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Antibacterial and Anti-inflammatory Properties of Cathelicidin in Iraqi Patients with Peri-Implant Mucositis

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Abstract
Background Peri-implant mucositis is a reversible inflammatory disorder of the soft tissue around functional dentals implant following the formation of biofilm around osseointegrated dental implants; Cathelicidins may directly harm Gram+ve/Gram-ve microorganisms and regulate the production of chemokines, pro-inflammatory cytokines, and anti-inflammatory cytokines to maintain pro- and anti-inflammatory response balances. **Objectives** The aim of the present study is to determine the protective mechanism of cathelicidin LL-37 as an important member of innate immune system against bacterial deposits and uncontrolled inflammation by its immuno-modulatory effect. **Materials and Methods** 80 participants in all, 40 of whom had healthy peri-implant tissue and 40 of whom had peri-implant mucositis; 42 men and 38 women attended at AL-Karama Specialized Dental Center and AL-Ma›amoun Specialized Dental Center, Baghdad, Iraq in the period between November 24, 2021 and May 25, 2022. The same 40 patients were followed up after three weeks to monitor and observe the progression of inflammation around the implant. For the analysis and detection of LL-37, enzyme-linked immunosorbent assay (ELISA) kits were applied. **Results** When compared to the control group, patients with peri-implant mucositis showed no discernible difference in the levels of LL-37 (P value =0.670) after three weeks when healing abutment is installed, then increased non significantly (P value=0.083) following 3 weeks of adequate oral hygiene training and patients follow up. **Conclusion** Present evidence suggests that cathelicidin has a restricted role as antimicrobial and anti-inflammatory peptide and could not be utilized as prognostic criteria for detecting of peri-implant mucositis.

Keywords: Antimicrobial peptides, cathelicidin, dental implants, LL-37, peri-implant mucositis.

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Introduction

In order to replace missing teeth, dental implants are becoming more and more popular (Derks et al, 2015) .Dental implants have made it possible to solve dental issues that were formerly the most challenging (Al-Jumaily, 2019). When they are utilized to support different kinds of dental prosthesis, they have a high rate of long-term survival (approximately10 years). Long-term success of dental implants is not the same as survival due to the sensitivity of functional implants and their restorations to mechanical and biological issues (Derks et al, 2015). The most common biological concerns are inflammatory conditions of the soft tissues and bone around implants and their restorative components. Pertaining to dental implants (Wang, Zhang and Miron, 2015). These conditions are referred to as periimplant mucositis and periimplantitis, respectively (Araujo and Lindhe, 2018). In past workshops, maintaining peri-implant bone support was the definition of peri-implant mucositis, an inflammatory lesion of the mucosa surrounding an endosseous implant (Turkoglu, Efeoglu and Atmaca, 2020). On the other hand, peri-implantitis is defined as an inflammation of the peri-implant mucosa accompanied by a little amount of bone loss (Lee et al, 2017). Periimplant mucositis is well recognized to occur from healthy periimplant mucosa after bacterial biofilms formation around osseointegrated dental implants (Meyer et al, 2017). Plaque and its byproducts are invariably the source of peri-implant infections which results in the stimulation of the host immune response and secretion of massive quantities of pro-inflammatory cytokines that influence periodontal tissue deterioration (Wang, 2020). The inflammatory response is mediated by the interaction of several innate and adaptive humoral and cellular components (Ahmed and Ad'hiah, 2022). Due to poor oral hygiene practices, there were visible indicators of mucosal inflammation for three weeks, including swelling, redness, and bleeding (Satheeshkumar and Mohan, 2015). The immunological response to infections determines the development of inflammation in periodontal tissues, and diverse humoral substances released by defense cells induce tissue damage (Warreth et al, 2015). The peri-implant soft tissue barrier is considered to indirectly prevent bacterial colonization by the action of antimicrobial peptides (AMPs) (He et al, 2018), they play a key role in innate immunity and are also referred to as host defense peptides that guard against infections. Numerous AMPs have been shown to influence the host›s innate immune responses, which subsequently increases pathogen clearance in an indirect manner (Czaplewski et al, 2016). Cathelicidins (LL-37), also known as human cationic antimicrobial peptide (hCAP18), are amphipathic proteins (Tzitzilis et al, 2020). To maintain the delicate balance between pro- and anti-inflammatory responses in check, it regulates the synthesis of chemokines, as well as pro- and anti-inflammatory cytokines (Yu et al, 2018). Epithelial cells and neutrophils both produce the antibacterial peptide LL-37. Inflammation causes blood arteries to dilate, and neutrophils move from the vessels to the site of inflammation (Kolaczkowska, 2016). Gram- positive and Gram-negative bacteria are both directly susceptible to cathelicidins› antibacterial properties (Florio et al, 2015), with LPS-neutralizing effects at low doses and pro-apoptotic capabilities at higher concentrations (Agier et al, 2018). These peptides can bind to negatively charged membranes of lipopolysaccharide (LPS) and disrupt them, causing cell death. They can also infiltrate membranes and target

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intracellular activities such as RNA and DNA synthesis, as well as inhibit enzyme and chaperone functions and cause protein breakdown LL-37 also controls the synthesis of chemokines, as well as pro- and anti-inflammatory cytokines (Mansour et al, 2014). To protect against infections and keep the immune system steady, one must be able to maintain equilibrium. If there are issues with the expression or processing of LL-37, this equilibrium will be upset (Verjans et al, 2016). Interesting, it has been suggested that aggressive periodontal problems are caused by a lack of cathelicidin LL-37 (Soldati et al, 2020).The aim of the present study is to determine the protective mechanism of cathelicidin LL-37 as an important member of innate immune system against bacterial deposits and uncontrolled inflammation by its immuno-modulatory effect.

