

Research Article

Potential role of matrix metalloproteinase-8 as a predictive marker for peri-implant mucositis progress

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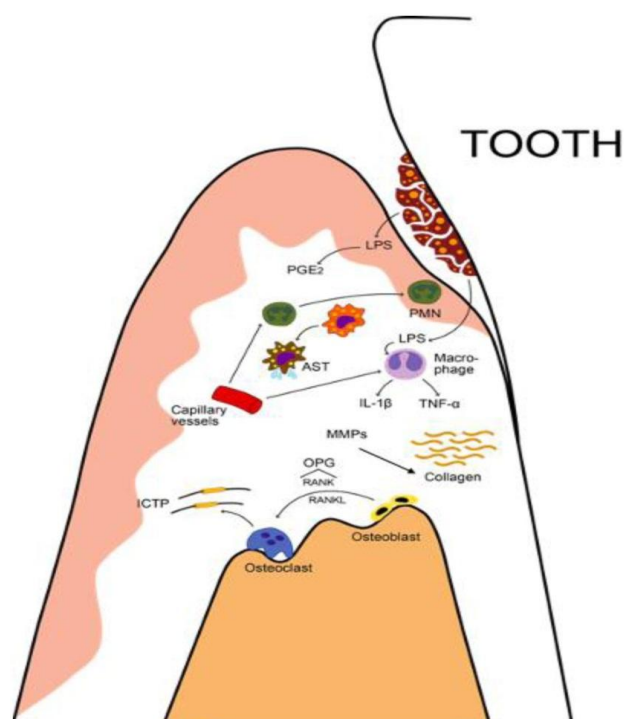
Abstract: Background: Osseointegrated dental implants have become increasingly common as a treatment option for missing teeth. Peri-implant infections are caused by bacterial plaque that may initiate an inflammatory release of cytokines, enhance accumulation of neutrophils in implant lesion, and trigger the production of matrix metalloproteinase-8 (MMP-8). MMP-8 is essential in inflammatory and degenerative processes of periodontal tissues and produced by activated cells. The purpose of this study was to detect the role of MMP-8 as a biomarker of active and aggressive peri-implant mucositis. Material and method: Eighty subjects (40 with peri-implant mucositis and 40 with successful and healthy peri-implant mucosa) were enrolled in this study. The 42 male and 38 female subjects were attended at AL-Karama and AL-Ma'amoun Specialized Dental Centers in Baghdad, Iraq from November 24, 2021 to May 25, 2022. Follow-up examinations were performed on patients to monitor the progression of disease. Peri-implant sulcular fluid was examined and identified using enzyme-linked immunosorbent assay technique for MMP-8. Results: Results showed that MMP-8 levels continue to rise after 3 weeks and are significantly higher in the patient group ($P=0.00000$) than the group with successful implants. Conclusion: MMP-8 can be used to reflect, associate, and predict clinical disease activity and progression of peri-implant mucositis properly.

Keywords: Implant, Inflammation, Matrix metalloproteinase-8, Mucositis, Peri-implant sulcular fluid.

Introduction

Dental implants have become the gold standard of care for replacement of lost teeth because the number of patients suffering from peri-implant diseases has been increasing ⁽¹⁾. Peri-implant diseases (PIDs) are divided into two categories on the basis of their clinical manifestations: peri-implant mucositis (PIM) and peri-implantitis (PI) ⁽²⁾. PIM affects the soft tissues around an implant and is considered a reversible inflammatory disease that causes mild probing and results in bleeding, suppuration, erythema, and even odema in some cases ⁽³⁾; these indications may be compared with gingivitis around natural teeth ⁽⁴⁾. PI is characterized by inflammation of soft tissues and progressive bone loss that may result in implant failure ⁽⁵⁾. Clinical research has demonstrated that the lack of preventative maintenance is closely linked to the advancement from PIM to PI; consequently, proper treatment of PIM can avoid the progression to PI ⁽²⁾. Clinical symptoms of inflammatory illness are commonly used to diagnose peri-implant mucositis. Signs of inflammation are screened in routine clinical tests, and radiographic images are reviewed to rule out bone level alterations ⁽⁶⁾. Peri-implant mucositis can occur from healthy peri-implant mucosa after bacterial biofilms form around osseointegrated dental implants ⁽⁷⁾. Microorganisms may initiate an inflammatory release of cytokines that will enhance the accumulation of neutrophils in the implant lesion ⁽⁸⁾ and lead to the secretion of significant amounts of proinflammatory cytokines and MMPs, thereby modulating the periodontal tissue destruction ⁽⁹⁾ (Figure 1). It also causes monocytes to create inflammatory mediators (TNF, thromboxane B, prostaglandin E2, and interleukins-1, -6, and -8), which are suitable disease activity indicators, and exacerbate the local degeneration of connective tissues and structural elements ⁽¹¹⁾.

