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A Clinical Evaluation of the Severity of Peri-Implantitis Following Immediate Implant Placement in the Maxillary Anterior Esthetic Zone based on Post-Inflammatory Fluctuating Levels of Biomarkers IL-1β and IL-6 in Peri-Implant Crevicular Fluid (PICF): An Original Research Study

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KEYWORDS
Peri-Implantitis, Biomarkers, Peri-Implant Crevicular Fluid (PICF), IL-1β, IL-6, Inflammation, Cone Beam Computed Tomography

ABSTRACT:

Aim: This study aims to evaluate the severity of peri-implantitis following immediate implant placement in the maxillary anterior esthetic zone based on post-inflammatory fluctuating levels of biomarkersil-1β and IL-6 in peri-implant crevicular fluid (PICF).

Materials and Methods: This study includes a total of 40 patients. Inclusion criteria included ages 35 to 60, excluding those with mental instability, smoking, or systemic diseases. After informed consent and CBCT assessment, a chlorhexidine rinse was used, and an infra-orbital nerve block was administered for anaesthesia. An immediate implant was placed, and healing abutments were added after two months. Sutures were removed a week later, and patients received oral hygiene instructions. Prosthesis fabrication began in the third month after peri-implant crevicular fluid (PICF) sampling. Samples were collected at four and eight months postoperatively for analysis of IL-1β in Group 1 and IL-6 in Group 2 (20 patients each). Statistical analysis evaluated the relationship between these biomarkers and peri-implantitis severity in the maxillary anterior aesthetic zone.

Statistical Analysis and Results: 40 patients underwent Cone Beam Computed Tomography (CBCT) for implant placement, followed by immediate placement and a two-month healing period. Healing abutments were attached, and prostheses were completed by the third month. Peri-implant crevicular fluid (PICF) samples were collected at four months and analysed for inflammatory biomarkers via ELISA. IL-1β levels averaged 3.64 at four months and rose to 5.12 after eight months, while IL-6 levels were 3.61 at 4 months and 5.105 at 8 months. The study indicated that

Journal of Chemical Health Risks

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JCHR (2025) 15(4), 1651-1658 | ISSN:2251-6727

IL-1β was a stronger inflammatory biomarker than IL-6, which showed significant anti-inflammatory effects, summarized through one-way ANOVA analysis.

Conclusion: This study found that inflammatory biomarkers IL-1β and IL-6 in peri-implant crevicular fluid are linked to inflammation. IL-1β initiates inflammation, while IL-6 amplifies it and has some anti-inflammatory roles. Elevated IL-1β levels in peri-implant fluid are associated with peri-implantitis, which causes inflammation and tissue destruction around dental implants.

Introduction

Dental implants are a common solution for tooth loss and are popular for replacing missing teeth or entire sets of teeth. They can improve people's quality of life. These implants are usually made of titanium or other biocompatible materials. The implant is placed into the jawbone, where it bonds with the bone through a process called osseointegration. Osseointegration is the complex interaction between the implant and bone tissue.[1,2] However, complications can arise after the procedure, such as infections, poor bonding, and other issues that may lead to implant failure. Factors like age, sex, smoking, the location of the implant, existing health problems, the amount and quality of bone, and oral care can affect these outcomes.[3] Peri-implant disease refers to inflammation in the tissue around an implant. There are two types: peri-implant mucositis, which is a reversible inflammation of soft tissues, and peri-implantitis, which involves inflammation and loss of bone support around the implant. Both peri-implant mucositis and peri-implantitis are common.[4,5] Currently, there is no predictive model for these diseases, but biomarkers could help. Biomarkers are measurable indicators of disease or response to treatment. In periodontitis, gingival crevicular fluid (GCF) biomarkers are moderately effective for diagnosis. Similarly, biomarkers in peri-implant crevicular fluid (PICF) show promise for diagnosing and predicting diseases around implants. This review aims to summarize what we know about PICF biomarkers and their ability to predict disease progression.[6,7] Understanding biomarkers can help detect peri-implantitis early. They can assist in classifying and understanding periodontitis. PICF, also known as peri-implant sulcular fluid, might contain indicators that help diagnose and plan treatment. A biomarker is a measured parameter that indicates normal biological processes or disease responses.[8] An imbalance between bacteria and the body's defence at the tissue-implant interface triggers inflammation. Cytokines like Tumour Necrosis Factor alpha (TNFα), Interleukin-1-beta (IL-1β), and Interleukin-6 (IL-6) are released by various cells. Enzymes such as matrix metalloproteinases are also produced, leading to the breakdown of tissues and bone. More than 90 different molecules in GCF have been studied for diagnosing periodontal disease, especially in natural teeth. Most studies on peri-implantitis biomarkers focused on the differences in enzymes and cytokines between healthy and diseased implants. These components include pro-inflammatory cytokines like TNFα, IL-1β, IL-6, IL-12, IL-17, and anti-inflammatory cytokines like IL-4 and IL-10.[9,10] The ELISA test helps find and measure tiny amounts of a substance in a sample using special proteins called antibodies. It can detect really small amounts, even less than a grain of sugar.[11]This study aims to evaluate the severity of peri-implantitis following immediate implant placement in the maxillary anterior esthetic zone based on post-inflammatory fluctuating levels of biomarkersil-1β and IL-6 in peri-implant crevicular fluid (PICF).

