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Biomarkers in the Diagnosis of Peri-implantitis - A New Paradigm

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Abstract

Diagnosis of peri-implantitis is still at large dependent on use of conventional diagnostic parameters which mainly includes mobility, BOP, probing depth (PD), bone loss. Main drawback of above clinical diagnostic parameters is that they lack the sensitivity and specificity sufficient enough for early diagnosis of peri-implant tissue destruction, thus proper management can't be initiated before considerable supporting bone is lost and it leads to failure of implant. This review was aimed to analyse various studies based on biomarkers present in peri-implant crevicular fluid (PICF) which are released following bone destruction and inflammation, can serve as specific and sensitive parameters for early detection of peri-implantitis, so that proper management can be initiated much before considerable peri-implant tissue destruction has occurred.

Keywords: BOP, PD, PICE.

Introduction

In present era dental implants made of titanium have become an imperative tool in the field of dentistry. Especially, as a replacement for teeth missing due to several disparate clinical conditions apart from crown and bridges. Over a period of 10 years survival rates of 95-98% has been reported. This high survival rate has persuaded dental surgeons to explore this method of oral rehabilitation[1]. But in the last decade, there is increase in the number of reported evidences of peri-implant inflammation affecting both soft and hard tissues, ultimately leading to implant loss. Analogous to

gingivitis and periodontitis affecting the periodontium of natural teeth, peri-implant mucositis and peri-implantitis are terms given for inflammation and destruction of soft and hard tissues around an implant respectively.[2] Clinical and radiographic parameters, such as, bleeding on probing, probing depth, mobility, suppuration and marginal bone loss, are the ones which are mostly assessed for the diagnosis of peri-implantitis. But the drawback with these diagnostic parameters is that they lack the sensitivity. Early diagnosis of peri-implant destruction, helps in monitoring bone loss progression which aids in proper management before considerable amount of the supporting bone is lost. If peri-implantitis is not diagnosed early and not properly managed, it leads to loss of the implant and implant failure. Therefore, diagnostic procedures used for diagnosis of peri-implantitis should include specific and sensitive parameters for prompt and early detection of disease.

Focusing on disease entities like enzymes and biomarkers present in peri-implant sulcus fluid (PISF) released following bone destruction and inflammation should be the area of interest. To get more detailed informations regarding the pathogenesis of peri-implant diseases more research primarily focusing on relationship between certain biomarkers with health/disease should be conducted.[3]

The aim of this review is to explore the new vistas of diagnostic parameters that can aid in early detection of peri-implantitis even in asymptomatic cases so that prompt treatment can be provided as early as possible.

Definition and pathogenesis

Mucositis can be described as a reversible inflammatory process which is bacteria-induced in origin and characterized by symptoms like swelling, reddening and bleeding on periodontal probing[4]. American Academy of Periodontology (AAP) states that probing depth of ≥ 4 mm, bleeding on probing associated with suppuration, along with no radiographic evidence of bone loss beyond bone remodeling, are the signs that confirm the presence of peri implant-mucositis [5].

A progressive and irreversible condition of the soft tissues and the loss of bone around the ossointegrated dental implants which usually bears masticatory load, decreased osseointegration, suppuration and formation of deep pockets is referred to as Peri-implantitis [4]. Padial-Molina et al. described peri-implantitis as cases with probing depth > 6 mm and with bone loss of ≥ 2 mm which can be seen radiographically[6].

Loss of surrounding bone along with inflammation of the mucosa was defined as peri-implantitis by Sixth European Workshop on Periodontology (EWP)[7]. However the Seventh EWP states that, noteworthy changes in bone crest level along with bleeding on probing can be stated as the salient features of peri-implantitis[8].

Eight EWP and American Academy of Periodontology states that peri-implantitis is an inflammatory process around an implant, including inflammation of soft tissues, along with ongoing loss of supporting bone beyond limit of biological bone remodeling[9,10].

