



Original Article

The Role of Lipopolysaccharide in Initiation and Progression of Peri-implant Mucositis

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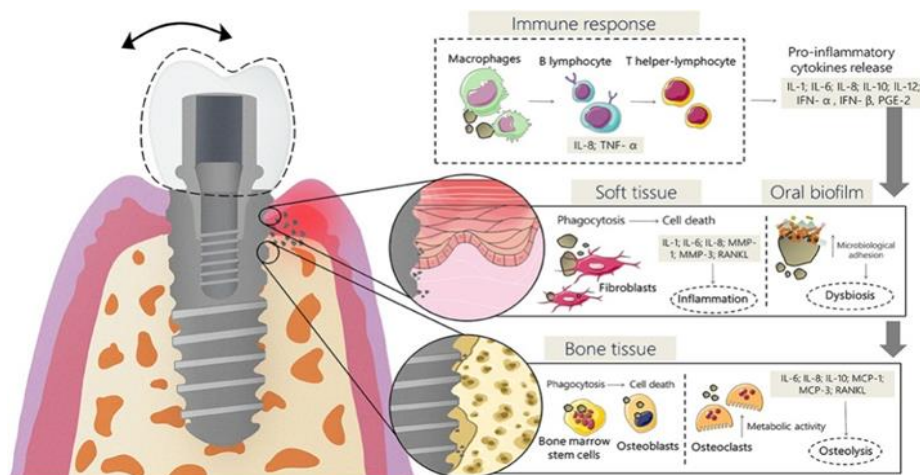
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ABSTRACT

Osseointegrated dental implants are becoming more common as an option for replacing the missing or damaged teeth. Peri-implant infections are caused by anaerobic Gram-negative bacteria. This may initiate an inflammatory release of cytokines that will enhance the accumulation of neutrophils in the implant lesion that is essential for the inflammatory and degenerative processes in periodontal tissues. Eighty subjects were enrolled in this study, 40 with peri-implant mucositis and 40 implants that were successfully integrated (42 males and 38 females). The same 40 patients were followed up after three weeks to monitor and observe the progression of inflammation around the implant. Peri-implant sulcular fluid (PISF) samples were collected by perio-paper from all subjects attending the department of Oral and Maxillofacial Surgery at AL-Karama Specialized Dental Center and AL-Ma'amoun Specialized Dental Center, Baghdad, Iraq. (PISF) samples were examined and identified by using the enzyme-linked immunosorbent assay (ELISA) technique for bacterial lipopolysaccharide (LPS). Compared with patients with a successful implant, those with peri-implant mucositis exhibited a higher level of lipopolysaccharide (LPS) in PISF ($P=0.00000$), and then declined significantly following 3 weeks of adequate oral hygiene instructions. The current study concluded that lipopolysaccharide (LPS) reflect, associate, and predict well with the clinical disease activity and progression of peri-implant mucositis.

GRAPHICAL ABSTRACT



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Introduction

As dental implants have become the gold standard for replacing missing teeth, the number of patients suffering from peri-implant diseases has been increased [1]. In addition to improving the stability of alveolar bone with the peri-implant soft tissues, implant dentistry is responsible for achieving the best aesthetic, functional, and phonological results [2]. The majority of biological problems linked to dental implants are soft tissue inflammations, bone, and restorative materials that surround the implants and are brought on by the buildup of bacterial biofilm. These illnesses are described to as peri-implant mucositis (PIM) as well as peri-implantitis (PI) [3]. PIM affects the soft tissues around an implant and is a reversible inflammatory condition, producing moderate probing that ends in bleeding, suppuration, erythema, and edema in certain instances [4], similar to gingivitis surrounding the real teeth [5]. PI, on the other hand, is a complex chronic inflammatory disease characterized by a progressive attachment loss, bone resorption, pocket development, and gingival bleeding [6], which may lead to implant failure [7].

Peri-implant mucositis has a complicated etiology that is intricately connected to microorganisms and immunity [8], and it is well known that it develops from healthy peri-implant mucosa after the formation of bacterial biofilms surrounding osseointegrated dental implants [9].

Biofilms are surface-attached, multicellular populations of bacteria encased in an extracellular matrix (ECM). It has been shown that quorum sensing (QS), a kind of cell-to-cell communication, plays a crucial role in the biofilm development with its surrounding ECM [10].

The World Health Organization (WHO) announced in 2001 that overuse, global trade, and excessive consumption of antibiotics contributed to the development of drug resistance [11].