Materials and Methods

A total of 60 patients with a missing maxillary right central incisor sought replacement options. Of these, 40 patients expressed interest in replacing the missing tooth with implant placement and an implant-supported prosthesis. The inclusion criteria for the study included individuals aged 35 to 60 years, encompassing both males and females with a missing right central incisor. The exclusion criteria involved patients who were mentally unstable, smokers, or had systemic diseases. Informed consent was obtained from all willing patients. To ensure accurate assessment and planning for implant placement, a cone beam computed tomography (CBCT) analysis was conducted. Additionally, a chlorhexidine mouthwash rinse was administered as part of the pre-operative protocol. For local anesthesia, an infra-orbital nerve block was performed. Immediate implant was placed in the position of the right central incisor. After two months,

Journal of Chemical Health Risks
www.jchr.org
JCHR (2025) 15(4), 1651-1658 | ISSN:2251-6727

healing abutments were placed, and the gingival tissue was sutured around them. One week later, sutures were removed, and patients were given reinforced oral hygiene instructions. The fabrication of the prosthesis was conducted in the third month, following the completion of the initial peri-implant crevicular fluid (PICF) sampling recall. Subsequent PICF samples were collected during the fourth and eighth months postoperatively. Before collecting the crevicular fluid, the implant site was isolated using cotton rolls and thoroughly dried. After removing any supragingival plaque, a standardized volume of 3 µL of PICF was obtained using calibrated volumetric microcapillary pipettes, which were positioned extracrevicularly at the gingival margin. The samples were promptly transferred to an Eppendorf tube containing a phosphate-buffered solution and subsequently frozen at -70°C. Samples exhibiting visible contamination with blood or saliva were discarded to ensure data integrity. The experimental procedures began with applying an IL-1β ELISA test kit, a sensitive method for measuring cytokine levels. A total of 40 patients who underwent dental implant placement and received implant-supported prostheses after a three-month healing period were enrolled in the study. These patients were further divided into two groups for comparison. In Group 1, consisting of 20 patients wherein interleukin IL-1β levels were meticulously evaluated using the ELISA technique. Meanwhile, in Group 2, 20 patients underwent assessment of interleukin IL-6 levels. These evaluations occurred after surgical implant placement, at two key times: four months and eight months post-implant placement. Peri-implant crevicular fluid was carefully collected from the all four surfaces (mesial, distal, lingual, and buccal) adjacent to each implant. This fluid was analyzed in the laboratory to quantify IL-1β and IL-6 biomarker levels, providing insights into the inflammatory response related to the implants. A thorough statistical analysis was conducted to assess the severity of peri-implantitis following immediate implant placement in the maxillary anterior aesthetic zone. This analysis was based on the fluctuating levels of post-inflammatory biomarkers IL-1β and IL-6 in peri-implant crevicular fluid, aiming to explore the relationship between these biomarkers and peri-implantitis onset.

Statistical Analysis and Results

In this study, all statistical analyses were performed using SPSS software, a comprehensive tool tailored for statistical computing and data analysis within the social sciences. To evaluate the significance of our findings, we utilized the chi-square test, which is particularly effective for assessing differences in proportions across various groups. This methodology facilitated a thorough and rigorous comparison of categorical data, thereby ensuring that our results accurately reflect the underlying trends and relationships present within the dataset.

