INTERNATIONAL JOURNAL OF CURRENT MEDICAL AND PHARMACEUTICAL RESEARCH

IJCMPR

Available Online at http://www.journalcmpr.com

REVIEW ARTICLE

ROLE OF MATRIX METALLOPROTEINASES IN IMPLANT DENTISTRY: A DIAGNOSTIC PARADIGM IN PERI-IMPLANTITIS- A REVIEW

Anshul Chugh., Divya Dahiya., Harleen Thukral

Department of Prosthodontics, PGIDS

ARTICLE INFO

Article History:
Received 29 th, July, 2016,
Received in revised form 4 th,
August, 2016, Accepted 16th, September,
2016, Published online 21st, October, 2016

Key words:

Peri-implantitis, matrix metalloproteinases, peri-implant sulcular fluid, gingival crevicular fluid.

ABSTRACT

As it is well known that the integrity of connective tissues surrounding dental implants is influenced by a levels of matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs). The purpose of this review was to provide an overall assessment of TIMP-1, MMP-1 and -8 levels as well as collagenase activities during the wound healing process after implant placement and diagnostic role in peri-implantitis.[1,7]

INTRODUCTION

Although implant-supported oral rehabilitation has gained worldwide popularity throughout the last decades due to its efficient clinical success rate and substantiated improvement of individual's quality of life. Recent reports on the long-term success of implant therapy have presented surprisingly high prevalence rates of periimplant diseases; perimucositis and periimplantitis which has been reported to occur in 6–10% of the installed implants and eventually can lead to implant mobility and loss.[1,3,14] In the initial stage, plaque accumulation can cause perimucositis, a reversible inflammation of the soft tissues surrounding functional implants. Periimplantitis is defined as an inflammatory process, with microorganisms associated in patterns known from the chronic periodontitis of natural teeth, affecting soft and hard tissues surrounding an osseointegrated implant associated with breakdown of the peri-implant epithelial seal, pocket formation, purulence, and progressive bone loss[1,2].

Clinical Implications

The degradation of peri-implant and periodontal tissues can be mainly mediated by matrix metalloproteinases (MMPs). Also, bone matrix turnover is regulated by the extracellular zinc dependent endopeptidase, family of matrix metalloproteinases (MMPs) comprising collagenases, gelatinases, stromelysins and membrane-type MMPs. Bone development and remodeling requires activity of MMPs for matrix maintenance and repair, bone resorption and the coupling to bone formation and the coupling to bone formation. Fibrillar collagens are the major components of periodontal extracellular matrix, during periodontal homeostasis and pathologic conditions they are cleaved into smaller fragments by collagenases (MMPs -1, -8, and -13) and further degraded by active gelatinases (MMPs -2 and -9) and other non specific tissue proteinases[5,6,12]. MMP-2 is responsible for the breakdown of type IV collagen of extracellular matrix, which is a major structural component of a typical basement membrane. In addition, MMP-2 is also able to cleave native type I collagen, which is the abundant component of gingival connective tissue matrix, this protein is widely expressed by a number of normal and transformed cells. MMP-2 plays a critical role in invasion, metastasis, angiogenesis and tissue remodelling. MMP-2 has been immunolocalized in fibroblasts and macrophages, as well as in epithelial cells of gingival tissues in periodontitis affected patients. Elevated levels of matrix metalloproteinase-1, 2, 9 have also been detected in gingival crevicular fluid, peri-implant sulcular fluid and gingival tissues of periodontititis / peri-implantitis patients[3,4].

