concentrations of Ig A, IgG, and Ig M have been found in periodontal disease when compared with healthy patients and their concentration drops significantly following treatment.[12]

IgG levels rise to periodontal pathogens Porphyromonas gingivalis and Treponema denticola as compared to saliva from control subjects. Sandholm *et al.*. found increased concentrations of salivary IgG to Aggregatibacter actinomycetemcomitans in patients with aggressive periodontitis.

It's important to note that the specific Ig responses in chronic periodontitis can vary depending on the individual's immune status, the stage of the disease, and the presence of other systemic conditions. Further research is needed to fully understand the role of immunoglobulin markers in chronic periodontitis and their potential as diagnostic or prognostic indicators.

INFLAMMATORY

Cytokines

Salivary interleukin-1 beta: . Interleukin-1 (IL-1): IL-1 is a pro-inflammatory cytokine that plays a key role in the pathogenesis of periodontal disease. Elevated levels of IL-1 have been detected in the gingival crevicular fluid of patients with periodontitis, indicating its potential as a biomarker for disease activity.[2,12,13] IL-beta is considered a discriminating biomarker between active and inactive periodontal disease.[13]

Salivary levels of interleukin-6: It is a pleiotropic cytokines present in individuals with periodontitis compared with healthy subjects. And is associated with tissue destruction in peri-implant disease.[1,13]

Salivary levels of tumor necrosis factor-alpha: Studies have shown that increasing concentration of TNF-alpha correlates with clinical parameters that indicate the presence of generalized chronic periodontitis and have also demonstrated significant changes after nonsurgical periodontal therapy.[13]

Prostaglandin E2 (PGE2): PGE2 is a lipid mediator involved in the inflammatory response and bone resorption. Elevated levels of PGE2 have been detected in the gingival crevicular fluid of patients with periodontitis, likewise in saliva suggesting its potential as a biomarker for assessing disease severity.[15,16]

Tumor Necrosis Factor-alpha (TNF-á): TNF-á is a key pro-inflammatory cytokine that plays a central role in the initiation and perpetuation of the inflammatory response. Studies have demonstrated elevated levels of TNF-á in the salivary fluid and gingival crevicular fluid of patients with periodontitis, implicating its involvement in the pathogenesis of the disease.[12,17]

C-reactive protein(C-RP)

C-RP is produced by the liver and is stimulated by circulating cytokines, such as tumor necrosis factor-alpha and interleukin-1, from local and/or systemic inflammation such as periodontal inflammation.[16] Circulating C-reactive protein may reach saliva via GCF or the salivary glands. High levels of C-reactive protein have been associated with chronic and aggressive periodontal diseases and with other inflammatory biomarkers.[17] C-reactive protein has recently been shown to be measurable in saliva from periodontal patients using a lab-on-a-chip method.

Various observations were made which revealed that the higher the levels of CRP, the more severe are the periodontal diseases.

In addition, a link between CRP and cardiovascular disease has been discovered as increase concentration of serum CRP is known to be a strong independent risk factor for the development of cardiovascular disease. Hence, salivary CRP may represent a novel method for diagnosing and monitoring CVD and periodontal diseases.[4]

Macrophage Inflammatory Protein (MIP-1á)
It is a bone-remodeling-related molecule in chronic periodontitis. MIP-1á levels were found to be 18-fold higher in periodontitis patients than normal and clinical measures correlated significantly with MIP-1á levels and achieved excellent sensitivity, specificity, and accuracy, Al-Sabbagh *et al.*[18]

Cathepsin B
A lysosomal cysteine protease of the papain family produced by macrophages can be found in GCF and assessed in salivary fluid as biomarker of periodontal disease. Its levels increase while the progression of the periodontal disease persists. Cathepsin B may have potential use in distinguishing periodontitis from gingivitis and in planning treatment and monitoring treatment outcomes.[6,21]

Table 1: Classification of periodontal biomarkers[9]

Proteomic biomarkers	Genetic Biomarkers	Microbial biomarkers	Other biomarkers
Cystatatins, α-glucosidase, Acid Phosphatase, Akalinephosphatse, Aminopeptidase, Lactoferrin, Translactoferin, IgM, MMP-13, MMP-8, MMP-9, Cathepsin B, Osteonectin, Osteocalcin, Osteopontin, Elastase, Platelet-activating factor, Epidermal growth factor, Platelet-derived growth factor, Esterase, Pyridinoline crosslinked carboxy-terminal telopeptide, Fibronectin, sIgA (Sceretory IgA), Gelatinase, IgA, Trypsin, Vascular endothelial growth factor, IgG	CathepsinC gene Mutation, Collagen gene mutation,IL-1 polymorphisms,IL-10 polymorphisms, TNF polymorphisms	Aggregatibacter actinomycetemcomitans, Camylobacter rectus, Porphyromonas gingivalis, Prevotella nigrescens, Tannerella forsythia	Calcium, Cortisol, Hydrogensulphide ,

