Original Article

Interleukin – 17 and Interleukin-10 as Inflammatory and Prevention Biomarkers in Periimplant Diseases

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Abstract

Background: Periimplant diseases are inflammatory diseases. Thus, the level of preinflammatory cytokines which has important role in the inflammation processes can consider as biomchemical markers for early diagnosis and prevention of periimplant diseases. The aim of this study was to determine and compare the level of interleukin (IL)-17 and IL-10 in patients with periimplant mucositis and periimplantitis. **Methods:** This case--control study was conducted on 51 patients with implants which were loaded at least 1 year previously, 17 patients with periimplant mucositis, 17 patients with periimplantitis, and 17 individuals with healthy implants. After clinical examination, gingival crevicular fluid sampling was carried out by paper point number 25 for 4 min and the mean value of IL-17, IL-10 in samples was measured using enzyme linked immunosorbent assay (ELISA), least square differences (LSD) reader in laboratory. The data was analyzed using statistical software SPSS 22. Quantitative analysis was done using One-way analysis of variance (ANOVA) test and LSD past test. **Results:** The results of analysis showed that there was a significant difference in the mean value of IL-17 and IL-10 between the three study groups ($P < 0.001$). Individuals with healthy implants showed a significant lower level of IL-17 than patients with periimplantitis ($P = 0.001$) and for patients with periimplantitis, the level of IL-17 was significantly lower than that of patients with periimplant mucositis ($P < 0.001$) and IL-10 level was significantly lower in mucositis than periimplantitis ($P < 0.001$). **Conclusions:** The level of IL-17 and IL-10 increased in patients with periimplant compared to individuals with healthy periimplant tissues and the results showed that the highest concentrations of IL-17 and IL-10 were observed in patients with periimplant mucositis and periimplantitis, respectively.

Keywords: *Interleukin-10, interleukin-17, mucositis, periimplantitis*

Introduction

Implantology is considered as an important field of study in modern dentistry. Implants as the useful treatment provides the opportunity to restore the function and esthetic to the patients. However, like any other treatment, the complications and adverse consequences are considered as an integral part of this treatment as well. Among these complications, occurrence of inflammation and infection in tissues around the implant are more important.

Tissues around the implants are prone to bacterial infection, which causes inflammation and development of periimplant mucositis and periimplantitis, consequently resulting in periodontal diseases like gingivitis and chronic periodontitis.[1]

Mucositis is a reversible inflammatory lesion caused by microbial plaque and is limited to the soft tissue around dental implants and has no bone involvement. If the inflammation progress reaches to the bone, mucositis turns into periimplantitis, which is diagnosed using radiographic images prepared by radiolucency around the implant in radiographic image.[2]

In periodontal diseases, cytokines are released in response to bacterial invasion into periodontal tissues, which increase the immune responses and will be effective in regulation of inflammatory-immune responses and infection suppression fundamentally.[3]

Belibasakis[4] in a study on human biopsies showed that periimplantitis and periodontitis lesions had common microbiological and immunological characteristics.

Al-Majid *et al*.[5] indicated that the analysis of the disease-specific oral and systemic biomarkers in saliva and oral fluids exerts the strong potential to serve as a useful adjunctive diagnostic and preventive

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biotechnological tool in periodontal and periimplant diseases, also Zani *et al.*,[6] in their study suggested that periimplant crevicular fluid biomarkers might be helpful in distinguishing healthy periimplant from diseased one.

Cytokines cause tissue destruction and bone loss through activating collagenase, osteoclast activating enzymes, and other destructive enzymes.[7] Duarte *et al.*[8] in their systematic review study mentioned that proinflammatory cytokines specially interleukin (IL)-1, IL-6, IL-12, IL-17, and tumor necrosis factor alpha (TNFα) were among the cytokines which have been studied most commonly.

IL-17 is a proinflammatory cytokine that increases in periodontal disease and has an important role in the regulation of other destructive cytokines.[9]

The findings of a recent study conducted in 2015 by Chitrapriya *et al.*[10] on biopsy samples revealed that the level of IL-17 increased through the inflammation occurring in periodontal tissues.

Also, de Araujo *et al.*[11] in a study on periimplant tissue showed that the level of IL-17 increased through the inflammation occurring in these tissues.