REVIEW OF LITERATURE

A number of clinical and experimental studies have shown that endosseous implants may bring predictable long-term success as replacements for the missing teeth of fully and partially edentulous patients (Branemark *et al*. 1969; Buser *et al*. 1997; Ohtsu *et al*. 1997; Fujii *et al*. 1998). In unfortunate cases,

breakdown of the peri-implant epithelial seal and pocket formation, bleeding on probing, purulence, and progressive bone loss have been manifested as so called ''peri-implantitis'' (Lindhe *et al*.1992; Jovanovic *et al*. 1993).[3]

Analyses of peri-implant crevicular fluid (PICF) constituents may offer important information around implants for the inflammatory or immune responses of the host. Connective tissue degradation in periodontal diseases is thought to be due to excessive matrix metalloproteinases (MMPs) activities over their specific inhibitors (Birkedal-Hansen 1993; Reynolds 1996). [4]

Principal collagenases responsible for collagen degradation in gingival tissues may be MMP-1 (fibroblast-type collagenase) and MMP-8 (neutrophil-type collagenase). Currently available literature has shown that the major collagenase in gingival crevicular fluid (GCF) from adult periodontitis patients is MMP- 8, while MMP-1 is predominant in GCF from juvenile periodontitis patients (Sorsa *et al*. 1988; Suomalainen *et al*. 1991; Ingman *et al*. 1996). [8]

Tissue inhibitor of metalloproteinases-1 (TIMP-1) may be the major inhibitor of MMPs present in gingival tissue (Nomura *et al*. 1993; Kubota *et al*. 1996, 1997; Nomura *et al*. 1998). Higher TIMP-1 protein levels in GCF from inflamed gingiva than from healthy subjects were indicated (Haerian *et al*. 1995; Ingman *et al*. 1996; Nomura *et al*. 1998). In contrast, the collagenase inhibitor level in GCF (Larive´e *et al*. 1986) was found to be higher in healthy subjects than in periodontitis-affected patients.[9]

MATERIAL AND METHODS

From the data searched from ebsco host, hinari and pubmed with keywords – matrix metalloproteinases, peri-implantitis, peri-implant sulcular fluid, gingival crevicular fluid. Out of around 50 articles searched, 10 were taken for the present review. After studying the literature available, the common methodology can be summarized as[5,6,7,10]:

Gingival Crevicular Fluid (GCF) and PISF collection

Samples were obtained at mesiobuccal and distobuccal sites from all selected teeth and implants.

Densitometric Analysis of Serum Albumin in Crevicular Fluid Samples

Human serum albumin (HSA) is the major protein species in crevicular exsudate.20, 21 It is readily detected as a 68 kDa band when running samples on sodium dodecyl sulfate-polyacrylamide gel electrophoresis.

Gelatin Zymography for Determining the Relative Activity of MMP-9

ELISA for Quantitative Determination of Human TNC[11,12]

PICF was collected longitudinally, i.e. at 1, 2, 4, and 12 weeks after implantation, from osseointegrated implants. The implants contrary to the criteria of success (Buser *et al*. 1990, 1997) were comprised in peri-implantitis cases; presence of 1) persistent subjective complaints, such as pain, foreign body sensation and/or dysaesthesia, 2) recurrent peri-implant infection with suppuration, 3) mobility, and 4) continuous radiolucency around the implant. The alveolar bone loss around the implant was determined as a percentage of the distance between implant shoulder and first visible bone contact on the implant surface relative to the distance between implant shoulder and implant base on radiographs.

Determination of TIMP-1 protein level

TIMP-1 protein level in PICF and GCF was determined by using hTIMP-1 assay kit (Fuji Chemical Industries, Toyama city, Japan), based on one step sandwich enzyme immunoassay (Kodama *et al*. 1990), according to the manufacturer's protocol.

Determination of MMP-1 and MMP-8 protein levels

The MMP-1 and MMP-8 protein levels in PICF and GCF were determined by using human MMP- 1 and MMP-8 ELISA systems (Amersham, Japan), based on the immunoassay to MMP-1 (Zhang *et al*. 1993) and the immunoassays to MMP-8 (Matsuki *et al*. 1996), according to the manufacturer's protocol, respectively. The MMP-8 genotype was determined by the PCR-RFLP assay.