BONE REMODELING

Alkaline Phosphatase (ALP)
Alkaline phosphatase is an enzyme that plays a role in bone mineralization and has been investigated as a potential biomarker for periodontal disease in the saliva. It is derived from the actual salivary secretions, host immune cells, tissue degradation, and disposed bacterial cells from dental biofilms and mucosal surface. And is produced by osteoblasts and other cells involved in bone formation.[19]

Alkaline phosphatase is a distinct member of metalloenzymes which functions during osteoblastic bone activity such as matrix mineralization. Infections; bone infections, can predispose to elevated tissue-nonspecific alkaline phosphatase levels (TNAP) as is seen in peri-implant disease.[23,24]

The level of this enzyme activity is observed higher in individuals who have periodontitis as compared to gingivitis and in turn with periodontal disease than non-diseased individuals. Higher concentration of ALP in saliva correlates with clinical parameters such as bleeding on probing, and suppuration.[22,25]

Osteocalcin
Osteocalcin: It has been found that the level of Osteocalcin increases in conditions where there is increase bone metabolism[21] as seen in osteoporosis, multiple myeloma and during fracture repairs.[22] And when a combination of biochemical markers: osteocalcin, collagenase, prostaglandin E2, alpha-2 macroglobulin, elastase, and alkaline phosphatase were evaluated, increased diagnostic sensitivity and specificity values of 80% and 91%, respectively, were reported.[22] A positive correlation between osteocalcin concentration and clinical parameters of periodontitis and gingivitis patients have been shown from studies.[11,21,31]

Osteopontin (OPN)
It is a biomarker which is useful in bone turnover assessment. Noted to be the non-collagenous calcium-binding glycosylated phosphoprotein in the bone matrix and is produced by several cells including osteoblasts, osteoclasts, and macrophages.[23] Kido *et*

Table 2:[10]

DENTAL BIOFILM	INFLAMMATORY	COLLAGEN BREAKDOWN	BONE REMODELLING
Immunoglobulins (IgA, IgM, IgG)	B-glucuronidase	α 2-macroglobulin	Alkaline phosphatase
Mucin	C-reactive protein	MMP-8	Osteoprotegrin
Lysozyme	IL-1β	MMP-9	Osteocalcin
Lactoferrin	IL-6	Aspartate amino transferase	SPARC/osteonectine
Histatin	MIP 1 α	Alanine aminotransferase	RANKL
Peroxidase	Tumor necrosis factor- α	TIMPs	β C-terminal type-1 collagen telopeptidase

al. (2001) demonstrated that OPN level in saliva was increased with the progression of periodontal disease.[22]

Osteoprotegerin

Osteoprotegerin (OPG) is a glycoprotein that inhibits osteoclast differentiation and reduces bone resorption by attaching to the RANK.[24] There is now a wide body of evidence in the literature indicating that alveolar bone destruction is associated with an imbalance in RANKL and OPG.[6,34] Current study shows decrease OPG levels in GCF, saliva, and tissue of chronic periodontitis patients compared to healthy controls thus provide further evidence regarding the role of OPG downregulation in periodontal disease.[9,33]

COLLAGEN BREAKDOWN

Matrix metalloproteinases (MMP): These are host proteinases accountable for both tissue degradation and remodeling. Matrix metalloproteinase 8 and 9 are the major matrix metalloproteinase in saliva; in smaller amounts, saliva also contains matrix metalloproteinase 1, 2, 3, 7, 12, 13, 14, 25, and 26 and tissue inhibitors of matrix metalloproteinase 1 and 2. Host cell-derived interstitial collagenases are implicated in the destructive effect on gingival and periodontal ligaments collagen in the process of periodontal disease.[4]