Like many other inflammatory cytokines, IL-17 plays both protective and pathogenic role in the immune system.[12] IL-17 has a central role in starting and sustaining the immune responses[13] and plays an important role in host defense against various microorganisms.[14]

IL-10 is a human cytokine influencing immunoregulation and inflammation. It also has patent anti-inflammatory properties that play a crucial role in limiting immune response to pathogens, thereby preventing damage to the host.[15] Ghighi *et al.*[16] in their study showed that the level of IL-10 increased significantly in periimplantitis tissues. Tzach-Nahman *et al.*[17] in a study on oral infection with Porphyromonas gingivalis in mice had implant showed the bone loss and a shift in cytokines expression of gingival. In 2016, Severino *et al.*[18] found that the level of IL-17 was significantly higher in patients with periimplantitis and periimplant mucositis but there were no of the level of IL-10 between experimental groups. The result of the study by Ata-Ali *et al.*[19] suggested that there was a relationship between the concentration of cytokines such as IL-10 and the inflammatory response in periimplant tissues.

Considering that IL-17 and IL-10 are among the new cytokines that has not been investigated extensively in prior researches and due to the contradictory results of the previous studies, for example Kadkhodazadeh *et al.* in 2013[20] revealed no significant role for IL-17 in the development of periodontitis and periimplantitis and according to the fact that, for more accurate diagnostics of periodontal disease activity and progression using a chair-side test or other similar test may help to reduce oral health care costs by reducing patient overtreatment, improving patient outcome, and reducing the need for complex periodontal therapies as well as the importance of ILs as biochemical marker for early diagnosis and early prevention of periimplant disease, the present study was designed to determine and compare the levels of IL-17 and IL-10 in patients with mucositis, periimplantitis, and also in individuals with healthy gingiva.

Methods

This case–control study was conducted on 17 patients with mucositis, 17 patients with periimplantitis, and 17 individuals with healthy implants, who were aged between 35 and 65 years old, who were selected according to the criterion stating that the time interval ranging between 1 and 5 years should passed since the restoring of the prosthesis on their implants, among patients referred to dental clinic affiliated with Islamic Azad University, in Isfahan province, Iran.

The patients with mucositis had symptoms including inflammation, pocket depth of less than 4 mm, and maximum bone loss to the first thread.[2] The patients with periimplantitis had symptoms such as a probing depth (PD) more than 4 mm and maximum bone loss to the second thread, along with signs of inflammation in the soft tissues.[21] The X-ray images taken at the time of screwing the healing showed the bone height was positioned at least equal to the first thread.

The patients with certain systemic diseases, patients using certain drugs, pregnant and lactating women, patients using tobacco and alcohol, patients who had the history of using broad-spectrum antibiotics in the last 6 months, patients who had the history of periodontal treatments in the previous year, patients with plaque index (PI) of more than 40%, were excluded from the study. Ultimately, according to these criteria from 94 patients, 51 patients were included in this study.

After completing an informed consent form, doing preliminary examinations, completion of periodontal chart and taking radiographic images for each patient, the clinical parameters, including bleeding on probing (BOP), PD, and PI were measured by one observer and were recorded in the specific forms.[3]

After washing the mouth, it was dried completely and then, the examined area was isolated. After that, the GCF samples were taken from two areas around the implant (the deepest sulcus or periodontal pocket) using paper point No. 25 for 4 min. Then, the paper points were transferred into the test tubes containing special transport medium and were transferred to special chambers immediately in the laboratory while maintaining the cold chain (2–5°C), and then, they were stored at −70°C.

Then, all the solution samples, which were frozen, were melted until reaching to room temperature. Samples were

prepared according to the special laboratory procedures to measure the amounts of IL-17 and IL-10 using enzyme linked immunosorbent assay (ELISA) Readerand special Elisa kits for assessment of IL-17 and IL-10 (eBioscience, Germany) according to the manufacture's protocol. Finally, the level of IL-17 was determined in each sample and was recorded using ELISA Reader device at 450 nm.

Statistical analysis

The sample size was calculated based on the frequencies reported in previous studies, with a power of 80% and a minimum detectable odds ratio of 2.5. Students *t*-test and Mann–Whitney U test were used for analyzing quantitative variables and Chi-square test or Fisher's exact test were used for analyzing categorical variables. All statistical analyses were performed using SPSS software, version 16 (SPSS Inc, Chicago, IL, USA). One-way ANOVA test was used for comparing the frequencies between the three groups. *Post hoc* LSD test was performed to compare the two groups. Two-side *P* value less than 0.05 was considered as statistically significant.

Results

This study was conducted on 51 patients who had implants divided into three equal groups: healthy individuals, patients with mucositis, and patients with periimplatitis.