RESULTS

It has been seen in various studies:

TIMP-1, MMP-1 and -8, and collagenase activities in PICF

1) *Changes in TIMP-1, MMP-1 and -8, and collagenase activities during wound healing process after implantation.* The TIMP-1 level was found to be significantly higher at week 1 than at weeks 4 and 12. The MMP-8 level was significantly higher at week 1 than at weeks 4 and 12. The MMP-8 level at week 1 was significantly higher than that in h-GCF
2) *TIMP-1, MMP-1 and -8, and collagenase activities in PICF from peri-implantitis (p-PICF), GCF from periodontitis.*

TIMP-1 in PICF was not found significantly different from those in either GCF. There was no significance in MMP-1,8 levels among PICF and GCF, but the levels increase with the level of inflammation and bone remodeling.

DISCUSSION

Despite the long-term success shown by longitudinal multicenter studies, failure is inevitable. Matrix metalloproteinases (MMPs) represent the major class of enzymes responsible for extracellular matrix metabolism MMPs are zinc-dependent metallopeptidases belonging to the subfamily M10A which are collectively capable of cleaving virtually all extracellular matrix substrates, including collagens, laminin, fibronectin, vitronectin, and proteoglycans [3,4]. Like other peptidases in subclan, the peptidases of family M10 are synthesized as inactive precursors (zymogens), and their activation occurs in the tissue by cleavage of the N-terminal pro-peptide domain by other proteinases. MMPs have important roles in diverse physiological and pathological processes as they regulate various cell behaviors such as angiogenesis, cell proliferation, apoptosis, alteration of cell motility, effects on the immune system and host defense, and modulation of the bioactivity of chemokines. In fact, MMPs are expressed in response to specific stimuli by resident connective tissue cells as well as the major inflammatory cell types that invade the tissue during remodeling events, inclusive in implant osseointegration. Previous studies have also shown that MMPs are present in peri-implant sulcular fluid and can play a pathologic role in peri-implant bone loss. Various studies have investigated the frequencies of the polymorphism in the promoter of MMP-8 gene in individuals

with failure of implant so as to verify a possible relationship between this polymorphism and early failure of osseointegrated oral implants [7,8].

Osseointegration is called as direct contact of vital bone to a load bearing titanium implant surface. Branemark *et al*., (1977) demonstrated the utilization of osseointegrated titanium dental implants for the rehabilitation of edentulous patients. The results were quite satisfactory for the patients. Matrix metalloproteins are produced by inflammatory cells and responsible of extra cellular matrix metabolism which associated with collagen processing. A human study by Golub et. al., (1995) reported elevated levels of MMPat the crevicular fluid around failing implants and teeth affected by periodontitis. Fibroblast type collagenase (MMP-1) is associated with collagen degradation. Collagen types of I, II, III and IX are degraded by MMP-1, hence these are the most common protein components of extracellular matrices (Nomura *et al*., 2000; Sorsa *et al*., 2004). Expression of MMP-1 is normally low but induced by phorbol esters, growth factor, and inflammatory cytokinins. If MMP-1 is overexpressed, some pathological problems has associated with this overexpression. The guanine insertion at position 1607 of the human MMP-1 gene creates the 2G allele, which has been shown to increase transcriptional activity (Santos *et al*., 2004).[13,14]

