BALANCING INFLAMMATION AND IMMUNE REGULATION IN PERI-IMPLANTITIS: INSIGHTS FROM THE PISF TNF-A/IL-10 CYTOKINE RATIO

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Abstract

Background: Peri-implantitis is a severe inflammatory condition that affects both the hard and soft tissues around dental implants. It often results in progressive bone deterioration and eventually the failure of the implant. A crucial element in its development is the interaction between pro-inflammatory and anti-inflammatory cytokines in the local immune response. The ratio of tumour necrosis factor-alpha (TNF-α) to interleukin-10 (IL-10) has been suggested as a potential indication of this immunological balance.

Aim: To evaluate the diagnostic relevance of the TNF-α/IL-10 ratio in peri-implant sulcus fluid (PISF) for distinguishing peri-implantitis from healthy and successfully osseointegrated implants.

Materials and Methods: In this case control study, a total of 90 participants were recruited and divided into three equal groups: healthy controls, successful implant group, and peri-implantitis group. The clinical parameters in this study included Plaque Index (PI), Gingival Index (GI), Bleeding on Probing (BOP) and Probing Depth (PD). PISF samples were collected from all subject and TNF-α and IL-10 concentrations were measured using enzyme-linked immunosorbent assay (ELISA).

Results: The peri-implantitis group revealed significantly elevated levels of both TNF-α and IL-10 compared to the control group and successful implants ($p < 0.001$). The TNF-α/IL-10 ratio was significantly decreased in the peri-implantitis group (3.94 ± 1.22) compared to the control group (8.53 ± 1.56) and the successful implants group (7.92 ± 1.44) ($p < 0.001$).

Conclusion: The TNF-α/IL-10 ratio in PISF indicates the local inflammatory balance and may be an important biomarker for finding peri-implantitis. A lower ratio, together with higher cytokine levels, indicating an anti-inflammatory response that doesn't bring the immune system back to normal.

Keywords: Peri-implantitis, TNF-α, IL-10, cytokines, peri-implant sulcus fluid (PISF), ELISA.

1 Introduction

Peri-implant diseases are biologically driven conditions that affect the soft and hard tissues surrounding dental implants. These diseases are broadly classified into peri-implant mucositis, a reversible inflammation of the peri-implant soft tissues, and peri-implantitis, an advanced destructive condition involving progressive loss of supporting bone [1,2]. The rising number of dental implants worldwide has paralleled an increase in the incidence of associated disorders, with peri-implant mucositis impacting up to 80% of patients and peri-implantitis involving between 28–56% of persons with implants [3,4].

The pathophysiology of peri-implantitis resembles that of chronic periodontitis, typically beginning with microbial biofilms that build on implant surfaces. These biofilms, mostly consisting of anaerobic gram-negative bacteria such as *Porphyromonas gingivalis*, *Aggregatibacter actinomycetemcomitans*, and *Fusobacterium nucleatum*, elicit host immunological responses that result in tissue inflammation and bone damage [5,6]. However, unlike natural teeth, implants don't have a periodontal ligament and have different anatomical and immunological interfaces. This means that the host's immune response is very important in how the illness progresses [7].

Neutrophils, macrophages, and T lymphocytes are some of the innate and adaptive immune cells that are at the front of this reaction. These cells invade peri-implant tissues when they come into contact with microbes and emit a lot of cytokines and other inflammatory substances. Among them, tumour necrosis factor-alpha (TNF-α) and interleukin-10 (IL-10) serve as principal pro-inflammatory and anti-inflammatory indicators, respectively, that regulate tissue damage and repair [8,9].

TNF-α is recognised for its ability to enhance osteoclast activity and facilitate bone resorption, serving a crucial function in the aetiology of peri-implantitis. IL-10, on the other hand, is a regulatory cytokine that stops pro-inflammatory cytokines like TNF-α from being made. This keeps inflammation and tissue damage to a minimum. An imbalance among these cytokines might distort the immune response towards deleterious pathways, particularly in the presence of a chronic microbial challenge [10,11].

Examining the TNF-α/IL-10 ratio provides a more comprehensive understanding of the local inflammatory environment than assessing a single marker alone. This ratio has been investigated in several inflammatory diseases but remains little explored concerning peri-implantitis. Assessing these indications in peri-implant sulcus fluid (PISF), a crevicular exudate rich in immune cells and signalling molecules, offers a non-invasive method for the early identification of illness and the monitoring of immunological activity at implant sites [12,13].

