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Review Article

Peri-implantitis – A Review of Diagnostic Methods

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Abstract
Peri-implantitis is the inflammation around soft tissue along with bone demineralization around an implant. It is extremely important to diagnose peri-implantitis and to monitor its progression. This has a direct impact on determining implant success or failure. Radiograph and periodontal probing help in determining the pre-existing destruction. Biomarkers help in evaluating current disease activity and its progression. The biomarkers in Peri-implant crevicular fluid is the promising tool in diagnostic and prognostic evaluation of peri-implantitis. The aim of this article is to summarize the use of different biomarkers and evaluate their use in predicting disease progression. This article also mentions about sampling method and interpretation of biomarkers. Finally, article concludes that cytokines, bone markers and enzymes are important in determining peri-implantitis present activity as well as it's progression.

Key Words: Peri-Implantitis, Peri-Implant Crevicular Fluid, Biomarkers, Cytokines

Introduction
Peri-implantitis is a pathologic condition causing inflammation around the implant. It is characterized by inflammation in the connective tissue around implants, bone loss which can lead to mobility of implant. Hence, Implant failure when the bone loss in severe [1]. It is often preceded by Peri-mucositis which is defined as inflammation of soft tissue surrounding an implant without demineralization of bone around the implant. [2] Prevalence of peri-implantitis and peri-mucositis is 22% and 43% respectively. [3] World Workshop on the classification of Periodontal Disease and Peri-implant disease and Conditions 2017 stated that the bone loss of more than or equal to 3mm is diagnostic criteria for peri-implantitis. [4] Normally, there can be a non-linear bone loss of 0.4 mm around implant. If it accelerates more than 0.4 mm per year then it is an abnormal finding. [5] Peri-implantitis is triggered by microbes like Porphyromonas gingivalis, Tannerella Forsythia, gram negative like Aggregatibacter actinomycetemcomitans, Fusobacterium nucleatum and many more. [6] These microbes change the balance of oral fluids which can be detected by biomarkers which therefore aids in accessing peri-implantitis [7]. The primary treatment for peri-implantitis is surface decontamination. In severe cases of peri-implantitis, implant removal is also indicated [8].

Table 1: Keywords and abbreviation used in the article

PI	Peri-implantitis
PICF	Peri-implantitis crevicular fluid
IL	Interleukin
TNF	Tumour necrosis factor
Cat	Cathepsin
OPG	Osteoprotegerin
RANKL	Receptor activator of nuclear factor kappa-B ligand
s-RANKL	Soluble receptor activator of nuclear factor kappa-B ligand
ICTP	C-telopeptide pyridinolone cross linkage of type I collagen

Biomarkers
1. PICF disease mediators (Cytokines)
An inflammatory process occurs when microbes superimpose

host's defence system. PI sites revealed higher concentration of IL-1β and TNFα levels. These are related to osteo-clast formation and thus, are responsible for bone demineralization [9]. IL-1β which is produced by macrophages is responsible for regulation of breakdown of extracellular matrix components. TNFα is produced by fibroblast and it initiates fibroblast apoptosis which delays the repairing capacity of peri-implant tissue [10].

2. Bone Loss Markers

The key factors responsible for alveolar bone destruction are RANKL and OPG. RANKL is an apoptosis regulator gene which binds with OPG and controls cell proliferation by modifying protein levels of Id4, Id2 and cyclin D1. Thus, increase in RANKL and OPG indicates a higher cellular apoptosis and bone degradation. ICTP also indicates bone destruction. New Collagen fibrils deposited in the extracellular matrix of bone are stabilized by mature cross-links formed by lysyl oxidase on lysine and hydroxylysine residues in the N-and C-terminal regions of collagen chains. This process results in the formation of divalent collagen cross-links that by further condensation yield trivalent Pyridinoline (hydroxylysl pyridinoline or Pyr) and deoxypyridinoline (lysyl pyridinoline or Dpy). Osteoclastic bone resorption initiates the release of cross-linked immunoreactive telopeptides Pyr and Dpy. According to some studies, ICTP is also found in higher quantity in patients with PI. However, s-RANKL and osteocalcin's role is questionable in bone resorption. Thus, the high OPG/ RANKL ratio indicates presence of PI [11].

3. Enzymes

Osteoclasts highly expresses a cysteine protease called CatK. CatK plays a significant role in bone remodelling and cartilage breakdown. This is achieved by hydrolysing extracellular bone matrix proteins which results in bone turnover [12]. Moreover, peri-implant connective tissue can be irreversibly destructed by proinflammatory mediators like MMP upregulation. MMP-8 synthesis and secretion are triggered by IL-1β which breaks the triple helix of collagen. Thus, MMP-8 is a specific marker to detect peri-implant inflammation initiation [13]. Along with MMP-8(collagenase-2), MMP-9(Gelatinase B) and MMP-13(Collagenase-3) are responsible for more bone loss and causing osteolysis around implants [14].

Method of Sampling and Interpretation

Chair side diagnostic test The chair side diagnostic test is convenient for dentist and patients and is easy to perform. It is valuable aid to predict the subclinical peri-implantitis as well as its progression. This ability to predict future of implant in place is important in preventing irreversible damage. A chewing gum test is used to detect MMP-8. Studies have found that MMP-8 levels are elevated at PI sites [15]. The patient tastes bitter if they have high level of MMP-8 in their oral fluids. MMP-8 level above 20ng/mL is considered pathologic [16].

Conclusion

The radiograph and probing depth only address the damage done around implants in the past. To address the present state and to predict progression of peri-implantitis we need help of biomarkers. This article described the various biomarkers to detect peri-implantitis. IL-1β and TNFα are the cytokines that are found in significant higher and IL-10 has negative correlation in peri-implantitis. RANKL, OPG, ICTP are the bone markers which are highly related to bone demineralization as they aid in osteoclastic activity. Moreover, sRANKL showed no significant relation in bone demineralization. In addition, MMP-8,9,13, Myeloperoxidase, Elastase and CatK are the enzymes which are found in abundance in peri-implantitis. Presently, the chair side test of MMP-8 test is effective in detecting peri-implantitis. The combination of biomarkers will offer acceptable diagnosis of peri-implantitis due to high sensitivity and specificity when compared to individual biomarker.

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