For many years, a systemic antibiotic injection was used to try and prevent bacterial colonization and encrustation. However, the antibiotic resistance in the organisms made this approach useless [12].

Treatment failure in patients taking antibiotics has been linked to antimicrobial resistance, drug

persistence, and tolerance by persisters [13]. Also, biofilm is one of the reasons for antibiotic resistance and failure to treat bacterial infections [14]. Any disruption of this mechanism can result in pathological circumstances, which can lead to a number of disorders affecting the soft and hard tissues of the mouth [15].

Normal flora in the oral cavity is nonpathogenic and has a stable relationship with the host. However, in certain circumstances, such as when the immune system is compromised, normal flora can be transformed into a pathogen [16]. The oral cavity is not a homogeneous environment due to the differences between the mucosal and tooth surfaces, as well as the warm temperature, moisture, and rich nutrient environment that can promote the growth of microorganisms, leading to infection [17] and the development of more complex health conditions if not managed properly [18].

Different anatomical surfaces, physical and chemical factors in the oral cavity favor the growth of more than 300 Gram positive and Gram negative bacterial species (Figure 1) [19].



Figure 1: The formation of bacterial biofilm around dental abutments

The microorganisms may initiate an inflammatory release of cytokines that will enhance accumulation of neutrophils to the implant lesion [17]. Interleukin2 (IL-2) is involved in immunity and inflammatory responses, and tumor necrosis factor- (TNF-) increases vascular endothelial cell permeability and activates lymphocytes and IL-2 [20]. *Streptococcus mutans* is a major player in the development of the dental plaque biofilm as an early colonizer and produces adhesins that bind

the organism to the teeth's acquired pellicle [21]. Plaque and its byproducts are invariably the source of peri-implant infections, according to the 7th European Workshop on Periodontology's conclusion [22]. The formation of dental plaque inhibits the penetration of agents that in turn increase resistance to antibiotics. The absence of oral hygiene practices for three weeks resulted in the appearance of obvious indications of bleeding, edema, and other symptoms of mucosal inflammation [23].

Peri-implant infections are largely caused by gram-negative anaerobic bacteria [24], especially *Porphyromonas gingivalis*, *Tannerella forsythia*, and *Prevotella intermedia* [25,26]. Lipopolysaccharide (LPS), the main element of Gram-negative cell wall, is regarded as a

significant virulence factor because it can encourage Gram-negative bacterial cell adhesion, the invasion of oral mucosal cells, and the activation of the host immune response, leading to the secretion of significant amounts of pro-inflammatory cytokines and MMPs, which modulate periodontal tissue destruction [27]. The secretion of significant amounts of pro-inflammatory cytokines and MMPs, which modulate periodontal tissue destruction, is regarded as a significant virulence factor because it can encourage Gram-negative bacterial cell adhesion, the invasion of oral mucosal cells, and the activation of the host immune response, leading to the secretion of significant amounts of pro-inflammatory cytokines and MMPs (Figure 2) [28].