Therefore, this study aims to assess the diagnostic relevance of the TNF-α/IL-10 ratio in peri-implant sulcus fluid samples from three groups: patients with peri-implantitis, persons with successful implants, and healthy controls.

2 Materials and Methods

Subjects

This observational case-control study included 90 participants (39 females and 51 males) who attended the Dental College Teaching Hospital, Al-Iraqia University. All individuals were recruited from patients undergoing implant follow-up or treatment at the Department of Oral and Maxillofacial Surgery. Subjects were categorized into three groups:

- 30 Control group (healthy individuals without implants),
- 40 Successful implant group (individuals with stable implants and no signs of peri-implant inflammation),
- 20 Peri-implantitis group (patients diagnosed clinically and radiographically with peri-implantitis).

Informed consent was obtained from all participants prior to sample collection, and ethical approval for the study was granted by Al-Iraqia University College of Dentistry.

Inclusion Criteria

- Adults aged 25–65 years.
- Presence of dental implants for at least 6 months.
- Clinical and radiographic diagnosis according to peri-implantitis classification.
- Willingness to participate and sign informed consent.

Exclusion Criteria

- Systemic diseases affecting periodontal health (e.g., diabetes, immunosuppression).
- Recent antibiotic or anti-inflammatory therapy (within 3 months).
- Smoking or tobacco use.
- Pregnant or lactating women.

Oral Examination

Plaque Index (PI): This index measures the thickness of plaque at the gingival edge using the Silness and Löe Index. The buildup of plaque is a key element in the start and growth of inflammation around implants. It is the main cause of both peri-implant mucositis and peri-implantitis [14,15].

Gingival Index (GI): Löe and Silness also came up with the GI, which is used to check for gingival inflammation by looking for changes in colour, consistency, and bleeding when the gums are gently probed. Although originally developed for natural teeth, this index remains valid around implant-supported prostheses due to the comparable soft tissue behavior [16].

Bleeding on Probing (BOP): BOP is a good way to tell whether there is inflammation. To measure it, a periodontal probe is gently inserted into the peri-implant sulcus. If bleeding occurs while probing, it means that there are inflamed and vascularised tissues, which means that there is either peri-implant mucositis or peri-implantitis, depending on whether there is bone loss at the same time [17].

Probing Depth (PD): PD measurements were recorded using a calibrated periodontal probe at six sites per implant (mesiobuccal, midbuccal, distobuccal, mesiolingual, midlingual, and distolingual). A PD greater than 5 mm, particularly

with concurrent BOP and radiographic bone loss, is often diagnostic of peri-implantitis [18].

Sample Collection: Peri-implant Sulcus Fluid (PISF)

90 minutes prior to the sample collection, patients were prepared for sample collection between 9:00 and 11:00 a.m. The patients were told to avoid eating and brushing their teeth the targeted sites were cleansed with water, separated with cotton rolls, and gently sprayed with air. "Perio Paper" was used to collect fluid samples from the test groups. After removing the supragingival plaque with dry gauze, a regular paper strip was placed in the sulcus, left it for 30 seconds. Blood-stained strips were removed from the sample. To preserve the integrity of the sample, the paper strips were immediately placed in sterile Eppendorf tubes, containing 0.5 ml preservative (PBS) centrifuged at 3000 rpm for 10 minutes, and stored at -80° C until laboratory analysis [19].

Enzyme-linked immunosorbent Assay (ELISA) was employed for the detection of pro-inflammatory biomarkers using the Human ELISA quantitative immunoassay kit (tumor necrosis factor-alpha (TNF-α) /Lot No: E25DYH836, Feiyuo company, China) and (interleukin-10 (IL-10)/Lot No: E25DAJ660, Feiyuo company, China) in peri-implant sulcus fluid (PISF) samples. The readings were obtained using an ELISA reader from BioTek (USA).

Statistical Analysis

Data were analyzed using SPSS version 26. Normality was tested using the Shapiro-Wilks test. Comparisons between groups and genders were conducted using ANOVA test, Chi-square and Ratio Statistics, with significance set at $p < 0.05$.