Materials and Methods

This cross-sectional study included 80 individuals, 40 with peri-implant mucositis (25 male and 15 female, of mean age 41±10.431 years).

Patients group include two samples

a. Forty cases diagnosed by a maxillofacial surgeon as peri-implant mucositis after three weeks when healing abutment is installed (which is adequate time to develop indications of peri-implant mucositis around the healing abutment) (Salvi et al, 2012) according to certain criteria including bleeding on probing, redness and odema. The peri-implant sulcular fluid was collected by perio-paper by the specialized dentist.

b. A second sample of peri-implant sulcular fluid was collected by perio- paper by the dentist from the same cases within three weeks.

Control group

Include forty individuals having healthy peri-implant tissue (17 male and 23 female, with an average age of 37±7.616 years). The system of implant used in this study was (titanium grade 5 dental implants/ Dentaurum implant system).

Inclusion Criteria: selection of cases based on the followings

1. The people are in good general health and have no history of chronic inflammatory or autoimmune disease.
2. Should have one or more than one implant unit.
3. The patient of the first group must be diagnosed by a maxillofacial surgeon as peri-implant mucositis (after the healing abutment is installed) in at least 1 implant with absence of pathological radiographic bone loss.
4. Patients older than 18 years.

Exclusion criteria: certain measures were avoided including

1. Patients with history of systemic illness related to periodontal status, diabetes or with a history of cardiovascular and metabolic bone diseases.
2. Patients with peri-implantitis.
3. Patients with pockets, muco-gingival problems, and periodontitis.
4. Patients with chronic desquamative gingivitis.
5. Smokers are excluded.

Ethical approval

The University of Baghdad›s Faculty of Medicine approved the study protocol and informed consent at the Basic Science Department/Oral Microbiology/College of Dentistry/University of Baghdad on November 21, 2021, and all patients received a copy of the study›s objectives in detail and completed an informed consent form to confirm their information and

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acceptance to participate in the study. The study was carried out between November 24th, 2021 and May 25th, 2022.

Sample collection

After three weeks after healing abutment installation, sample collection for the patients was set from 9 a.m. to 11 a.m. To prevent salivary contamination, the targeted sites were washed with water, separated with cotton roles, and dried with a gentle air spray. Fluid samples were collected from the test groups using uniform absorbent paper strips (perio paper). A standardized paper strip was put into the sulcus then deposited in sterile Eppendorf tubes with 0.5 ml of Phosphate Buffer Saline (PBS) preservative, centrifuged for 10 minutes at 3000 rpm, and then firmly wrapped to be kept at -80°C until laboratory analysis (Bhardwaj and Prabhuji, 2013). After three weeks of patient follow-up, the surgeon collects a second sample of Peri-Implant Sulcus Fluid (PISF) using perio-paper. Using Enzyme-Linked Immunosorbent Assay (ELISA) kits, LL-37 was indicated from the patient›s peri-implant sulcular fluid sample.

Statistical Methods

In this investigation, SPSS version 22 and Microsoft Excel 2010 were employed. To evaluate the difference between two groups, use an independent sample T test, a paired T test, or a parametric test to test the linear correlation between two quantitative variables.

Results

Demographic features of age and gender among study groups

In this study, males 25 (62.50%) were more likely than females 15(37.50%) in the peri-implant mucositis group, while higher number of females in control group 23(57.50%) than males 17(42.50%) were observed, however, the difference was non-significant as shown in Table 1 and Table 2.

a. PISF level of Cathelicidin LL-37 (ng/mL)

A comparison of patients with peri-implant mucositis and those with health peri-implant tissue in the present study indicated a higher mean of LL-37(1810.525±60.859), (1851.700±74.659) respectively , although there was no obvious difference (P=0.670), as shown in Table 3.

b. Mean LL-37 alterations in peri-implant mucositis and mucositis follow-up groups

Table 4 demonstrate that the mucositis follow-up group had a higher changing level of LL-37 in PISF (2041.000±85.963) than the peri-implant mucositis group (1831.113±47.911), although the difference was not significant (P=0.083).

c. Comparison of the health status among mucositis follow up groups

Table 5 show that 22 of patients are recovered from inflammation after 3 weeks (early recovery), and their percentage is 55%, which is higher than the percentage of patients who have had the infection for a longer period (persistent mucositis), which is 45% and their number is 18.

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Table (1): Demographic data of gender among peri-implant mucositis and control groups.