In implantology the tissue reaction seen in case of inflammation are similar to those confronted in cases of gingivitis and periodontitis. The plaque formation pattern on implant and teeth does not have any differences. Neutrophils are the first cells that are seen in the peri-implant pocket as soon as the buildup of plaque begins. This occurs due to release of chemotactic peptides produced by the bacteria present in the vicinity of implants and natural teeth alike. As the process of damage of the epithelial cells by the bacteria continues, they bring about the release of more cytokines which

further leads to attraction of leucocytes to the crevice. These leucocytes eventually phagocytose the bacteria, thus eliminating the bacteria from the pocket. But with this if the neutrophil becomes saturated with bacteria, it subsequently degranulate to release toxic enzymes and further cause tissue damage. [11].

The efficiency of neutrophils and epithelial cells to control the infection is hampered, if there is overload of microbial plaque. In such cases inflammation around peri-implant tissue occurs which is clinically diagnosed as peri-implant mucositis. When the inflammation spreads from the marginal gingival into supporting peri-implant tissues, it results in bone destruction and loss of bone attachment; a process termed as peri-implantitis.[12].

Etiology and Epidemiology

Quantification of incidence rate of peri-implantitis in patients with history of peri-implantitis was done by Zitmann et al; he states chances of peri-implantitis is almost 6 times more than in patients which have no history of periodontitis[13]. Lindhe and Meyle reported an incidence of peri-implant mucositis up to 80% and of peri-implantitis ranging from 28%-56%, based on consensus report of 6th EWP [7].

In a systematic review by Mombelli et al, prevalence rate of peri-implantitis is found to be 20% during 5 - 10 years after implant placement[14].

Spectrum of pathogenic micro-organisms which can be detected in peri-implantitis includes: Aggregatibacter actinomycetemcomitans, Treponema denticola, Tannerella forsythia, Prevotella intermedia, Prevotella nigrescens, Porphyromonas gingivalis and Streptococcus constellatus. Rams et al. revealed 71.7% of patients in a group of 120 patients show resistance to at least one antimicrobial substance [15].

Even though peri-implantitis is an infection caused by numerous anaerobic micro-organisms, but as compared to periodontitis, peri-implantitis distinctly harbors bacteria which generally do not contribute to the microbiota of typical periodontal pathogenesis. Staphylococcus aureus has been demonstrated to have a substantially high affinity for titanium and thus, has been implicated to play a pivotal role in the development of peri-implantitis. Salvi et al. demonstrated that this bacterium has increased positive (80%) and negative (90%) predictive value[16].

Risk Factors

When implant loss occurs within one year of placement it is termed as “Early implant loss”. When it occurs after a time period of more than 1 year after placement it is termed as “Delayed implant loss”[13]. Factors considered as risk factors for development of peri-implantitis can be listed as under: [17,18]

- Smoking:
- History of periodontitis
- Poor oral hygiene and lack of compliance.
- Systemic diseases
- Iatrogenic causes
- Poor quality soft tissue at site of implantation.
- History of implant failure.

Wallowy et al conducted a study in which he found that the history of cigarette smoking or presence of periodontitis or cigarette smoking increases the risk of peri-implantitis upto 4.7 times. A meta-analysis finding reported that annual rate of bone loss in smokers is increased by 0.16 mm per year.[19]

Additional factors leading to implant loss can be summed up as under:

- Implant overloading
- Faulty material and techniques.
- Poor bone quality at the implant site

Square thread design implants with more than 10mm length shows higher rate of success[20]. Also rough implant surfaces (>2 microns) shows better osseointegration than smooth (<0.5 microns) or moderate surfaces (1–2microns)[21].

Conventional Diagnostic Parameters

Pain: Evaluation of pain or discomfort in implant cases are done by percussing with force up to 500 gm. Until and unless the implant is mobile and surrounded by inflamed tissues, or has rigid fixation which impinges on nerve, pain doesn't occur from implant body. If pain occurs during function it is placed under failure category [22].

Mobility: Numerous studies suggested that advanced stage of peri-implantitis in which there is total loss of direct bone to implant interface is indicated by implant mobility [6.7,10,22,23].