Results

This research study comprised a cohort of 40 patients, aged between 35 to 60 years, all of whom were seeking to replace a missing maxillary right central incisor through the placement of dental implants and the subsequent fitting of implant-supported prostheses. The participant group was evenly balanced in terms of gender, consisting of 20 males and 20 females. Initially, each participant underwent a Cone Beam Computed Tomography (CBCT) evaluation to assess the bone structure and determine the optimal placement for the implants. Following this imaging assessment, the implants were placed immediately. A healing period of two months was then observed, during which the implants integrated with the surrounding bone. After this period, healing abutments were attached to facilitate the next phase of treatment. By the third month, the construction of the implant-supported prostheses was completed, marking a significant step forward in restoring the patients' dental function and aesthetics. In the fourth month post-implantation, peri-implant crevicular fluid (PICF) samples were collected from the study participants. These samples were analysed using an Enzyme-Linked Immunosorbent Assay (ELISA) to assess the levels of inflammatory biomarkers, providing insights into the biological response surrounding the implants. Table 1 offers a concise statistical overview of the ages and gender distribution among the patients in the study, while Graph 1 visually depicts the demographic characteristics and relevant details of these individuals. Delving into Group 1 (n=20), where implant placements took place, Table 2 records the analysis of interleukin IL-1β levels in the PICF after four months. This analysis utilized the ELISA method, with results subjected to statistical examination through

Journal of Chemical Health Risks
www.jchr.org
JCHR (2025) 15(4), 1651-1658 | ISSN:2251-6727

the Pearson Chi-Square test to ascertain the significance of the findings. The ELISA evaluation revealed a combined mean IL-1β level of 3.64 across all four surfaces—mesial, distal, buccal, and lingual—indicating the inflammatory status at that time. Further extending the investigation, Table 3 details the assessment of IL-1β levels in Group 1 after an additional eight months. The analysis, again employing the ELISA method, indicated a rise in the combined mean IL-1β levels from the PICF, reaching 5.12. Table 4 presents a focused analysis of interleukin IL-6 levels within Group 2 at the 4 months mark, which was also evaluated using the ELISA method. The reported combined mean from all four surfaces was recorded at 3.61, providing essential information on the inflammatory response during this period. Additionally, Table 5 showcases the findings for Group 2 at the 8 months follow-up, where IL-6 levels in the PICF were reassessed using the ELISA method. This analysis revealed a combined mean of 5.105, signalling an ongoing evaluation of the inflammatory profile surrounding the implants. Following the evaluation conducted between the groups, it was observed that IL-1β emerges as a moderately more potent inflammatory biomarker when compared to IL-6. In contrast, IL-6 exhibits significant anti-inflammatory effects. This distinction highlights the varying roles these cytokines play in mediating inflammation within the body. Finally, Table 6 encapsulates the estimations derived from all studied groups, presenting a comprehensive summary through one-way ANOVA analysis, further contributing to the understanding of the inflammatory variables observed throughout the study period.

Table 1: Age & gender based statistical description of contributing patients

Age Group (Yrs)	Male	Female	Total	P value
35-40	4	4	8	0.01*
41-45	6	5	11	0.30
46-50	3	7	10	0.01*
51-55	3	2	5	0.30
56-60	4	2	6	0.20
Total	20	20	40	*Significant
*p<0.05 significant				