Gender	Groups				Chi square *p*-value	Total	
	Control		Peri-implant mucositis				
	N.	%	N.	%		N.	%
M	17	42.50	25	62.50	0.073 NS	42	52.50
F	23	57.50	15	37.50		38	47.50

NS= not significant at p>0.05, S=significant at p<0.05.

Table (2): Demographic data of age among peri-implant mucositis and control groups.

Groups	Mean	±SD	±SE	T test	*P*-value
Control	37.800	7.616	1.204	1.934	0.057 NS
Peri-implant mucositis	41.750	10.431	1.649		
Total	39.775	9.290	1.039		

NS= not significant at p>0.05, S=significant at p<0.05.

Table (3): Comparison of LL-37 level (ng/mL) between control group and patients with peri-implant mucositis.

Groups	Mean	±SD	±SE	T test	*P*- value
Control	1810.525	384.904	60.859	0.427	0.670 NS
Peri-implant mucositis	1851.7	472.186	74.659		
Total	1831.113	428.527	47.911		

NS= not significant at p>0.05, S=significant at p<0.05.

Table (4): LL-37 (ng/mL) change from peri-implant mucositis to mucositis follow

Statistics	Peri-implant mucositis	Mucositis follow up	Paired T test	*P*-value
Mean	1831.113	2041	1.777	0.083 NS
±SD	428.527	543.679		
±SE	47.911	85.963		

NS= not significant at p>0.05, S=significant at p<0.05.

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

Groups	N.	%
Early recovery	22	55.00
Persistent mucositis	18	45.00

Discussion

Peri-implant mucositis is regarded to be a precursor to peri-implantitis since it only affects the soft tissues around implants and shows no evidence of bone loss after the initial bone remodeling that occurs during recovery (kamal, 2020). Antimicrobial peptides (AMPs) are produced by the innate immune system in humans (Dang and Wang, 2020). LL-37, a cathelicidin-derived AMP, is of relevance in this investigation because it acts as an immunomodulatory agent and has direct antibacterial activity against a wide range of Gram-positive and -negative bacteria (Yang et al, 2018). The current investigation found that the levels of LL-37 in the peri-implant mucositis and successful implant groups were not significantly different. These findings align with Turkoglu et al, (2020), who published only one study that involved LL-37 disclosure in peri-implant disorders. They noticed no significant differences in the PISF level of LL-37 between dental

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implants with various clinical statuses and a healthy control group. Additionally, according to the findings of Carlisle et al, (2009), Maisetta et al, (2011) and Eick et al, (2014), the levels of LL-37 in gingival crevicular fluid (GCF) and saliva were examined, and shown that there was a deficit in the immunomodulatory and antibacterial capabilities of LL-37 in GCF, resulting in severe periodontal disorders. Hosokawa et al. (2016) on the other hand, as well as Türkoglu et al, (2017) reported that a level of LL-37 was shown to be greater in gingivitis patients compared to healthy controls, and these levels were found to be positively connected to gingival crevice depth. This could be because there is no periodontal ligament between the implant and the surrounding bone, as opposed to natural teeth, which receive their circulatory supply from the periodontal ligament, the vascular plexus near the junctional epithelium, and the capillaries of the connective tissue beneath the epithelium. However, the alveolar ridge›s supra-periosteal arteries are the sole vascular supplies for the peri-implant mucosa, which may explain the LL-37 shortage during inflammation (Lucarini et al, 2018). After three weeks of patient follow-up, 45% of them still had inflammation around the implant and according to the study›s findings, the level of LL-37 increased, but not significantly. This result is in consistent with the other researches as Puklo et al, (2008) who detected a local deficiency in LL-37 in the presence of bacterial biofilm. Blanca et al, (2015) detected that LL-37 had no effect on the regulation of inflammatory response. Mishra et al, (2016) and Luo et al, (2017) also suggested a weak correlation between LL-37 and bacterial biofilm and explained that LL-37 does not disrupt pre-formed biofilms, inhibit bacterial attachment, or prevent early biofilm formation. While on the contrary, Lee et al, (2010) reported that LL-37 suppresses the pro-inflammatory activities of LPS from Gram-negative bacteria in both monocytes and gingival fibroblasts. The results of the current study could be related to the ability of certain periodontopathogens to proteolytically inactivate the antimicrobial activity of peptides or down-regulate their expression, especially proteases of Gram-negative bacteria that may degrade LL-37 fragments. And that›s what diminishes the role of LL-37 as an immunomodulatory and anti-microbial agent.

Conclusion

In summary, antimicrobial peptides have a special function in the oral cavity, where they are essential for overall health. Therefore, as a result of persistent inflammation in 45% of patients, present evidence suggests that LL-37 has a restricted role as an antimicrobial and anti-inflammatory peptide and could not be utilized as a prognostic indicator for peri-implant mucositis detection.

Conflict of interest

We are the author's (Noor Ibrahim Dhaidan and Ghada Ibrahim Taha) declare that the manuscript for this article is original, that it has not been published before and is not being considered for publication anywhere, and that the final version has been viewed and approved by all authors.

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