Probing: Periodontal probing using light pressure. (.25 Ncm) is one of the foremost and reliable tool for diagnosis of Per-implant tissue inflammation and for monitoring its progress .

Bleeding on probing is a salient parameter that is suggestive of soft-tissue inflammation and micro-ulceration. Mucositis showed increase bleeding on probing at 67% sites while peri-implantitis showed increased bleeding on probing at 91% sites in an experimental study [24].

Ata-Ali et al. stated that Peri-implant probing is a compelling tool in diagnosing peri-implant disease but contrary to this Misch et al stated that probing around implants holds little diagnostic value and its use routinely is not recommended [22,25].

Various thresholds to classify Peri-implantitis given by different authors can be enumerated as follows:

- 6 mm probing depth [6]
- Initial peri-implantitis (≥ 4 mm), Moderate peri-implantitis (≥ 6 mm), Severe peri-implantitis (≥ 8 mm) [26]
- Koldsland et al differentiated peri-implantitis severity in different levels based on two PD: ≥ 4 mm, ≥ 6 mm [27].
- Seventh European Workshop of Periodontics[8] and Padial-Molina et al.[6], stated that when there are changes in clinical parameters like increased values in BOP, increased probing depth (> 5 mm), which indicates progression of disease, the clinician should take radiograph for the evaluation of possible bone loss.

Bone Loss

Intra-oral periapical radiographs and panoramic radiographs are recommended for peri-implantitis diagnosis[6,23,26]. However three-dimensional radiographs, aids in evaluating buccal and lingual/palatal bone walls along with mesial and distal ones.

Padial-Molina et al [6]. suggested the threshold of bone loss > 2 mm to diagnose peri-implantitis, while Misch et al [27]. suggested the threshold of > 4 mm.

Kadhazahed et al give the implant success index in which he reported that bone loss of ≤ 2 mm (≤ 20%) indicate the initiation of hard-tissue breakdown, bone loss of 2 - 4 mm (< 40%) indicates hard-tissue breakdown, and > 40% bone loss indicates severe bone loss [23].

Depending on the amount of marginal bone loss Ata-Ali et al suggested using different stages of peri-implantitis: Stage I: ≤ 3 mm; Stage II: > 3 mm but < 5 mm; Stage III: ≥ 5 mm; Stage IV: ≥ 50% of the implant length [25].

Froum et al describe a new classification system depending upon the measurements between the percentage of bone loss compared to the length of the implant. They classified the disease into categories of

early, moderate, and advanced , which have probing depth of ≥ 4 mm, ≥ 6 mm, or ≥ 8 mm and bone loss of > 20%, 25 - 50% and > 50%, respectively [26].

The Sixth, Seventh and Eight EWP [7,8,28] proposed that diagnosis of peri-implantitis is ensured when there is observable changes in the level of crestal bone is seen comparing it to baseline data. If there is absence of previous radiographic records, then 2mm threshold vertical from the expected marginal bone level following remodeling post-implant placement is recommended provided peri-implant inflammation is evident.

New Paradigm in the field of Diagnosis

A biomarker is fundamentally an indicator of a biological state and it helps in differentiating normal and pathological processes[3]. In present scenario, medical science researches are emphasizing on utilizing biomarkers as diagnostic tool as they can indicate disease presence much before considerable clinical damage has occurred. But, to establish this relationship much more research is needed to be done[3]. Saliva and gingival crevicular fluid/ peri-implant crevicular fluid (PICF) are the main sources from which biomarkers sample can be obtained. At present, clinical and radiographic parameters such as, probing depth, clinical attachment level and bleeding on probing are generally used for diagnosis of peri-implant inflammatory conditions. Non-invasive nature of obtaining samples and repeatability are the main advantages of utilizing biomarkers as a diagnostic tool.