Graph 1: Patients demographic distribution and associated details

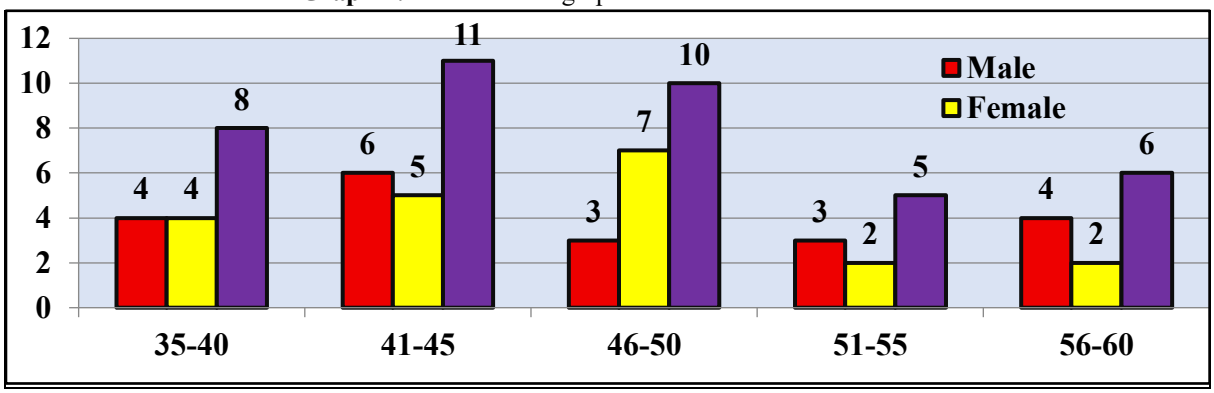

Table 2: In Group 1 (n=20), implants were placed, and after 4 months, the interleukin IL-1β levels were evaluated using the Enzyme-Linked Immunosorbent Assay (ELISA) method in Peri-Implant Crevicular Fluid (PICF). Subsequently, statistical analysis was conducted employing the Pearson Chi-Square test to ascertain the significance of the results

Surfaces	N	Mean	Std. Dev.	Std. Error	95% CI	Pearson Chi-Square	df	p value

Journal of Chemical Health Risks
www.jchr.org
JCHR (2025) 15(4), 1651-1658 | ISSN:2251-6727

						Value		
Buccal	20	1.16	2.21	2.195	2.115	2.26	2.116	1.0
Lingual	20	1.06	2.12	1.126	1.204	2.16	2.104	2.0
Distal	20	1.15	2.20	2.089	1.040	1.08	1.158	0.02*
mesial	20	1.06	2.12	1.126	1.204	2.16	2.104	2.0
Cumulative	All Surfaces= 3.64		2.45	2.234	2.224	2.36	2.344	4.0
*p<0.05 significant								

Table 3: In Group 1 (n=20), implants were placed, and after 8 months, the interleukin IL-1β levels were evaluated using the Enzyme-Linked Immunosorbent Assay (ELISA) method in Peri-Implant Crevicular Fluid (PICF). Subsequently, statistical analysis was conducted employing the Pearson Chi-Square test to ascertain the significance of the results

Surfaces	N	Mean	Std. Dev.	Std. Error	95% CI	Pearson Chi-Square Value	df	p value
Buccal	20	1.90	2.24	2.095	2.125	2.26	2.126	1.0
Lingual	20	1.07	2.15	1.206	1.214	2.18	2.114	0.03*
Distal	20	1.89	2.23	2.009	1.141	1.45	1.255	0.02*
mesial	20	1.07	2.15	1.206	1.214	2.18	2.114	0.03*
Cumulative	All Surfaces= 5.12		2.26	2.238	2.245	2.45	2.344	0.06
*p<0.05 significant								

Table 4: In Group 2 (n=20), implants were placed, and after 4 months, the interleukin IL-6 levels were evaluated using the Enzyme-Linked Immunosorbent Assay (ELISA) method in Peri-Implant Crevicular Fluid (PICF). Subsequently, statistical analysis was conducted employing the Pearson Chi-Square test to ascertain the significance of the results

Surfaces	N	Mean	Std. Dev.	Std. Error	95% CI	Pearson Chi-Square Value	df	p value
Buccal	20	1.15	2.20	2.089	1.040	1.08	1.158	0.02*
Lingual	20	1.06	2.12	1.126	1.204	2.16	2.104	2.0
Distal	20	1.14	1.29	1.235	0.986	1.364	1.345	0.04*
mesial	20	1.06	2.12	1.126	1.204	2.16	2.104	2.0
Cumulative	All Surfaces= 3.61		2.36	2.225	2.236	2.46	2.254	3.0
*p<0.05 significant								

Table 5: In Group 2 (n=20), implants were placed, and after 8 months, the interleukin IL-6 levels were evaluated using the Enzyme-Linked Immunosorbent Assay (ELISA) method in Peri-Implant Crevicular Fluid (PICF). Subsequently, statistical analysis was conducted employing the Pearson Chi-Square test to ascertain the significance of the results

Surfaces	N	Mean	Std. Dev.	Std. Error	95% CI	Pearson Chi-Square Value	df	p value
Buccal	20	1.89	2.23	2.009	1.141	1.18	1.255	0.02*
Lingual	20	1.06	2.12	1.126	1.204	2.16	2.104	2.0
Distal	20	1.89	2.23	2.009	1.141	1.18	1.255	0.02*

