Review Article

Scope of Biomarkers as Diagnostic Tool in Peri-implantitis

Mohammed Azamulla[1]*, Sufia Khan[2], Abhijit Dutta[2], M. Geetha Kumari[2], Shipra Kumari[3], Ankita Rai[4]

[1]Department of Periodontology, Awadh Dental College and Hospital, Jamshedpur, Jharkhand, India.
[2]Department of Oral Pathology, Awadh Dental College and Hospital, Jamshedpur, Jharkhand, India.
[3]Department of Periodontics, Awadh Dental College and Hospital, Jamshedpur, Jharkhand, India.
[4]Department of Conservative Dentistry and Endodontics, Awadh Dental College and Hospital, Jamshedpur, Jharkhand, India.

Abstract

Rehabilitation of edentulous region in oral cavity through surgical procedure known as dental implant is an alternative novel technique in modern dentistry. Multiple advantages of their application include avoidance of vital anatomical structures (inferior alveolar nerve and maxillary sinus), increased patient comfort, shortened treatment time, and reduced cost. Extensive reviews have supported the current perspective of using short dental implants. Various enlisted factors affecting the future of implants such as smoking, genetic, diabetes mellitus, a history of periodontitis, and a combination of smoking and a history of periodontitis were described as risk factors for Peri-implantitis. For the development of future therapeutic strategies, it is essential to understand the molecular pathophysiology of human dental peri-implant infections. None of these therapeutic strategies has proven to be highly effective against peri-implantitis, and a gold standard for the treatment of peri-implantitis and peri-implant mucositis has yet to be defined. However, numerous biomarkers are studied in peri-implant sulcular fluid and gingival crevicular fluid and are then measured by numerous techniques.

Keywords: Gingival crevicular fluid, Peri-implant mucositis, Peri-implant sulcular fluid, Peri-implantitis.

Introduction

Today's modern era of dentistry includes rehabilitation of teeth by dental implants through a process known as osseointegration into the alveolar bone.[1] Prolong survival of these implants depends on various systemic as well as local factors such as implant surface, surface structure, bone quality, mechanical loading, and several systemic diseases, as well as the adherence of bacterial biofilms.[2]

One of the most common complication of dental implant therapy is the development of peri-implantitis, which is characterized as a reversible destructive inflammatory process affecting hard soft tissues of osseointegrated implants in function, leading to peri-implant pocket formation and loss of supporting bone, deep probing depths (typically >5 mm), bleeding on probing, and/or suppuration.[3,4]

The term peri-implantitis (PI) was introduced by Mombelli *et al*.[3] Average prevalence rate of peri-implantitis varies between 4% and 45%.[4] However, these clinical parameters were not considered sensitive enough to provide accurate diagnostic information, prognosis, and treatment outcome of the disease. There comes the role of biomarkers, a measurable indicator of some biological state, or condition of periodontal tissues thus could serve as a potential diagnostic or prognostic solution thereby compensating some of the referred limitations of the routine clinical tools in implant therapy.[5-9]

Access this article online

Website: www.jrad.co.in

DOI: https://doi.org/10.53064/jrad.2022.13.4.243

Etiopathogenesis of Peri-implantitis

Presence of foreign body

Periodontal diseases are usually represented as molecules related to three pathological phases, that is, inflammation, collagen degradation, and alveolar bone turn over. Peri-implantitis is a chronic inflammatory disease characterized by inflammation of the peri-implant mucosa and by loss of the implant. Among the various put forth hypothesis, it was found that, in case of peri-implantitis, there is continuous attempt to improve the interface between bone and implant to speed up the process of osseointegration and improve its quality. However, accumulation of plaque remains the primary causative agent around implant.

Address for correspondence: Dr. Mohammed Azamulla, Department of Periodontics, Awadh Dental College and Hospital, Jamshedpur - 580 009, Jharkhand, India.
Email: drmedazam@gmail.com

Received: Jun. 15, 2022; **Accepted:** Jul. 07, 2022; **Published:** Aug. 09, 2022

How to cite this article: Azamulla M, Khan S, Dutta A, Kumari MG, Kumari S, Rai A. Scope of Biomarkers as Diagnostic Tool in Peri-implantitis. J Res Adv Dent 2022;13(4):253-256.