The information regarding the age and gender of subjects is presented in Table 1. The mean age of participants in healthy, mucositis, and periimplantitis groups was equal to 49.3 ± 7.8, 46 ± 7.09, and 49.3 ± 7.8 years old, respectively. There was not a significant difference in mean age of three groups ($P = 0.53$), and there was no significant difference in mean gender of three groups ($P = 0.31$).

The mean BOP was significantly lower in healthy group than the two other groups ($P < 0.001$), but there was no significant difference in mean BOP between patients in mucositis and periimplantitis groups ($P = 0.32$). No significant difference was found in mean pocket depth ($P = 0.32$) between healthy and mucositis groups, but the level of PD was significantly higher in periimplantits group than the two other groups ($P = 0.02$) [Table 2].

The lowest level of IL-17 belonged to the healthy implant group, which was equal to 2.7 ng/dL, while the highest level was observed in the mucositis group, which was equal to 83.1 ng/dL. The highest and lowest mean values of IL-17 were observed in the mucositis and healthy control groups, respectively. But the highest and lowest mean values of IL-10 were observed in periimplantits and healthy control groups, respectively. There was a significant difference in mean values of IL- 17 and IL-10 in GCF between all three study groups ($P = 0.001$) [Table 3].

The mean value of IL-17 was significantly lower in healthy control group than periimplantitis group ($P < 0.001$), it was also significantly lower in periimplantitis group than mucositis group ($P < 001$), and it was also significantly lower in healthy control group than mucositis group ($P < 001$). Thus, the level of IL-17 was found to be significantly higher in mucositis group than other groups.

The mean value of IL-10 was significantly lower in healthy control group than periimplantitis group ($P < 0.001$), and it was also significantly lower in mucositis group than periimplantitis group (P, 0.001), and it was also significantly lower in healthy control group than mucositis group ($P < 0.001$) [Table 3].

Table 1: Subject's age and gender

Variables	Mucositis	Periimplantitis	Implants healthy	*P*
Age (mean±Sd)	46±7.092	49.33±7.89	49.33±7.89	0.31
Sex (No %)				
Men	6 (35.29)	9 (52.94)	7 (41.17)	0.53
Women	11 (64.71)	8 (47.05)	10 (58.82)	

Table 2: The average of Bleeding on Probing (BOP), Probing Depth (PD)

Variables	Mean±SD			*P*
	Mucositis	Peri-implantitis	Implants healthy	
BOP	77±16.86	85.73±13065	0±0	0.001
PD	2.53±0.64	6.02±1.12	2.10±0.80	0.01

Table 3: The average value of IL-17 and IL- 10 (ng/dl)

Variables	Mean±SD			*P*
	Mucositis	Peri-implantitis	Implants healthy	
IL-17	57.7±14.6	19.9±10.3	5.8±0.5	0.001
IL-10	38±10.3	56.5±16.4	7.7±3.03	0.001

Discussion

Periimplant inflammatory diseases are considered as the infectious diseases involving the tissues around the osseointegrated implants.[22] Following the presence of bacterial biofilm, innate and adaptive immune systems are activated, which is followed by the production and secretion of inflammatory mediators with the purpose of protection; however, tissue damage occurs subsequently. The presence and function of many of these inflammatory mediators has been proven in development of periodontal diseases; however, there is a need for further studies due to the complex network of the mediators and overlaps existing regarding their functions.[3]

According to similarities and differences between periimplant and periodontal tissues and also between periimplant and periodontal diseases, a number of studies have recently focused on the mechanisms of development and progress of periimplant diseases involving the immune system and inflammatory mediators. The results of the study by Recker *et al.*[23] in 2016 pointed to the difference

in expression level of specific biomarkers in GCF compared to that of periimplant crevicular fluid in periodontal maintenance patients, which has been considered as an critical information to be evaluated before applying these fluids as diagnostic tools.

IL-17 is a proinflammatory cytokine that plays both protective and pathogenic roles in the immune system. The most important role of IL-17 in immunity against infection is performed by influencing on neutrophils at the site of infection and activating the macrophages. Due to infectious origin of periodontal diseases, a number of previous studies have been recently focused on investigating the presence and action of IL-17 in these diseases[12]