The data from various studies showed a significant increase in the TIMP-1 level at 1 week after implantation as compared with those in PICF from peri-implantitis as well as GCF from periodontitis patients and healthy subjects. The TIMP-1 level began to decrease by Week 2 and reached the same level as in h-GCF at Week 4. The increased TIMP-1 production at 1 week in wound healing may also be found in skin (Stricklin *et al*. 1994a, 1994b), the cornea (Ye & Azar 1998), anastomosis in the intestine (Savage *et al*. 1998), and in nerves (La Fleur *et al*. 1996). Our data also disclosed a higher collagenase activity level at Week 1 than at Weeks 2, 4, and 12, which coincided with the change in the MMP-8 level. The over-production of TIMP-1 at 1 week after implantation in the wound area could contribute to inhibiting excessive tissue destruction and degradation of the neo-matrix in wound repair due to MMPs. TIMP-1 and MMP-8 levels, for the most part, decreased by 4 weeks after implantation to those levels found in GCF from healthy subjects. Collagenase activities (especially in active collagenase) decreased by 2 weeks after implantation to the levels found in GCF from healthy subjects. So far, few studies investigating collagenase and/ or MMP-8 and the inhibitor levels in PICF have been conducted in order to monitor peri-implant health and disease, and to serve as a useful biochemical marker (Apse *et al*. 1989; Ingman *et al*. 1994). Apse *et al*. (1989) showed a strong inverse relationship between collagenase activity and collagenase inhibitory activity in crevicular fluid collected from osseointegrated dental implants and teeth. A study has shown a higher TIMP-1 level in GCF from periodontitis than from healthy subjects. This is consistent with previous reports (Haerian *et al*. 1995; Ingman *et al*. 1996; Nomura *et al*. 1998). an up-regulation of TIMP-1 synthesis in inflamed tissue would contribute to the suppression of progressive tissue destruction through increased levels of MMP activity to defend the integrity of the connective tissue. That the TIMP-1 protein level hardly elevates despite the inflammatory lesion may, however, be a notable feature of peri-implantitis, and could conceivably result in the comparatively rapid tissue destruction around implants. The MMP-8 protein level and collagenase activities in PICF from peri-implantitis were found to be significantly higher than that in GCF from healthy subjects, whereas there was no significant correlation between PICF from peri-implantitis and GCF from periodontitis. This may be in accord ance with results by functional and immunoblot assay (Ingman *et al*. 1994; Teronen *et al*. 1997a). One data has shown the similarity of collagenase and MMP levels between peri-implantitis and periodontitis[7,9].

Another study has measured MMP-9, has, and TNC, and has shown that they can be detected equally in the sulcus fluid of teeth and implants, with a wide individual range of volume. MMP-9 is known to be a marker of bone resorption and bone remodeling, particularly in conjunction with loosening of prostheses, such as hip, in the human body. Relative MMP-9 activity was increased in periimplantitis samples when compared with healthy tooth sites or implant sites with classification I or II. It might not be surprising that MMP-9 was significantly related to increased PD, which is a sign of bone loss around implants.The hypothesis that concentration of MMP-9 is increased in affected sites is confirmed by the present results, and the findings are comparable with other results. It was suggested that the absence of BoP be used as a criterion for stability rather than a predictor of disease activity. If positive BoP is an overt sign of inflammation and peri-implantitis then increased MMP-9 might be rather a marker for bone turnover and aseptic bone resorption than for an infectious process. TNC levels were low in sulcus fluid obtained from healthy implant sites, but a significant increase was observed in sites of classification III, indicating that this ECM protein might be of potential use as a molecular marker of bone resorption. Thus, the bone resorption might be due first of all to a bone remodeling processes and not infection. A possible degradation of TNC by MMPs or other (eg, bacterial) proteases needs to be studied in the future when the process of peri-implant bone loss is investigated.[3]

An abnormal immune response involving different cell types such as macrophages, polymorphonuclear neutrophils, T and B lymphocytes, endothelial cells, fibroblasts, keratinocytes, osteoclasts, and osteoblasts can destroy periimplant tissues . The MMP-8 gene, located on chromosome 11, has functional polymorphisms in the promoter region-799 characterized by a substitution on a cytosine by timina (rs11225395) and has been associated with breast cancer. In this study, the C-799T polymorphism in the promoter region of MMP-8 gene was associated with early implant failure in nonsmokers. Patients bearing this genotype or T allele seem to be more likely to have implant loss. This allele can provide the molecular basis for a more intense degradation of extracellular matrix, which might indicate an increased susceptibility to osseointegration failure.[5]

CONCLUSION

Within the limitations of the present study, the following conclusions can be drawn: The polymorphism in the promoter of the MMP-8 gene could be a risk factor for early implant failure. Tenascin C is already known to increase in inflammation. It is concluded that in the context of peri-implantitis, TNC might be a marker of bone remodelling rather than inflammation and infection. MMP-1,8,9 and 13 was detected in GCF and PICF which may contribute to the collagenase activity in PICF, thereby have role in progression of periimplantitis.