Figure 2. Matrix metalloproteinase and inflammatory cytokine production results in ECM collagen degradation, connective tissue detachment loss, and osteoclastic activation ⁽¹⁰⁾



Matrix metalloproteinases (MMPs), collectively called matrixins, are proteinases that participate in ECM degradation ⁽¹²⁾. MMPs are Ca^{2+} - and Zn^{2+} -dependent endopeptidases (Figure 2) that play a role in physiologic development, tissue remodeling, and pathologic tissue destruction. Various MMPs, including MMP-1, -2, -3, -8, -9, and -13, exist ^{(13) (14)}.



Figure 3. Matrix metalloproteinase-8 structure with additional C-terminal, propeptide, zinc-ion catalytic domain, hemopexin domain, and signaling N-terminal ⁽¹⁰⁾

The degradation of extracellular matrix (ECM) proteins, such as laminin, fibronectin, proteoglycans, and collagens, is carried out by enzymes and result in enhanced inflammatory cell migration and tissue damage ⁽¹⁵⁾. Tissue inhibitors of MMPs (TIMPs) strictly control the activities of MMPs ⁽¹⁶⁾. An imbalance of TIMPs and MMPs as well as aberrant MMP activity control can result in peri-implant destructive disease, which is permanent ⁽¹⁷⁾. MMP-8, commonly known as neutrophil collagenase or collagenase-2, is a proteolytic enzyme secreted primarily by neutrophils and observed in inflamed gingiva and can be activated by both host and bacterial enzymes ^{(18) (19)}. Collagen types I, II, III, and IV serve as substrates for these enzymes and are crucial proteins in the periodontal attachment system and soft tissues around implants ⁽¹⁵⁾. However, it is extremely valuable in detecting the rapid breakdown of connective tissue that occurs as peri-implant mucositis and peri-implantitis ⁽⁶⁾. If the inflammation progresses and is left untreated, then stromal tissue cells may also propagate and lead to the increase of infiltrates of proinflammatory cells; promotion of further tissue breakdown ⁽⁸⁾; and eventually lead to loss of osseointegration, implant mobility, and ultimately implant failure ⁽²⁰⁾.

An abundance of humoral markers of inflammation in peri-implant sulcular and gingival crevicular fluids is highly useful in determining the degree inflammation severity inside periodontal tissues, especially in early peri-implant diseases ⁽²¹⁾. PISF represents the inflammatory response around the implant, is equivalent to gingival crevicular fluid ⁽²²⁾, and may present the same diagnostic potential in determining the level

of inflammation and implant-related tissue damage as GCF in natural teeth ⁽²³⁾. The quantity of exudate flowing into the implant sulcus from the surrounding tissue increases during the inflammatory phase ⁽²⁴⁾.

This study aims to determine the association of MMP-8 in the destructive process and maintenance of chronic inflammation in tissues around implants and its ability to facilitate tissue damage and progression of peri-implant mucositis.

Materials and Methods

The 80 subjects of this cross-sectional study include 40 with peri-implant mucositis (15 female and 25 male) diagnosed by a maxillofacial surgeon as peri-implant mucositis according to certain criteria (including bleeding on probing, redness, and odema) and 40 with successful and healthy peri-implant mucosa (17 male and 23 female). Patients who meet the inclusion criteria must be in good general health, without allergies or history of systemic illness associated to periodontal state, and have not had any antibiotic treatment in the past 3 months. Subjects with peri-implantitis, mucogingival problems, chronic desquamate gingivitis, and periodontitis are excluded from this study. The study was carried out from November 24th, 2021 to May 25th, 2022 at AL-Karama and AL-Ma'amoun Specialized Dental Centers in Baghdad, Iraq. The University of Baghdad/ College of Dentistry approved the study protocol and informed consent.

Sample collection

Samples were collected after an adequate time to develop indications of peri-implant mucositis around the healing abutment of 3 weeks of healing abutment insertion ⁽²⁵⁾. Water was used to clean the chosen areas, which were then isolated with cotton rolls. Gentle air was used for drying to avoid salivary contamination. Fluid samples were obtained from the test groups using uniform absorbent paper strips (Perio Paper). Blood-stained strips were not utilized in the experiment; however, a standardized paper strip was inserted into the sulcus for 30 seconds at a depth of 1–2 mm. Paper strips were gathered, placed in sterile Eppendorf tubes with 0.5 ml of phosphate buffer saline (PBS) preservative, centrifuged for 10 minutes at 3000 rpm, and then stored in a [] at –80 °C until laboratory analysis ⁽²⁶⁾. A second sample of PISF was collected with perio-paper by the surgeon after 3 weeks at the follow-up examination to detect the progression of the disease. MMP-8 was investigated in the patient's peri-implant sulcular fluid sample using an enzyme-linked immunosorbent assay (ELISA) kit.