Cytokines can be defined as soluble proteins that bind to specific receptors on target cells and initiate intracellular signaling cascades which via altered gene regulation results in phenotypic changes in cells. Effectiveness at low concentration and transient nature of production is characteristic feature of interleukins. Their induction mode can be either autocrine or paracrine in nature. The PICF levels of 13 different cytokines (IL-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-17, IFN-γ, PGE-2 and TNF-α) have been compared in different clinical peri-implant conditions. Majority of studies had targeted IL-1β and TNF-α as the potential diagnostic biomarkers. IL-β and TNF-α contributes in osteoclast formation and bone resorption. IL-1β exerts its effect mainly by regulating the degradation of plasminogen system extracellular matrix components and also modifying activity of collagenase in wound healing and inflammation[29]. Reduction in the progression of tissue inflammation and tissue breakdown have been shown by inhibition of IL-1β [30]. There are vast numbers of studies which have showed higher levels of IL-1β in PICF than healthy implant sites[31-43]. But there are also few studies which had showed that no statistically significant differences between healthy and diseased groups[44-49].

TNF-α belongs to pro-inflammatory cytokine category which is secreted majorly by monocytes and macrophages. Its mechanism of action consists of collagenase secretion by fibroblasts, bone resorption by activation of osteoclasts, and has been also associated with periodontal tissue destruction in periodontitis. Few of the studies showed no relationship of TNF-α with peri-implant inflammation[36,37,45], while majority of studies showed significant relationship .[42,43,48,50,51,52]

MMPs belongs to endopeptidases group which has modifying actions on cell proliferation, differentiation, migration, apoptosis and is also responsible for degradation of various extracellular matrix proteins [53]. MMP-1, MMP-3, MMP-8, and MMP-13 are some of the important MMPs which were included in the studies assessing PICF in different peri-implantitis lesions. According to various studies, MMPs were reported to be positively correlated with clinical inflammatory conditions around implants[53-58].

Myeloperoxidase (MPO) can be described as a leukocyte-derived anti-microbial enzyme found in primary granules of leukocytes in high concentrations. Reactive oxidant species formation gets catalyzed by MPO[59]. Studies have reported significantly higher amounts of MPO in PISF collected around peri-implantitis lesions.[60-62]

Elastase, an enzyme which is released from human leukocytes and contributes in the process of tissue damage during inflammation, has been found in significantly higher amounts in PISF around implants with peri-implantitis compared with healthy controls[63].

Prostaglandin E2 (PGE2) a vasodilator increases vascular permeability at inflammation sites and also causes bone resorption. There is a study which reports that PGE2 showed positive correlations with gingival index and PD[64].

Cathepsin-K, is a protease enzyme which is released after tissue injury and accelerates inflammatory process. Yamalik et al [65] conducted a study in which he indicated that Cathepsin- K can be used as biomarker to assess peri-implantitis as there is a positive co-relation of Cathepsin – K with the volume of PISF peri- implant inflammatory lesion which has bone loss.

Osteoblasts are the sites of production of OPG and RANKL. Binding of RANKL takes place with RANK which originates on the surfaces of osteoclast precursors as well as mature osteoclasts. Differentiation of an osteoclast precursor into a mature osteoclast is inhibited by the binding of OPG therefore preventing the binding of RANKL and RANK. Arikan et al [66] reported that OPG and RANKL concentrations were notably lower in peri-implantitis group when compared to group of healthy implant cases. Contrary to this, OPG, RANK and RANKL concentrations were reported to be notably higher in periimplantitis sites as compared to healthy implant sites, but the ratio of OPG/RANKL was not different[67]. Treatment of peri-implantitis sites has shown to improve OPG/RANKL ratio [68].

Conclusion

At present Peri-implantitis diagnostic parameters are mainly clinical and radiographical, but these parameters lack specificity and doesn't lead to early prompt diagnosis of Peri-Implantitis. Hence in most cases significant amount of damage has already occurred before diagnosis of Peri-implantitis is done. Inflammatory mediators present in PISF can assist in the early diagnosis of Peri-implant inflammatory conditions, so that prompt treatment can be started before extensive damage and alteration to peri-implant tissue occurs. So there is need of more studies to be conducted for establishing a standardized set of methods and protocol based on inflammatory mediators for more specific and sensitive diagnosis of peri-implantitis.

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