These efforts have been focused in improving the implant interface either chemically (by incorporating inorganic phases on or into the titanium oxide layer) or physically (by increasing the level of roughness) or through electrochemical anodization of the titanium surface or combination of both techniques. Literature review has concluded that "moderately rough surfaces such as those coated with hydroxyapatite (HA) have greater bone integration in comparison with smooth and minimally rough surfaces." In addition, the coronal most portion of the implant, which was initially designed to facilitate osseointegration, gradually becomes exposed to the oral environment as a result of peri-implantitis, poses a higher complications. Beginning of bone loss around such implants is usually associated with the delamination of the HA coating. These failures have raised a suspicion that an exposed rough surface, due to poor oral hygiene, can harbor increased microbial/plaque accumulation and eventually lead to peri-implantitis.[10-14]

Role of immune response

Second, changes in the level of inflammatory biomarkers could result in etiology. This was supported by a study done by Kalsi where he reported a higher level of inflammatory biomarkers or differences in their ratios in peri-implantitis compared with periodontitis. Few studies reported a significant differences in the levels of biomarkers present between peri-implantitis and periodontitis for transcripts of aquaporin 1, tissue inhibitor of metalloproteinases 2 (TIMP-2), interleukin (IL)-10, receptor activator of nuclear factor kappa-B ligand (RANKL), sRANKL, cellular fibronectin, tumor, TNF-α, IL-6, IL-8, chemokine receptor type 5 (CCR5), CXCR3 and collagenase-2, as well as the ratios of TIMP-1 versus (MMP-1)+MMP-8 and sRANKL to osteoprotegerin (OPG). Another report where increased level of biomarkers reflective of extracellular matrix metabolism was noticed in peri-implantitis than in periodontitis.[13-16]

Presence of chemical mediators such as arachidonic acid metabolites, cytokinesand nitric oxide induce osteoclastogenesis by promoting theexpression of receptor activator nuclear factor kappa-b (RANK). Activation of the RANK receptor leads to the generation of several transcription factors, such as nuclear factor kappa-b or c-Jun N-terminal kinase, which, in turn, upregulate the biosynthesis of pro-inflammatory cytokines, resulting in an enhancement of the activity of matured osteoclasts. RANKL (osteoclasts differentiation factor) is a protein expressed by osteoblasts, binds directly to RANK on the surface of pre-osteoclasts and osteoclasts stimulating both the differentiation of osteoclast progenitors and the activity of mature osteoclasts.[17-19]

Furthermore, during remodeling phase, that is, rate of bone formation and resorption are also influenced by rapid colonization of microbes, for example, mainly Prevotella intermedia (PI) and Peptostreptococcus micros. These microorganisms encompass periodontal pathogen species. The microbes less likely to cause peri-implantitis are *Staphylococcus* spp., enteric bacteria, and candida. The area of deep pocket in peri-implantitis is suitable environment for the growth of obligate anaerobes (Gram–ve rod) and Gram +ve saccharolytic anaerobic bacteria in which the causative microorganism of peri-implantitis prevails. Peri-implantitis and periodontitis lesions both harbor Gram-negative anaerobic bacteria compared with healthy sites. However, peri-implantitis has higher microbial diversity than periodontitis.[16-18]

Moreover, peri-implantitis is penetrated predominantly by inflammatory cells, chiefly B-lymphocytes and plasma cells, and frequently lacks a protective tissue layer over the bone, which is typically present in periodontitis. Histologically, peri-implantitis lesions were twice as large and had more number of blood vessels and can infiltrate into the connective tissue compared with periodontitis. Peri-implantitis demonstrated a 97% higher matrix metalloproteinases (MMPs) level, such as MMP-8, which was only 78% greater in chronic periodontitis compared with healthy gingiva. Furthermore, peri-implantitis tissue contains extracellular matrix antibodies.[14] The rate of disease progression is faster in peri-implantitis, causing faster and more severe bone loss compared with periodontal disease. Another variation occurs due to the presence of different types of microbes at the site of implant, the host's defense mechanism, and absence of a periodontal ligament (PDL) resulting in a non-linear fashion of bone loss.[17-22]