Journal of Chemical Health Risks
www.jchr.org
JCHR (2025) 15(4), 1651-1658 | ISSN:2251-6727

mesial	20	1.06	2.12	1.126	1.204	2.16	2.104	2.0
Cumulative	All Surfaces= 5.105		2.56	2.257	2.267	2.23	2.564	3.0
*p<0.05 significant								

Table 6: Estimation amongst all studied groups using one-way ANOVA

Variables	Degree of Freedom	Sum of Squares ∑	Mean Sum of Squares m∑	F	Level of Sig. (p)
Between Groups	4	1.510	1.352	1.2	0.001*
Within Groups	16	1.216	1.435	_	
Cumulative	112.10	01.123	*p<0.05 significant		

Discussion

French D et al reviewed in their study that dental implants are important for replacing missing teeth and can last a long time. However, dentists are seeing more studies about problems with these implants, especially a condition called peri-implantitis. Research shows that up to 56% of patients may have peri-implantitis, though estimates range from 12% to 43%. This condition happens because of bacteria, which cause inflammation in the soft and hard tissues around dental implants. This inflammation can impact how successful the implant is.[12,13] Bartold K et al included in their study that when tissues are incapacitated, they react with inflammation. This process includes increased blood flow and permeability, leading to the buildup of white blood cells, fluids, and cytokines, which are proteins that help the immune system. In the early stages of inflammation, the body begins to develop specific immune responses. During both acute and chronic inflammation, the body releases various soluble factors.[14,15] Chan MH et al showed in their study that interleukins (ILs) are important proteins involved in this process. More than 35 ILs have been identified, each serving a unique role in the body. ILs acts as signalling molecules that allow communication among immune cells. They help recruit cells needed for both immune and inflammatory responses.[16] Germolec DR et al reviewed in their study that ILs significantly impact periodontal disease. For example, IL-1α is involved in breaking down bone, while IL-1β plays a key role in periodontal disease by inhibiting bone formation and increasing bone loss. IL-1β is also crucial in the inflammatory response to bacteria. It boosts the activity of certain enzymes and compounds that further promote inflammation.[17,18] Vignali DA et al reviewed in their study that IL-2 and IL-6 contribute to the destruction of periodontal tissue and increase bone loss. The interaction between IL-1 and IL-6 heightens inflammation and can even cause fever, which helps mobilize immune cells. The production of interleukins is a temporary process because their messenger RNA is unstable, leading to brief bursts of synthesis. Once made, these molecules are quickly released into the body.[19] Zorina OA et al included in their study that a sensitive and highly specific diagnostic technique known as the enzyme-linked immunosorbent assay (ELISA) has been meticulously developed to detect interleukin-8 (IL-8), a pivotal cytokine that plays an essential role in the body's immune response. IL-8 is instrumental in drawing in and activating neutrophils, which are crucial immune cells tasked with combating infections and maintaining the body's defence mechanisms. The ELISA method distinguishes itself as an affordable yet highly effective tool for investigating cytokines, enabling researchers to delve deeply into the complex interactions within the immune system across a variety of research and clinical contexts.[20,21] Nemzek JA et al showed in their study that the ELISA technique is not limited to detecting just IL-8; it is designed to accurately identify and quantify an array of significant biomarkers. This method prioritizes precision, providing dependable results that can significantly enhance our understanding of immune responses. Furthermore, the insights gained through ELISA can aid in discovering potential therapeutic targets, thus contributing to advancements in medical treatments and interventions.[22]

Conclusion

Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(4), 1651-1658 | ISSN:2251-6727

Within the limitations of this research evaluated the severity of peri-implantitis following immediate implant placement in the maxillary anterior aesthetic zone within its limitations. The assessment is based on fluctuating levels of inflammatory biomarkers IL-1β and IL-6 in peri-implant crevicular fluid (PICF) after inflammation. The results indicated that IL-1β and IL-6 are both pro-inflammatory cytokines, serving as mediators that promote inflammation. IL-1β is a strong initiator of inflammation, while IL-6 has a broader role, amplifying inflammation and exerting some anti-inflammatory functions. The study showed that elevated IL-1β levels in PICF are clearly linked to peri-implantitis, a condition marked by inflammation and tissue destruction around dental implants. Comprehensive and extended research studies will be essential in the future to gain a deeper understanding of the subject.

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