The present study investigated the level of IL-17 and IL-10 in the periimplant diseases (mucositis and periimplantitis) and compared it with those in implants surrounded by healthy tissues. The results of the present study showed that there was a significant difference in the mean value of IL-17 and IL-10 between healthy control, mucositis, and periimplantitis groups. The findings of the study indicated that the mean value of IL-17 was significantly higher in mucositits group than the two other groups and also there was a significant increase in the mean value of IL-10 in periimplantitis group than the two other groups. No quantitative study has been done on the level of IL-17 and IL-10 in patients with mucositis and comparing it with those of healthy and periimplantitis groups in the chain of investigations carried out on the role of IL-17 and IL-10 in development of periimplant diseases. Therefore, this study was the first study conducted in this regard. However, there is a need for further researches in order to study this subject extensively. Due to the proximity of mucositis to gingivitis regarding their pathogenesis, the results of this study can be compared with the results of studies on gingivitis. The results of the current study are consistent with the results of the studies by Oda *et al*.[24] and Chitrapriya *et al*.[10] stated that the level of IL-17 was higher in gingivitis than that of periodontitis and healthy control groups. The difference in the results is attributed to the methods used in the above-mentioned studies, such that the method used in above studies was an invasive biopsy method, while in the present study, the patient's GCF sampling was done using paper point. Likewise, Mardegan *et al*.[25] showed that there was no difference in the level of IL-17 m-RNA between the healthy control and periimplantits groups, but their study investigated the level of m-RNA using real-time polymerase chain reaction (PCR) to determine the profile of IL-17 gene expression.

Considering the role of IL-17 in starting and sustaining the immune responses as well as the accumulating and activating the neutrophils and macrophages, these results are not far-fetched and they emphasized proinflammatory properties of IL-17. In case of level of IL-17 in periimplantitis, the results of the study were consistent with the results of the study by Severino *et al*. in 2011[9] conducted on 23 patients with periimplantitis. The results also reported an increase in the level of IL-17 in the GCF of patients with periimplantitis compared to the individuals with healthy implants. Furthermore, the results of the present study are consistent with the results of the studies by Darabi *et al*.[21] and Fonseca *et al*.[26] and Severino *et al*.[18] in 2016 conducted on 40 patients, showing that the level of IL-17 was significantly higher in periimplantits and mucositis groups and they hypothesized that this cytokine was also contributing to the inflammatory process observed in these disease.

In a study by Johnson *et al*.[27] in 2004, the level of IL-17 was measured in pockets with different depths around natural teeth, and the highest level of IL-17 was found in pockets with 4–5 mm depth. The results of the study showed that the level of IL-17 reduced in the presence of higher pocket depth. According to the severity of inflammation and infiltration of more inflammatory cells to the sites of infection in periimplant diseases compared to periodontal diseases, as well as considering that the present study was focused on patients with PDs of less than 4 mm in the mucositis group and since the highest level of IL-17 was observed in this group, the results of the study by Johnson *et al*.[27] can be considered somewhat consistent with those of the present study. The results of the present study showed that the average level of IL-17 reduced while changing from mucositis to periimplantitis. According to the infectious origin of inflammation in both diseases, it is suggested to study on the probability of negative feedback through dynamic mechanisms and different regulatory systems in the production of IL-17 path way.

Different regulatory mechanisms such as STAT-3 (a transcription factor that is required critically for determining the level of Interlukin-17) cells[28] have been mentioned so far for describing the role of IL-17.

Regarding the mean value of IL-10 determined in this study, it was concluded that Ghighi *et al*.[16] suggested that periimplant and periodontitis connective tissues exhibit differences in response to nonsurgical treatment and stated that IL-10 significantly increase in periimplant tissues. Casado *et al*.[29] in their research on periimplant disease stated that there was an increase in mean value of IL-10 in periimplantitis. Ata-Ali *et al*.[19] in evaluation of clinical and microbiological properties of periimplant tissues concluded that there was a significant increase in the mean value of IL-10 in periimplantitis. Likewise, Severino *et al*.[18] showed there was no significant differences in the mean value of IL-10 in periimplant disease. Andreiotelli *et al*.[30] in genetic evaluation reported that polymorphism IL-10 had no role in implant disease and failure. Such differences in results might be due to racial differences, and various type of study design, furthermore, the differences in measurement technique, and personal habits.

Since IL-17 and IL-10 is among the cytokines studied in recent years and few studies have been conducted on the

role of interleukins in the pathogenesis of periodontal diseases, and periimplant diseases in particular, therefore there is a need for further research in order to obtain definitive results in this regard.

Conclusions

A key characteristic of active periodontal and periimplant diseases is the sustained pathological elevation and activation of inflammatory biomarkers in periodontal and periimplant tissues, which are reflected in oral fluids. Moreover, inflammatory cytokines can also serve as a predictive and preventive biological tool to indicate and time preventive intervention.

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Conflicts of interest

There are no conflicts of interest.

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