Clinical measurements demonstrate significant positive correlations with elevated levels of salivary matrix metalloproteinase 8. The level of MMP8 reduces following therapy suggesting it as a potential marker for monitoring periodontal disease activity.[25] Base on standardized mouth rinse sample cut-off points of MMP8 the following values have been determined for a healthy state (<6.46 ng/mL), Gingivitis/Peri-mucositis (6.64–20 ng/mL), Periodontitis/Peri-implantitis that respond favorably to the treatment (20–60 ng/mL). And Progressive periodontitis that does not respond to the treatment (>60 ng/mL).[1]

Gelatinase (MMP-9): Collagenase is produced by neutrophils and degrades collagen, an intercellular ground substance. MMP-9 levels are found in patients with progressive attachment loss. Posterity holds monitoring of periodontal treatment in MMP-9 salivary diagnostics. A recent study revealed that MMP-9 appears to be associated with cardiovascular disease, cancer, multiple sclerosis, and neuropsychiatric disorders such as schizophrenia and bipolar mood disorder.[25]

Collagenase-3: Otherwise known as MMP-13, is another collagenolytic MMP with exceptionally wide substrate specificity.[26] According to recent studies, MMP-13 may be useful for diagnosing and monitoring the course of periodontal disease as well as for tracking the efficacy of therapy in the future.

Tissue Inhibitors of Metalloproteinases (TIMPs): TIMPs are endogenous inhibitors of MMPs and play a crucial role in regulating the activity of these enzymes. Imbalances in the ratio of MMPs to TIMPs have been implicated in the dysregulation of tissue remodeling processes in periodontal disease and have been suggested as potential biomarkers for disease progression.[27]

Carboxyterminal Telopeptide of Type I Collagens (ICTP)

ICTP, a degradation product of type I collagen, has been investigated as a potential indicator of collagen degradation and periodontal tissue destruction.[28]

Carboxyterminal telopeptide of type I collagen is a useful biomarker for alveolar bone turnover hence a predictor of both future alveolar bone and attachment loss.[23,30]

Pyridinoline cross-linked carboxy-terminal telopeptide (ICTP) is a breakdown product of Type I collagen.

The pyridinolines are deoxypyridinoline, N-telopeptides and C-telopeptides. Increased levels of ICTP are associated with most pathogens including, Tannerella forsythia P. gingivalis, P. intermedia, and T. denticola. Non-surgical mechanical therapy does not significantly reduce ICTP and IL-1 levels. Contrary to the foregoing statement, scaling and root planing with local drug delivery mitigate and decrease the concentration of GCF ICTP levels.[22]

HORMONES/STRESSOR PROTEINS MARKERS

Cortisol

Emotional stress is likely a risk factor for periodontitis. One mechanism proposed to account for the relationship is that elevated serum cortisol levels are associated with emotional stress, which exerts a strong inhibitory effect on the inflammatory process and immune response.[29] Furthermore an association between Chromogranin A(CgA) Furthermore, there is an association between chromogranin A (CgA) and cortisol levels as well as á-amylase activity in the saliva of persons with periodontitis, especially a significant relationship between salivary CgA and cortisol and aggressive periodontitis.[29,30]

Nitric oxide (Signaling molecule)

Nitric oxide (NO), which is synthesized from L-arginine by NO synthase, plays a protective role in infectious diseases.[31] NO is evident in the etiopathogenesis of inflammatory periodontal disease and expressed in saliva.[32] Hence, salivary levels of NO can be utilized as a good indicator of the inflammatory status of the periodontium. Research has proven that a higher level of salivary NO was observed in patients with periodontitis in comparison to healthy individuals and can be used as a valuable screening tool for periodontitis.[33,4]

8-Hydroxydeoxyguanosine

8-Hydroxydeoxyguanosine is presently considered as a predictive marker of periodontal disease as it has been found to be present in salivary and gingival crevicular fluid following assessment of patients with periodontitis and it is, a product of oxidative DNA damage.[34] The level of 8-OHdG can be also used as a prognostic indicator to monitor the progression of periodontal disease.[9]

In a study, it was shown that there is increase in 8-OHdG levels in saliva and mitochondrial DNA deletions in gingival tissue of patients with chronic periodontitis.[34,35] In same vein, periodontal status and efficacy of periodontal treatment can be evaluated based on the concentration of 8-OHdG level in saliva which has been found to correlate proportionately with the load of periodontal pathogens.[35]

Other Proteins

During the inflammatory phase of periodontal disease, some protein markers whose concentration correlate with the intensity of phase assayed in saliva are: platelet-