Role of oral fluid biomarkers

Recently, numerous data are available in the field of oral fluid diagnostics, which detected various biomarkers in oral fluids such as saliva and gingival crevicular fluid (GCF) of periodontitis patients. Biomarkers in periodontitis and peri-implantitis can be collected either through biopsy or peri-implant sulcular fluid and GCF and are then measured by immunoassay. Pro-inflammatory markers such as cytokines, chemokines, and others are involved in regulating peri-implant and periodontal conditions, as diagnostic as well as prognostic tools.[13-15]

These biomarkers include enzymes, proteins, hormones, host-derived biomolecules, deoxyribonucleic acid (DNA), ribonucleic acid (RNA), bacterial, and volatile products.

Biomarkers act as inflammatory mediators regulating DNA processes and growth factors that can stimulate endothelial cells and hence prevent connective tissue regeneration (FGF and PDGF). Enzyme linked Immunosorbent assay based study was done by Schincaglia who evaluated host inflammatory markers such as myeloperoxide , lactoferrin, IL-1 alpha, IL-1 beta, IL-1 ra, IL-8, TNF-α, & CCL22. IL-1 alpha, IL-1 beta, IL-1ra, IL-8, TNFα, and CCL22 were also quantified. Further, the subgingival microbiome was evaluated through 16S rRNA gene sequencing along with other inflammatory markers in crevicular fluid. It was, hence, concluded that a common microbial insult is associated with clinical inflammation around implants and teeth.[13,14,17,18-25]

Alkaline phosphatase

Bone-forming marker pays a key role in cementogenesis as well as homeostasis as it stimulates calcification during bone

remodeling process. Significant increase in the level of ALP is an indicator of any periodontal issues.[26]

OPG

A glycoprotein alveolar bone turnover marker plays an essential role in the process of osteogenesis and bone hemostasis. OPG acts on RANKL which inhibits osteoclastic activity. Severity of periodontal disease solely depends on RANKL/OPG ratio. Hence, RANKL/OPG ratio should be considered as a putative diagnostic tool in evaluating periodontal disease.[7,27]

Osteocalcin

Osteocalcin is the most abundant protein found in the extracellular matrix of bone. It contains glutamic acid residues, is synthesized by bone and cartilage cells. It actively binds to the Ca++ ions present in the hydroxyapatite crystals lattice of bone. In serum/plasma, it freely moves as the decarboxylated form, whereas in bone as the inactive carboxylated form. Osteocalcin is a marker of bone formation but due to its role in recruiting osteoclasts to the site of bone resorption, it is now widely accepted as a vital bone turnover marker. Increased levels of osteocalcin in serum are associated with metabolic diseases such as rheumatoid arthritis, multiple myeloma, and periodontitis.[27,28]

Osteonectin

A protein rich in cysteine is secreted by osteoblasts, fibroblasts, and RBCs act as chemoattractant to Ca++ ions present in bone. Its levels in bone matrix commensurate with the bone formation process during bone remodeling. It upregulates bone formation by accelerating the differentiation of immature osteocytes to mature osteoblasts and recruit them to an active bone deposition site. Osteonectin can be considered as a bone-regulating protein and maintains PDL hemostasis during the bone remodeling phase.[28]

Osteopontin

A glycoprotein found in non-mineralized tissues, primarily renal, endothelial cells, and epithelial cells. It plays a dual function both in bone mineralization and bone resorption. Osteopontin enhances dentine formation during the bone remodeling process and has been implicated in the recruitment of polymorphonuclear cells in response to infections.[29,30]

Calcium

Many studies supported the theory that increased levels of Ca++ ions in saliva develop a higher risk of periodontitis. Those individuals are at a higher risk to develop periodontitis due to alkaline oral pH that favors increased mineralization and elevated levels of calcium in saliva.[31,32]

Other Diagnostic tool to measure Peri-implantitis

Clinically, intraoral and panoramic radiographs are the imaging tools most commonly used to identify the peri-implant bone level. Although these techniques are readily available and can be performed quickly and cost-effectively, they have also been suggested to have limited diagnostic accuracy.