Statistical analysis

SPSS version 22 (Chicago, Illionis, USA) and Microsoft Excel 2010 were employed in this investigation. Independent sample T, paired T, or parametric test was used to evaluate the difference between two groups as well as the linear correlation between two quantitative variables.

Results

A. Demographic features of age and gender among study groups.

The results of the current study showed that subjects in the peri-implant mucositis group (41.750 ± 1.649) are older than those of the successful implant group (37.800 ± 1.204) and demonstrate no statistically significant differences ($P=0.057$). Although male subjects (25, 62.5%) were more likely to be included in the peri-implant mucositis group than female subjects (15, 37.5%) and female subjects were more likely to have successful implants (23, 57.5%) than male subjects (17, 42.5%), the difference was nonsignificant, as shown in Tables 1 and 2.

Table 1: Mean age among peri-implant mucositis and successful implant groups

Groups	Mean	±SE	T test	P value
Successful implants	37.8	1.204	1.934	0.057 NS
Peri-implant mucositis	41.75	1.649		

Note: NS= not significant at $p>0.05$ and S=significant at $p \leq 0.05$.

Table 2: Demographic data of gender between peri-implant mucositis and successful implant groups

Gender	Groups				Chi square p value		Total	
	Successful implants		Peri-implant mucositis					
	N.	%	N.	%			N.	%
M	17	42.5	25	62.5	0.073		42	52.5
F	23	57.5	15	37.5	NS		38	47.5

Note: S= not significant at $p>0.05$ and S=significant at $p \leq 0.05$.

B. Comparison between MMP-8 levels of patients with peri-implant mucositis and successful implants

Matrix metalloproteinase-8 levels were significantly higher ($P=0.00000$) in the group of patients with peri-implant mucositis (3280.475 ± 83.792) compared with those in the successful implant group (2086.2 ± 73.109) (Table 3).

Table 3: Mean level of MMP-8 in peri-implant mucositis and successful implant groups

Groups	Mean	±SE	T test	P value
Successful implants	2086.2	73.109	10.740	0.000
Peri-implant mucositis	3280.475	83.792		

Note: NS= not significant at $p>0.05$ and S=significant at $p \leq 0.05$.

C. Matrix metalloproteinase-8 levels in peri-implant mucositis and mucositis follow-up patients

As shown in Table 4, the mean of MMP-8 increased in the mucositis follow-up group (3336.9 ± 87.121) compared with the peri-implant mucositis group (2683.337 ± 86.983) although the difference was nonsignificant ($P=0.582$).

Table 4: Comparison of MMP-8 level between peri-implant mucositis and mucositis follow-up groups

Statistics	Peri-implant mucositis	Mucositis follow up	Paired T test	P value
Mean	2683.337	3336.9	0.554	0.582 NS
±SE	86.983	87.121		

Note: NS= not significant at $p>0.05$ and S=significant at $p \leq 0.05$.

Table 5 shows that 22 patients accounting for 55% of the total number of subjects recover from inflammation after 3 weeks (early recovery), while only 18 patients accounting for 45% of the total number of subjects suffer from the infection for a longer period (persistent mucositis).

Table 5: Comparison of early recovery and persistent mucositis according to their percentage

Groups	N.	%
Early recovery	22	55
Persistent mucositis	18	45

Discussion

Peri-implant mucositis is the inflammation of soft tissues surrounding a dental implant without evidence of bone loss following early bone remodeling during recovery ⁽²⁷⁾. This condition is similar to gingivitis around natural teeth and widely regarded as a precursor to peri-implantitis ⁽²⁸⁾. Interleukin (IL)-1 and tumor necrosis factor are proinflammatory mediators produced during the inflammatory response that can stimulate gingival fibroblasts to create collagenolytic MMPs, particularly MMP-8 ⁽²⁹⁾.

The mean level of MMP-8 in PISF in the peri-implant mucositis group was significantly greater than that in the successful implant group in this study. Consistent with these results, Kivela-Rajamaki *et al.* (2003) ⁽³⁰⁾ and Xu *et al.* (2008) ⁽³¹⁾ discovered that patients with peri-implant oral disease exhibit significantly greater levels of MMP-8 in PISF than those with healthy implants. Salvi *et al.* (2012) ⁽²⁵⁾ and Ramseier *et al.* (2016) ⁽³²⁾ both reported that elevated MMP-8 levels in PISF are consistently and markedly associated with peri-implant inflammation. According to Ziebolz *et al.* (2017) ⁽³³⁾ and Alassiri *et al.* (2018) ⁽³⁴⁾, MMP-8 levels in PISF can be effectively maintained at low levels in patients receiving supportive implant treatment, thereby indicating that a successful professional maintenance intervention is associated with low MMP-8 levels. These findings suggested that early detection of peri-implant mucositis may be possible by measuring the level or action of MMP-8 in PISF.