3 Results

Table 1 presents the distribution of sex among the three study groups: control group, patients with successful implants, and patients with peri-implantitis. Among the total 90 participants, 39 (43.3%) were female and 51 (56.7%) were male. In detail, the female distribution was 13 in the control group (33.3%), 16 with successful implants (41.0%), and 10 with peri-implantitis (25.6%). For males, 17 were in the control group (33.3%), 24 in the successful implant group (47.1%), and 10 in the peri-implantitis group (19.6%). The chi-square test yielded a p-value of 0.762

Table 2 summarizes the age characteristics of participants across the three groups. The control group had a mean age of 33.60 ± 9.17 years, the successful implant group had a mean age of 36.37 ± 9.20 years, and the peri-implantitis group had a mean age of 36.60 ± 11.05 years. The mean age in all groups was 35.52 ± 9.83 years. Statistical analysis using one-way ANOVA revealed non-significant difference in age distribution between the groups ($p = 0.426$).

The result of clinical parameter analysis revealed significant differences among the three groups. Bleeding on Probing (BOP) showed a progressive increase from the control group (mean = 0.0893) to the successful implant group (2.2050) and was highest in the peri-implantitis group (2.3375). Similarly, Probing Depth

(PD) increased from 1.783 mm in controls to 4.725 mm in successful implants and 5.200 mm in peri-implantitis. The Plaque Index (PI) also followed a sharp rise from 0.0363 in controls to 2.6500 and peaked at 5.5500 in peri-implantitis patients. Lastly, the Gingival Index (GI) values were 0.1990 in controls, 0.1348 in successful implants, and 0.1960 in peri-implantitis patients. All comparisons showed highly significant differences ($p = 0.000$) among the groups for each parameter, as demonstrated in Table 3.

The result of biomarker analysis in Table 4 demonstrates notable differences in inflammatory and anti-inflammatory cytokines across the groups. The TNF-α levels were lowest in the control group (131.31 ± 25.96 pg/mL), increased in the successful implant group (186.08 ± 47.51 pg/mL), and were highest in the peri-implantitis group (222.04 ± 20.30 pg/mL), reflecting a clear elevation in pro-inflammatory activity. Conversely, IL-10 levels, which represent anti-inflammatory response, followed an opposite trend: controls had the lowest levels (15.46 ± 0.89 pg/mL), followed by the successful implant group (25.31 ± 11.55 pg/mL), and the highest levels were observed in peri-implantitis patients (63.26 ± 20.99 pg/mL). These changes were statistically significant for both biomarkers ($p = 0.000$), as demonstrated in Table 4.

The result of post hoc multiple comparisons (Table 5) confirms that the differences in TNF-α and IL-10 levels among the three groups are statistically significant. For TNF-α, the mean differences were significant between the control group and successful implants (−54.77 pg/mL, $p = 0.000$), the control group and peri-implantitis patients (−90.74 pg/mL, $p = 0.000$), and between successful implants and peri-implantitis patients (−35.96 pg/mL, $p = 0.001$). Similarly, for IL-10, significant differences were noted between the control group and successful implants (−9.85 pg/mL, $p = 0.002$), control group and peri-implantitis patients (−47.80 pg/mL, $p = 0.000$), and between successful implants and peri-implantitis patients (−37.96 pg/mL, $p = 0.000$)— as demonstrated in Table 5.

The result of the TNF-α/IL-10 ratio analysis revealed a significant decline in the ratio from healthy to diseased states, reflecting an imbalance in the inflammatory response. The control group had the highest mean ratio (8.525 ± 1.779), followed by the successful implant group (7.916 ± 1.885), while the peri-implantitis group had the lowest mean ratio (3.938 ± 1.545). The observed differences were statistically significant ($p = 0.0001$), indicating a marked shift in cytokine balance as peri-implant inflammation progressed. Additionally, variability and dispersion indicators such as the coefficient of variation (CV) were highest in the peri-implantitis group (39.2%–41.1%), suggesting greater heterogeneity in immune response— as demonstrated in Table 6.

4 Discussion

The present study investigated inflammatory biomarkers in peri-implant sulcus fluid (PISF) among three groups: healthy controls, patients with successful implants, and those with peri-implantitis. Clinical parameters including Plaque Index (PI), Gingival Index (GI), Bleeding on Probing (BOP), and Probing Depth

(PD) were significantly elevated in the peri-implantitis group compared to controls, suggesting active inflammation and disease progression.