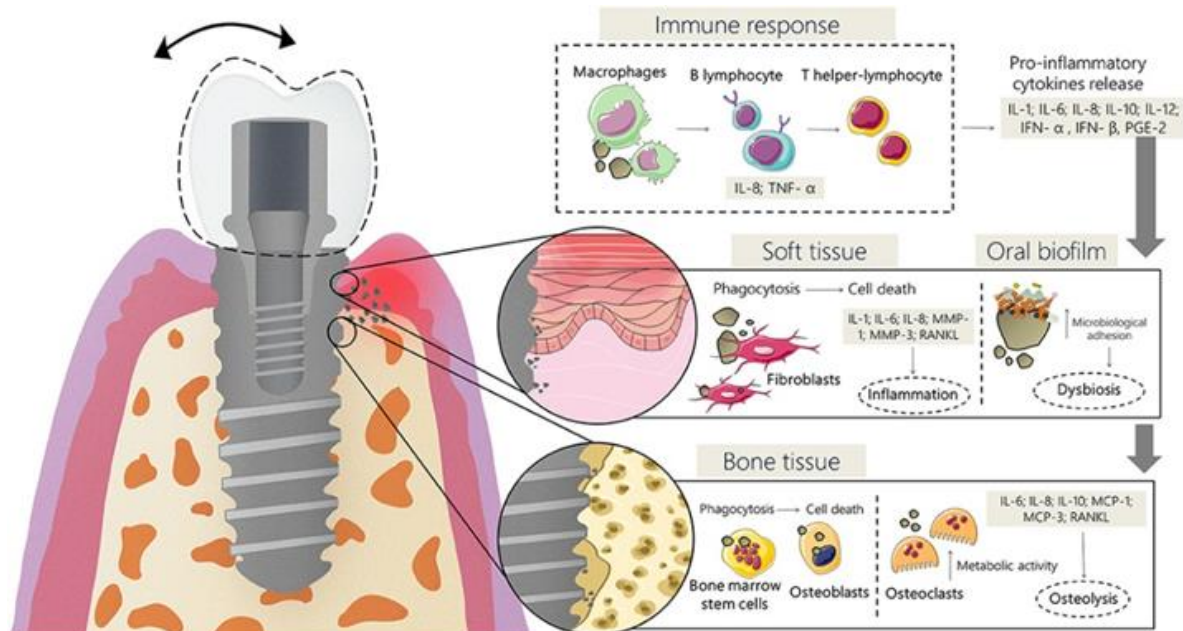


Figure 2: The role of bacterial biofilm and inflammation in peri-implant diseases

PISF represents the inflammatory response around the implant and is equivalent to gingival crevicular fluid [29]. It may have the same diagnostic potential to determine the level of inflammation and implant-related tissue damage as GCF in natural teeth [30].

In summary, the aim of this study is to determine the role of bacterial endotoxin (LPS) in the initiation of peri-implant mucositis and maintenance of chronic inflammation in the tissues around implants and its ability to facilitate tissue damage and progression of disease.

Materials and Methods

This cross-sectional study included 80 subjects: 40 with peri-implant mucositis (15 females and 25 males) and 40 with successful implants (17 males and 23 females). Patients who met the inclusion criteria had to be in good general health, having no allergies, or history of systemic illness associated with periodontal disease. They also did not have any antibiotic treatment in the past three months. Subjects having peri-implantitis, muco-gingival problems, chronic desquamate gingivitis, and periodontitis were excluded in this study. The Faculty of Medicine in University of Baghdad

approved the study protocol and informed consent.

Sample collection

Patients were scheduled for sample collection three weeks after healing abutment placement, which is the sufficient time for peri-implant mucositis to develop surrounding the healing abutment [31]. 90 minutes before the sample collection, the patients were instructed to avoid eating and to practice good oral hygiene. Water was used to clean the chosen areas, and then isolated by a cotton roll, and gentle air was used for drying to avoid salivary contamination. By using uniform absorbent paper strips (Perio Paper), fluid samples were obtained from the test groups. Blood-stained strips were not utilized in the experiment; instead, the typical paper strip was placed for 30 seconds at a depth of 1-2 mm into the sulcus. Strips of paper were collected, placed in sterile Eppendorf tubes with 0.5 ml of phosphate buffer saline (PBS) preservative, centrifuged at 3000 rpm for 10 minutes, and then stored at 80°C until the laboratory examination [32]. After three weeks of patient follow-up, the

surgeon collects a second sample of peri-implant sulcular fluid by using perio-paper to determine the condition course. By using an enzyme-linked immunosorbent test (ELISA) kit, the peri-implant sulcular fluid sample of the patient was analyzed for lipopolysaccharide (LPS).

Statistical analysis

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

Results and Discussion

A. Demographic features of age and gender among study groups

In this study, males were more likely than females in the peri-implant mucositis group, while a higher number of females was observed having the successful implants than in the mucositis group. However, the difference was non-significant, as displayed in Figure 3 and Table 1.

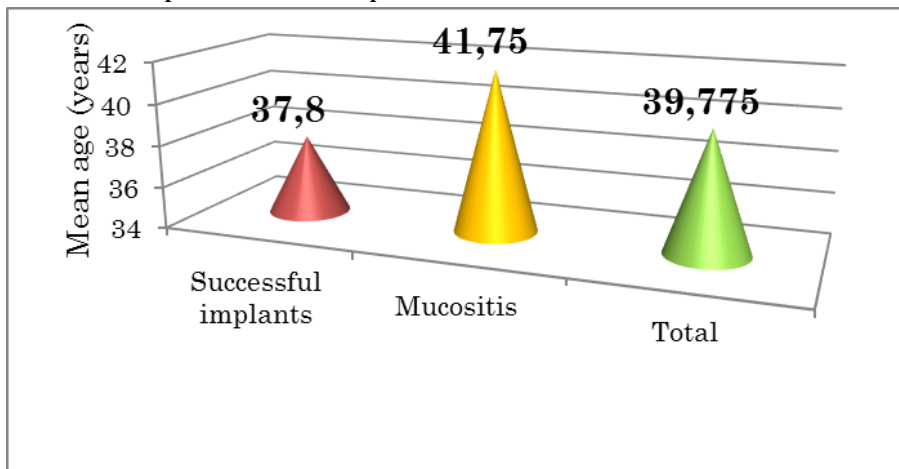


Figure 3: Demographic features of age in the study group

Table 1: Demographic data of gender among peri-implant mucositis and successful implants groups