Cone-beam computed tomography

CBCT is another complementary alternative modality as a three dimensional imaging technique. However, it is expensive, involving higher dose of radiation, and shows metal artifacts that may degrade visibility.[33]

Optical coherence tomography (OCT)

OCT is considered as one of the potential technique which utilizes an optical source to obtain a high- resolution image non-invasive without radiation.[34]

Conclusion

Given the variable predictability and potential invasiveness of peri-implantitis management, an understanding of the underlying pathophysiology is relevant, as an early diagnosis may help to prevent more serious aspects of the disease and morbidity associated with its treatment.

Peri-implantitis is a common problem resulting in tissue destruction and implant loss. Plaque accumulation and biofilm formation play a major role in its initiation and development. Prosthetic factors such as residual cement and overloading may result in peri-implantitis but need clinical evidence. Routine supportive therapy reduces the risk of the onset of peri-implantitis. Through knowledge of biomarkers could support as prognosticator in case of implant loading as well as any pathological conditions associated with implant in the future.

References

1. Branemark PI, Adell R, Breine U, Hansson BO, Lindström J, Ohlsson A. Intra-osseous anchorage of dental prostheses, I: Experimental studies. Scand J Plast Reconstr Surg 1969;3:81-100.
2. Zitzmann NU, Berglundh T, Marinello CP, Lindhe J. Experimental periimplant mucositis in man. J Clin Periodontol 2001;28:517-23.
3. Berglundh T, Armitage G, Araujo MG, Avila-Ortiz G, Blanco J, Camargo PM, *et al*. Peri-implant diseases and conditions: Consensus report of workgroup 4 of the 2017 world workshop on the classification of periodontal and peri-implant diseases and conditions. J Clin Periodontol 2018;45 Suppl 20:S286-91.
4. Berglundh T, Persson L, Klinge B. A systematic review of the incidence of biological and technical complications in implant dentistry reported in prospective longitudinal studies of at least 5 years. J Clin Periodontol 2002;29:197-212.
5. Derks J, Tomasi C. Peri-implant health and disease. A systematic review of current epidemiology. J Clin Periodontol 2015;42:S158-71.
6. Rakic M, Lekovic V, Nikolic-Jakoba N, Vojvodic D, PetkovicCurcin A, Sanz M. Bone loss biomarkers associated with peri-implantitis. A cross-sectional study. Clin Oral Impl Res 2013;24:1110-6.
7. Rakic M, Nikolic-Jakoba N, Struillou X, Petković-Curcin A, Stamatović N, Matić S, *et al*. A receptor activator of nuclear factor kappa B (RANK) as a determinant of peri-implantitis. Vojnosanit Pregl 2013;70:346-51.
8. Rakic M, Lekovic V, Nikolic-Jakoba N, Vojvodic D, PetkovicCurcin A, Sanz M. Bone loss biomarkers associated with peri-implantitis. A cross-sectional study. Clin Oral Impl Res 2013;24:1110-6.
9. Watts N. Clinical utility of biochemical markers of bone remodeling. Clin Chem 1999;45:1359-68.
10. Cochran D. Inflammation and bone loss in periodontal disease. J Periodontol 2008;79:1569-76.
11. Sanz M, Chapple IL. Clinical research on peri-implant diseases: Consensus report of working group 4. J Clin Periodontol 2012;39 Suppl 12:202-6.
12. Schminke B, VomOrde F, Gruber R, Schliephake H, Bürgers R, Miosge N. The pathology of bone tissue during peri-implantitis. J Dent