Tumor Necrosis Factor-α (TNF-α) is a key pro-inflammatory cytokine involved in the recruitment of immune cells and the stimulation of osteoclastogenesis via the RANK/RANKL pathway, contributing to bone resorption around implants [18]. Its elevated levels in peri-implantitis reflect an aggressive host response and progressive tissue destruction.

Interleukin-10 (IL-10), in contrast, is an anti-inflammatory cytokine that downregulates pro-inflammatory mediators including TNF-α, thereby limiting tissue damage [8]. The increased IL-10 levels observed in peri-implantitis may represent a compensatory mechanism aimed at mitigating chronic inflammation. However, this anti-inflammatory response appears insufficient to counteract the overwhelming pro-inflammatory state.

The current findings align with those of Duarteet al. (2009) and Gomes et al. (2019), who reported elevated levels of TNF-α and altered cytokine ratios in peri-implant disease. additinally to emphasized the role of TNF-α in peri-implant bone destruction, especially when not effectively counterbalanced by anti-inflammatory mediators like IL-10[20,21].

In agreement, Jansson et al. (2019) demonstrated significantly elevated TNF-α levels in PISF of peri-implantitis patients compared to healthy sites [22]. Similarly, Oliveira et al. (2023) found that IL-10 levels increased with disease severity but were insufficient to suppress inflammation, reinforcing the importance of evaluating the TNF-α/IL-10 ratio.

The TNF-α/IL-10 ratio is particularly important, as it reflects the balance between inflammation and immune regulation. A significantly higher ratio in peri-implantitis suggests that inflammatory pathways dominate despite the upregulation of IL-10. This imbalance likely contributes to the breakdown of peri-implant tissues and progressive bone loss.

Cytokine analysis revealed significantly higher levels of TNF-α and IL-10 in the peri-implantitis group, with the TNF-α/IL-10 ratio being markedly elevated as well. These results indicate a dysregulated inflammatory response in peri-implantitis characterized by pro-inflammatory dominance [23].

TNF-α and IL-10 are cytokines produced primarily by activated macrophages, and they serve opposing functions in regulating the innate and adaptive immune responses [24]. Actually, TNF-α acts as a potent pro-inflammatory mediator that enhances leukocyte adhesion and promotes the migration of immune cells into tissue spaces, thereby supporting neutrophil and macrophage antimicrobial activity [25]. In contrast, IL-10 is a well-known anti-inflammatory cytokine with immunosuppressive properties, secreted by T and B lymphocytes, activated monocytes, and macrophages. Goutoudi et al. (2004) reported that its primary function is to regulate and suppress excessive immune responses, helping to control tissue destruction and periodontal bone loss [26].

Interestingly, in a previous study by Grimbaldeston et al. (2007), an increase in TNF-α can stimulate a concurrent rise in IL-10 production as part of a

compensatory mechanism aimed at mitigating inflammation and limiting tissue damage [27]. This interrelationship helps explain the simultaneous elevation of both TNF-α and IL-10 observed in peri-implantitis patients in the present study. The body's attempt to balance pro-inflammatory and anti-inflammatory signals may reflect a regulatory feedback loop where TNF-α induces IL-10 in an effort to suppress further inflammatory progression.

Further supporting this mechanism, an animal study by Meng et al. (2018) in mice with arthritis demonstrated that elevated levels of hypoxia-inducible factor 1-alpha (HIF-1α) were associated with increased IL-10 production by B cells, contributing to a reduction in inflammation [28]. Extrapolating these findings to peri-implantitis suggests that higher IL-10 concentrations might alleviate inflammation in peri-implant tissues by improving local hypoxic conditions, thereby reducing HIF-1α levels [28].

5 Conclusion

This study demonstrates that the TNF-α/IL-10 ratio in peri-implant sulcus fluid indicates the equilibrium of pro-and anti-inflammatory responses in the tissues surrounding implants. Despite the elevation of both cytokines in peri-implantitis, the decreased ratio signifies an active but insufficient anti-inflammatory counter-response to the prevailing inflammation. The findings highlight the potential of the TNF-α/IL-10 ratio as a simple, non-invasive biomarker for identifying peri-implantitis and monitoring disease progression. Further research including larger cohorts and longitudinal techniques are necessary to validate this ratio as a diagnostic and prognostic tool, and to explore the possibility for targeted modulation of this cytokine balance to improve peri-implant disease management.