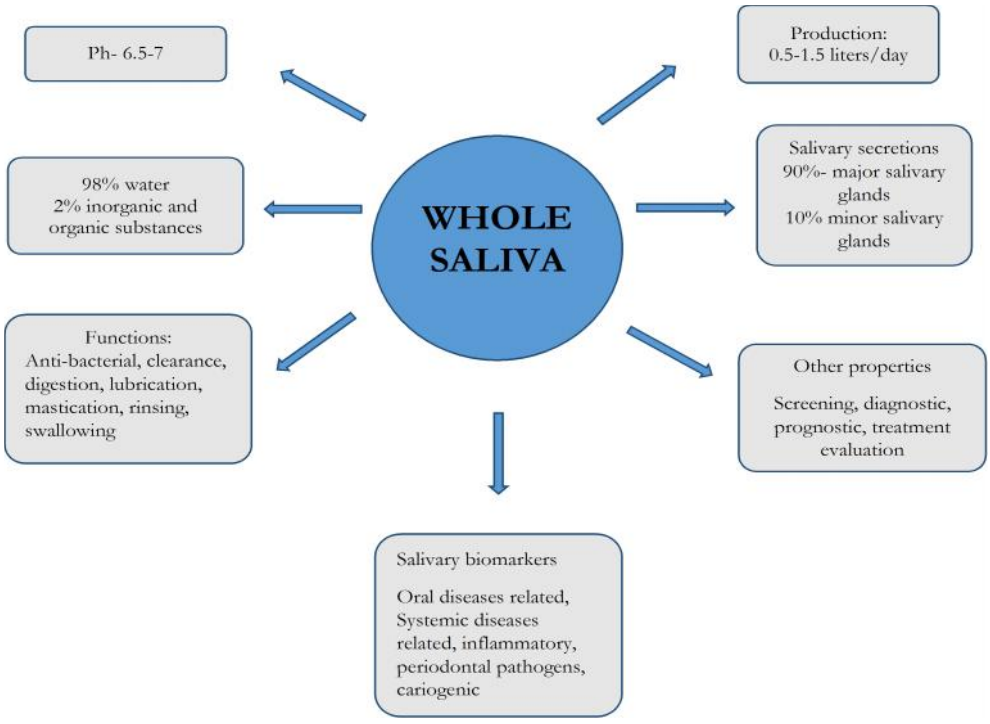


Figure 1: Characteristics of saliva

activating factor, vascular endothelial growth factor, hepatocyte growth factor and other non-specific markers: fibronectin, mucin, lactoferin, cystatins, neopterin and perioxidase.[5,9]

Diagnostic Aid

Micro/Nano Electro-Mechanical Sensor-(MEMS/NEMS)

The Micro/Nano Electro-Mechanical Sensor measures molecules as; gene transcripts (mRNA), proteins, electrolytes, DNA, and others in saliva, as well as overall profile, and correlates of a particular disease state, such as cardiovascular disease. The integrated detectors within the MEMS/NEMS are able to process and analyse minute sample and reagent volumes

Figure 2[36]

The envisioned product is the 'Oral Fluidic Nano Sensor Test' (OFNASET).

The handheld, automated, easy-to-use, integrated system will enable simultaneous and rapid detection of multiple salivary proteins and nucleic acid targets. Dentists and other health care providers can use the salivary biomarker device as POC in their office.

OralDNA Labs

My PerioPath

It uses a saliva sample to identify the type and concentration of the specific bacteria that cause periodontal diseases.

MyPerioID PST test

It also uses saliva to determine a patient's genetic susceptibility to periodontal diseases and which patients are at higher risk of more serious periodontal infections. Both tests require the shipping of saliva samples to a laboratory for results.

Classification of Point care (PoC) Kits

- **Microbiological Test Kits**-For example, Omnigen diagnostics takes hours to days to perform. Evalusite has very low sensitivity, and PerioScan can only determine the severity of the disease
- **Biochemical Test Kits-**namely PerioSafe® and ImplantSafe®, can provide results within 5–7 min, with sensitivity and specificity of 76.5% and 96.7%, respectively
- **Genetic Test Kits -**GenoTypePST® and MyperioID tests are used to determine the genetic susceptibility to periodontitis

Amongst the PoC test kits, PerioSafe® and ImplantSafe® have shown to be the most reliable and applicable.

Furthermore, they can differentiate gingivitis and periodontitis by the cut-off point of 20 ng/mL.

Additionally, these tests have been shown not to comply with WHO's ASSURED criteria (affordable, sensitive, specific, user-friendly, rapid and robust, equipment-free, and deliverable to end-users) for PoC devices.[37]

MICROBIAL BIOMARKERS

Microorganisms and their products.