The results in the current study estimated the presence of MMP-8 in PISF generated from both early recovery patients (individuals without clinical signs of developing mucositis) and those with persistent mucositis. Notably, although the MMP-8 level in PISF of the mucositis follow-up group was higher than that of the peri-implant mucositis group, the difference was nonsignificant ($P=0.582$) despite showing an improvement in the inflammation around the implant for 55% of patients. Similar to these findings, Pawel-Aleksandrowicz *et al.* (2017) ⁽³⁵⁾ revealed that MMP-8 levels are remarkably higher in PISF of patients without signs of mucositis than those in GCF of individuals with various degrees of periodontitis. These findings contradicted with the conclusions of Arakawa *et al.* (2012) ⁽³⁶⁾, in which the level of MMP-8 in PISF collected from individuals without signs of inflammation surrounding their implants was low.

Matrix metalloproteinase-8 has been associated with numerous physiological and pathological processes ⁽³⁷⁾, including inflammatory response. The prolonged increase of MMP-8 associated with a high chance of therapeutic failure ⁽³⁸⁾ can be due to the overactivation of proinflammatory cytokines. The persistent inflammation may extend further; reach deep portions of the peri-implant area; and lead to connective tissue collagen breakdown, bone resorption, and consequently increased mobility of the infected implant and peri-implantitis. Hence, the group of persistent mucositis is very important because they need additional follow-up examinations with the dentist until confirmation of their complete recovery to prevent the exacerbation of the disease.

Conclusion

The current study investigated the potential of MMP-8 as a diagnostic and predictive biomarker for peri-implant diseases. The results suggested that MMP-8 levels in oral fluids can appropriately reflect, associate, and predict the clinical disease activity and progression of peri-implant mucositis.

Conflict of interest:

The authors have disclosed no potential conflicts of interest.

Author contributions

NID; contributed to the conception or design of the work and was responsible for the acquisition of data. NID and GIT; contributed to the interpretation of results. NID, GIT and MA; drafted the work. All authors approved the final version of the manuscript and are responsible for all aspects of the work.

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الدور المحتمل لماتركس ميتالوبروتيناز-8 كعلامة تنبؤية لتقدم التهاب الغشاء المخاطي حول الزرع نور إبراهيم ضيدان , غادة إبراهيم طه , ماهر الشايب المستخلص:

الخلفية: غرسات الأسنان العظمية أصبحت أكثر شيوعاً كخيار علاجي للأسنان المفقودة. تحدث التهابات ما حول الغرسة بسبب اللويحات البكتيرية التي قد تؤدي إلى إطلاق التهابي من السيتوكينات التي من شأنها تعزيز تراكم العدلات حول الزرع وتحفيز إنتاج البروتينات المعدنية-8 (MMP-8) الضرورية للعمليات الالتهابية والتنكسية في اللثة والتي تنتجها الخلايا المنشطة. الهدف من الدراسة: كان الغرض من هذه الدراسة هو اكتشاف دور MMP-8 كمؤشر حيوي لالتهاب الغشاء المخاطي النشط والعنواني حول الغرسة. المواد وطرق العمل: تم تسجيل ثمانين شخصاً في هذه الدراسة (40 مصاباً بالتهاب الغشاء المخاطي حول الزرع و 40 ممن لديهم زراعات ناجحة) ؛ 42 ذكر و 38 أنثى حضروا في مركز الكرامة التخصصي لطب الأسنان و مركز المأمون التخصصي لطب الأسنان. بغداد، العراق في الفترة من 24 تشرين الثاني 2021 إلى 25 أيار 2022. تمت متابعة المرضى لمراقبة تطور المرض. تم فحص PISF وتحديده باستخدام تقنية مقايسة الممتز المناعي المرتبط بالإنزيم لـ MMP-8. النتائج: أظهرت النتائج أن مستويات MMP-8 كانت أعلى بشكل ملحوظ في مجموعة المرضى ($P = 0.00000$) مقارنة بمجموعة الزراعة الناجحة واستمرت في الارتفاع بعد ثلاثة أسابيع من متابعة المرضى. الخلاصة: خلصت الدراسة الحالية إلى أن MMP-8 يعكس نشاط المرض السريري ويقترن به ويتنبأ جيداً بتطور التهاب الغشاء المخاطي المحيط بالزرع.