ТАБЛИЦЫ

Table 1. Sex Distribution Across Study Groups in Peri-implant Status

		Group				
		Control group	successful implants	Peri-implantitis patients	Total	Chi-Square (*p-value*)
sex	Female	13 (33.3%)	16 (41.0%)	10 (25.6%)	39 (43.3%)	0.543 (*0.762*)
	Male	17 (33.3%)	24 (47.1%)	10 (19.6%)	51 (56.7%)	
Total		30 (33.3%)	40 (44.4%)	20 (22.2%)	90 (100.0%)	

Table 2. Age Distribution Among Control, Successful Implant, and Peri-implantitis Groups

	Age (years)	
Groups	Mean±Std. Deviation	Range
Control group	33.60±9.171	18-50
successful implants	36.37±9.197	19-59
Peri-implantitis patients	36.60±11.047	17-56
Total	35.52±9.829	17-59
F (p-value)	0.862 (0.426)	

ANOVA test

Table 3. Comparison of Clinical Parameters (BOP, PD, PI, GI) Among Study Groups

ANOVA Table

Groups		BOP	PD	PI	GI
Control group	Mean	.08933	1.783	.03630	.1990
	Std. Deviation	.154578	.2520	.024779	.05195
successful implants	Mean	2.20500	4.725	2.65000	.1348
	Std. Deviation	.554215	.586	1.672554	.09714
Peri-implantitis patients	Mean	2.33750	5.200	5.55000	.1960
	Std. Deviation	.498121	.6959	.510418	.08894
F		234.013	339.436	140.534	6.450
p-value		.000	.000	.000	.000

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Table 4. Comparison of TNF-α and IL-10 Levels Among Study Groups

Groups		TNF-α	IL-10
Control group	Mean	131.30737	15.45930
	Std. Deviation	25.955388	0.887437
successful implants	Mean	186.08068	25.30505
	Std. Deviation	47.505166	11.548259
Peri-implantitis patients	Mean	222.04485	63.26295
	Std. Deviation	20.295995	20.997643
F		40.111	.000
p-value		93.819	.000

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Table 5. Multiple Comparisons of TNF-α and IL-10 Levels Between Study Groups

Dependent Variable	(I) Groups	(J) Groups	Mean Difference (I-J)	Sig.
TNF-a	Control group	successful implants	-54.773308*	.000
		Peri-implantitis patients	-90.737483*	.000
	successful implants	Peri-implantitis patients	-35.964175*	.001
IL-10	Control group	successful implants	-9.845750*	.002
		Peri-implantitis patients	-47.803650*	.000
	successful implants	Peri-implantitis patients	-37.957900*	.000

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Table 6. Descriptive and Statistical Indicators of TNF-α/IL-10 Ratio Across Study Groups

Ratio Statistics for TNF-a / IL-10

Group	Mean	Std. Deviation	Sig.	Average Absolute Deviation	Price Related Differential	Coefficient of Dispersion	Coefficient of Variation: Mean Centered	Coefficient of Variation: Median Centered
Control group	8.525	1.779	0.0001	1.287	1.004	.146	20.9%	20.5%
successful implants	7.916	1.885		1.395	1.077	.168	23.8%	23.2%
Peri-implantitis patients	3.938	1.545		1.098	1.122	.291	39.2%	41.1%

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ТИТУЛЬНЫЙ ЛИСТ_МЕТАДАННЫЕ

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Блок 3. Метаданные статьи

BALANCING INFLAMMATION AND IMMUNE REGULATION IN PERI-IMPLANTITIS: INSIGHTS FROM THE PISF TNF-A/IL-10 CYTOKINE RATIO

Сокращенное название статьи для верхнего колонтитула:
TNF-A/IL-10 RATIO AND IMMUNE BALANCE IN PERI-IMPLANTITIS

Keywords: Peri-implantitis, TNF-α, IL-10, cytokines, peri-implant sulcus fluid (PISF), ELISA.

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