Res 2015;94:354-61.
13. Marshall G, Canullo L, Logan RM, Rossi-Fedele G. Histopathological and microbiological findings associated with retrograde peri-implantitis of extra-radicular endodontic origin: A systematic and critical review. Int J Oral Maxillofac Surge 2019;48:1475-84.
14. Fragkioudakis I, Tseleki G, Doufexi AE, Sakellari D. Current concepts on the pathogenesis of peri-implantitis: A narrative review. Eur J Dent 2021;15:379-87.
15. Kalsi AS, Moreno F, Petridis H. Biomarkers associated with periodontitis and peri-implantitis: A systematic review. J Periodontal Implant Sci 2021;51:3-17.
16. Basegmez C, Yalcin S, Yalcin F, Ersanli S, Mijiritsky E. Evaluation of periimplantcrevicular fluid prostaglandin E2 and matrix metalloproteinase-8 levels from health to periimplant disease status: A prospective study. Implant Dent 2012;21:306-10.
17. Fonseca FJ, Moraes M Jr., Lourenço EJ, Teles DM, Figueredo CM. Cytokines expression in saliva and peri-implant crevicular fluid of patients with peri-implant disease. Clin Oral Implants Res 2014;25:e68-72.
18. Koyanagi T, Sakamoto M, Takeuchi Y, Ohkuma M, Izumi Y. Analysis of microbiota associated with peri-implantitis using 16S rRNA gene clone library. J Oral Microbiol 2010;2:5104.
19. Rokaya D, Srimaneepong V, Wisitrasameewon W, Humagain M, Thunyakitpisal P. Peri-implantitis update: Risk indicators, diagnosis, and treatment. Eur J Dent 2020;14:672-82.
20. Matsuda S, Movila A, Suzuki M, Kajiya M, Wisitrasameewong W, Kayal R, *et al*. A novel method of sampling gingival crevicular fluid from a mouse model of periodontitis. J Immunol Methods 2016;438:21-5.
21. Carcuac O, Berglundh T. Composition of human peri-implantitis and periodontitis lesions. J Dent Res 2014;93:1083-8.
22. Zhang L, Li X, Yan H, Huang L. Salivary matrix metalloproteinase (MMP)-8 as a biomarker for periodontitis: A PRISMA-compliant systematic review and meta-analysis. Medicine (Baltimore) 2018;97:e9642.
23. Papi P, Di Carlo S, Rosella D, De Angelis F, Capogreco M, Pompa G. Peri-implantitis and extracellular matrix antibodies: A case-control study. Eur J Dent 2017;11:340-4.
24. Farsai PS. Supportive therapy (SPT) can potentially improve implant survival rate (sr), peri-implantitis, and peri-implant mucositis. J Evid Based Dent Pract 2020;20:101414.
25. Schincaglia GP, Hong BY, Rosania A, Barasz J, Thompson A, Sobue T, *et al*. Clinical, immune, and microbiome traits of gingivitis and peri-implant mucositis. J Dent Res 2017;96:47-55.
26. Malhotra R, Grover V, Kapoor A, Kapur R. Alkaline phosphatase as a periodontal disease marker. Indian J Dent Res 2010;21:531-6.
27. Cakal OT, Efeoglu C, Bozkurt E. The evaluation of peri-implant sulcus fluid osteocalcin, osteopontin, and osteonectin levels in peri-implant diseases. J Periodontol 2018;89:418-23.
28. Trombetta JM, Bradshaw AD, Johnson RH. SPARC/osteonectin functions to maintain homeostasis of the collagenous extracellular matrix in the periodontal ligament. J Histochem Cytochem 2010;58:871-9.
29. Dong M, Yu X, Chen W, Guo Z, Sui L, Xu Y, *et al*. Osteopontin promotes bone destruction in periapical periodontitis by activating the NF-κB pathway. Cell Physiol Biochem 2018;49:884-98.
30. Foster B, Ao M, Salmon MR, Chavez MB, Kolli TN, Tran AB, *et al*. Osteopontin regulates dentin and alveolar bone development and mineralization. Bone 2018;107:196-207.
31. Korte DL, Kinney J. Personalized medicine: An update of salivary biomarkers for periodontal diseases. Periodontol 2000 2016;70:26-37.
32. Fiyaz M, Ramesh A, Ramalingam K, Thomas B, Shetty S, Prakash P. Association of salivary calcium, phosphate, pH and flow rate on oral health: A study on 90 subjects. J Indian Soc Periodontol 2013;17:454-60.
33. Mark JY, Chung JH, Lee JS, Kim HJ, Choi SH, Jung UW. Comparisons of the diagnostic accuracies of optical coherence tomography, micro-computed tomography, and histology in periodontal disease: An ex vivo study. J Periodontal Implant Sci 2017;47:30-40.
34. Kim S, Kang SR, Park HJ, Kim B, Kim TI, Yi WJ. Quantitative measurement of peri-implant bone defects using optical coherence tomography. J Periodontal Implant Sci 2018;48:84-91.