Reference

Apse, P., Ellen, R.P., Overall, C.M. & Zarb, G.A. (1989) Micro-biota and crevicular fluid collagenase activity in the osseointegrated dental implant sulcus: A comparison of sites in edentulous and partially edentulous patients. *Journal of Periodontal Research* 24: 96–105.

Apte, S.S., Mattei, M.G. & Olsen, B.R. (1994) Cloning of the cDNA encoding human tissue inhibitor of metalloprotein- ases-3 (TIMP-3) and mapping of the TIMP-3 gene to chromosome 22. Genomics 19: 86–90.

Ashcroft, G.S., Herrick, S.E., Tarnuzzer, R.W., Horan, M.A., Schultz, G.S. & Ferguson, M.W.J. (1997) Human aging impairs injury-induced in-vivo expression of tissue inhibitor of matrix metalloproteinases (TIMP)-1 and -2 proteins and mRNA. *Journal of Pathology* 183: 169–76.

Birkedal-Hansen, H. (1993) Role of matrix metalloproteinases in human periodontal diseases. *Journal of Periodontology* 64: 474–84.

KryshalskyjE, SodekJ. Nature of collagenolytic enzyme and inhibitor activities in crevicular fluid from healthy and inflamed periodontal tissues of beagle dogs. *J Periodontal Res* 1987;22:264–9.

Esposito M, Hirsch JM, Lekholm U, Thomsen P. Biological factors contributing to failures of osseointegrated oral implants. (I). Success criteria and epidemiology. *Eur J Oral Sci* 1998;106:527–51.

Ingman T, Kononen M, Konttinen YT, Siirila HS, Suomalainen K, Sorsa T. Collagenase, gelatinase and elastase activi- ties in sulcular fluid of osseointegrated implants and natural teeth. *J Clin Periodontol* 1994; 21: 301–7.

Teronen O, Konttinen YT, Lindqvist C, et al. Human neutrophil collagenase MMP-8 in peri-implant sulcus fluid and its inhibition by clodronate. *J Dent Res* 1997;76:1529–37.

Santos MC, Campos MI, Souza AP, Trevilatto PC, Line SR. Analysis of MMP-1 and MMP-9 promoter polymorphisms in early osseointegrated implant failure. *Int J Oral Maxillofac Implants* 2004;19:38-43.

McKenna DF, Borzabadi-Farahani A, Lynch E. The effect of subgingival ozone and/or hydrogen peroxide on the development of peri-implant mucositis: a double-blind randomized controlled trial. *Int J Oral Maxillofac Implants*. 2013;28:1483–9

Hallström H, Persson GR, Lindgren S, Olofsson M, Renvert S. Systemic antibiotics and debridement of peri-implant mucositis. A randomized clinical trial. *J Clin Periodontol.* 2012;39:574–81.

Porras R, Anderson GB, Caffesse R, Narendran S, Trejo PM. Clinical response to 2 different therapeutic regimens to treat peri-implant mucositis. *J Periodontol. 2002*;73:1118–25.

Schwarz F, Schmucker A, Becker J. Efficacy of alternative or adjunctive measures to conventional treatment of peri-implant mucositis and peri-implantitis: a systematic review and meta-analysis. *International journal of Implant Dentistry* 2015; 1(22): 1-34.

Syndergaard B et al. Salivary Biomarkers Associated With Gingivitis and Response to Therapy. *Journal of Periodontology* 2014;85:295-303