A number of periodontal pathogens as Tannerella forsythia, Porphyromonas gingivalis, Treponema denticola, and Aggregatibacter actinomycetem-comitans have been implicated in the progression of chronic periodontitis.[38] The rationale for the use of microbial analysis for periodontitis monitoring is to target pathogens implicated in disease; identify specific periodontal diseases, identify antibiotic susceptibility of infecting organisms colonizing diseased sites, and to predict disease activity.

Determination of microbial species can be by the use of microscopy, culture, immunological, DNA Probe, checkerboard DNA-DNA hybridization, and PCR. The immunological test entails –ELISA, Membrane Assay, Direct, and Indirect Immunofluorescence Assay (IFA), and Flow cytometry.[39]

GENOMICS

Research have shown that not less than 68 genes are associated with periodontitis.[40]

A number of studies have examined links between polymorphisms within-host response factors and aggressive periodontitis.[28]

Differences occurring in humans DNA sequences present with certain disease condition sometimes is

referred to as polymorphism. It usually present in less than 1 percent of the population as human shares 99.9% of genetic information.[41]

IL-1 Gene Polymorphisms

Study on IL-1 gene polymorphisms is based on the premise that a single nucleotide polymorphism of the IL-1 gene is a susceptibility factor for periodontal disease. IL-1 polymorphisms connote the risk of tooth loss and advancing periodontal diseases as it was found to be associated with *IL1 gene* (3953/4C>T) polymorphisms.[42] It has been shown that individuals with IL-1 polymorphism are have high presence of the "orange" and "red" complex period-pathogens, implicated in periodontitis.[43] The susceptibility to periodontitis seems to be increased with IL-6 gene 174/G>C polymorphism.[1,50] TNF~, IL-10 and CD14 genes polymorphism are under studies in relation to periodontal disease.

Transcriptomic-Micro RNA [Mi. RNA]

Collection of transcripts, deoxyribonucleic acid (DNA) that is transcribed into ribonucleic acid (RNA), found in saliva is referred to as salivary transcriptome. It also includes mRNA molecules that cells use to convey the instructions carried by DNA for subsequent protein production.

This discovery has proven a new diagnostic, giving vent to another avenue of salivary transcriptomic diagnostics. Research has proven that miRNAs are associated with periodontitis.[44]

Some studies have shown that they are associated with the receptor activator of the nuclear factor Kappa-B ligand (RANKL) induced osteoclastogenesis.[45] Within these miRNAs, miR-223 was the first to associate with periodontal tissue, Others being considered as important and possible predictor biomarkers of periodontal status are miRNAs such as miR-15a, miR-29b, miR-125a, miR-146a, miR148/148a, miR-223, and miR-92.[46] Salivary miRNA diagnosis for periodontal disease is novel. Given the complexity associated with additional investigations and standardized methods more research work will be needed.[44]

Limitation and Recommendation of the Review

Although the majority of the studies reported a positive association between periodontal disease and some of salivary biomarkers, the heterogeneity of the specificity and sensitivity of the biomarkers and clinical parameters employed in the studies, complicated the comparison of the results, thus considered inconclusive. Another limitation of this study is limited literature searched given the time of the review to date. Further experimental studies, with longer follow-ups are needed to better understand the putative relation between some of the biomarkers especially the genomics and transcriptomics-Micro-RNA and periodontal disease, in order to pave the way for novel biomarkers for gingivitis and periodontitis.

CONCLUSION

There has been a steady growth trend to develop tools to monitor periodontitis. Presently, the diagnosis of periodontal disease relies primarily on clinical and radiographic parameters. The traditional methods of diagnostic are useful in determining the severity, or verifying periodontal health, but limited in providing information about 'at risk' patients before periodontal tissue destruction occurs. Recent diagnostic aids as salivary biomarkers help in determining disease activity and progression, and building up our understanding of this complex disease with the purpose of finding new therapeutic targets.

Several molecular signatures; proteomic, genomic, and microbial have been found in saliva to be useful as diagnostic of periodontal diseases. An Ideal, diagnostic test should demonstrate high specificity and sensitivity. Interest in saliva as a diagnostic medium is gaining wide acceptance due to its many advantages over other diagnostic biofluids. However, most reports on individual biomarkers and multiple biomarker panels have been only preliminary and require further validation before testing at the clinical level.

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