Gender	Groups				Chi square p-value	Total	
	Successful implants		Peri-implant mucositis			N.	%
	N	%	N	%			
Male	17	42.5	25	62.5	0.073	42	52.5
Female	23	57.5	15	37.5			

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

B. Levels of LPS in peri-implant sulcular fluid (pg/mL) in patients with successful implants and peri-implant mucositis

In the patient group, LPS revealed a significant rise ($p<0.05$) compared with that in subjects

having successful implants, as represented in Table 2.

Table 2: Comparison of LPS level between peri-implant mucositis and successful implants groups

Groups	Mean	±SD	±SE	T test	P-value
Successful implants	175.138	27.067	4.280	9.860	0.00000 Sig.
Peri-implant mucositis	516.118	217.045	34.318		
Total	345.628	230.332	25.752		

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

C. LPS levels in peri-implant sulcular fluid (pg/mL) among peri-implant mucositis patients and mucositis follow-up groups

In the mucositis follow-up group, the LPS amount was found to be significantly lower ($p<0.05$) compared with its higher level in the peri-implant mucositis group, as listed in Table 3.

Table 3: Comparison of LPS level between peri-implant mucositis and mucositis follow up group

Statistics	Peri-implant mucositis	Mucositis follow up	Paired T-test	P-value
Mean	345.628	278.542	6.478	0.00000 Sig.
±SD	230.332	128.020		

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

As its previously known, only Gram-negative bacteria produce lipopolysaccharide (LPS) [33], that represent the major component of bacterial cell wall and play a key role in pathogenesis by triggering the release of a vast number of inflammatory cytokines in various cell types cause an acute inflammatory response [27].

In addition to other systemic risk factors, peri-implant mucositis develops mostly due to a lack of adequate plaque control [34]. Therefore, it is imperative to start receiving intensive dental health care as soon as possible [35].

In the same vein, Leonhardt *et al.* [36] found that inflammation around the implant is linked to Gram-negative anaerobic bacteria.

According to Shibli *et al.* [37], *Porphyromonas gingivalis*, *Treponema denticola*, and *Tannerella forsythia* mean counts were elevated in inflammatory regions around implants. Other investigators like Casado *et al.* [38] examined the presence of five bacteria in sub-gingival peri-implant sites, including *Actinobacillus actinomycetemcomitans*, *Porphyromonas gingivalis*, *Prevotella intermedia*, *Tannerella forsythensis*, and *Treponema denticola*, which have been connected to the etio-pathogenesis of the periodontal disease.

According to the findings of this study, the existence of these microorganisms, and their LPS, in the peri-implant sulci, when combined with other factors such as genetics, inflammatory response, and occlusal loading leads to inflammatory symptoms and disease development.

After the patient stuck to better oral hygiene for 3 weeks as instructed by the specialist dentist, a significant decrease in the LPS level was detected in the mucositis follow-up subjects.

These findings are consistent with previous studies by Hernandez-Cott *et al.* [39], and Van

Leeuwen *et al.* [40] who claimed that the number of anaerobic bacteria had significantly decreased upon oral hygiene instructions.

The fact that minimal variations were detected as a result of implant status and the divergence across authors suggests that these pathogens are engaged in the implant disease process. In this study, PISF was a reliable source for bacterial sampling to help in the early detection of difficult-to-detect metabolic and biochemical lesions as well as to monitor the osseointegration process and the bone's reaction to occlusal loading, all of which contributed to improve the long-term implant success.

Conclusion

The present research examined the potential role of LPS in peri-implant mucositis, and according to the findings, it can be used as a diagnostic and prognostic biomarker for peri-implant illnesses due to its role in the initiation of peri-implant mucositis. It also reveals that LPS in oral fluids reflects and prognostically correlates with the clinical disease activity and the development of peri-implant mucositis.

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Authors' contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

Conflict of Interest

The author declared that they have no conflict of interest.

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