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Research Article

Salivary Interleukin-33 Level Decreases Following Non-Surgical Periodontal Treatment Through Scaling and Root Planning in Moderate Chronic Periodontitis

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Abstract

Periodontitis is a multifactorial inflammatory disease associated with alveolar bone degeneration. Few studies have investigated the effect of scaling and root planning on the levels of inflammatory cytokines in the saliva in patients with chronic periodontitis. Interleukin-33 (IL-33) has been recently identified as a relatively novel pro-inflammatory cytokine that plays an important role in the pathogenesis of periodontitis. IL-33 acts intracellularly as a nuclear factor and extracellularly as a cytokine. The present study was carried out to investigate the effect of non-surgical periodontal treatment on the salivary IL-33 level in relation to clinical parameters. Forty-eight subjects including 24 cases with Moderate Chronic Periodontitis (MCP) and 24 healthy subjects were included in this case-control study. Non-inoculated salivary samples were collected before and eight weeks after non-surgical periodontal treatment. Then, the salivary level of IL-33 was measured using ELISA. A statistically significant difference was found in the salivary levels of IL-33 between healthy subjects and patients with MCP ($P = 0.03$). The salivary level of IL-33 was 600.4 ± 44.6 and 479.4 ± 44.6 pg/ml before and after treatment in the MCP group ($P = 0.02$). There was a significant difference in PI, GI, BOP, and CAL before and after treatment in the MCP group ($p<0.001$). The correlation between the salivary IL-33 level and periodontal indices revealed that increased IL-33 levels increase the CAL and attachment loss in the MCP group ($P=0.001$). It is suggested that the IL-33 level decreases after non-surgical periodontal treatment. IL-33 is associated with the severity of periodontal disease and the degree of the success of non-surgical periodontal treatment. IL-33 may be an encouraging therapeutic target in MCP in the future.

Keywords: Interleukin-33; Chronic periodontitis; Saliva; Periodontal treatment

Abbreviations

IL33: Interleukin 33; PI: Plaque Index; GI: Gingival Index; BOP: Bleeding On Probing; CAL: Clinical Attachment Loss

Introduction

Periodontitis is a multifactorial inflammatory disease characterized by the production of periodontal envelopes and irreversible degeneration of collagen fibers and other components of the alveolar bone around the tooth [1]. Environmental factors, microbial agents, genetic factors, lifestyle, and the host immune system play a key role in the development and progression of periodontitis. Geographically, periodontitis is more frequent in Asian countries, and the rate of infection is also higher in men [2-4]. The importance of periodontal treatment is due to the association between periodontitis and diseases such as diabetes mellitus, angina pectoris, cerebrovascular disease, and rheumatoid arthritis [4]. Regarding its progression, periodontitis is classified into two categories of chronic and invasive according to the activity of the immune system against anaerobic gram-negative microorganisms/bacteria. The imbalance in immune responses may be due to genetic factors, systemic diseases, age, sex, and tobacco use or cigarette smoking. Therefore, exacerbation of the host inflammatory responses results in damage to the connective tissue [4,5].

Cytokines are low-molecular-weight polypeptide proteins produced in response to germs and pathogens that have a specific effect on the interactions and communications between cells. Destructive and protective roles of cytokines in periodontitis are well knowns. The role of IL-1, IL-6, and TNF-α cytokines in the inflammation process has been well established. Inflammatory cytokines contribute to bone resorption and formation directly and indirectly [6,7].

IL-33 is a relatively new member of the IL-1 superfamily of cytokines that is expressed by epithelial and endothelial cells and has been described as an inducer of T helper 2 immune responses. IL-33 binds to the ST2 ligand. ST2 is a member of Toll-like IL1 superfamily. IL-33/ST2 may lend itself to the finding of novel therapeutic targets for the treatment of diseases such as asthma, rheumatoid arthritis, atherosclerosis and heart failure [8]. IL-33 is known as a cytokine with a dual function, acting both intracellularly and extracellularly. The intracellular type of IL-33 acts as a pro-inflammatory cytokine. IL-33 is continuously produced by gingival epithelium, and its expression

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increases in response to Porphyromonas gingivalis causing a shift in immune responses towards Th2 cells exacerbating inflammatory conditions [9,10]. Previous studies found an association between some cytokines such as IL-36, IL-33 IL1,IL-6 and TNF-α and the pathogenesis of periodontal disease [2,4,6,9].

Some researchers found that cytokine inhibitors such as inhibitors of IL-1β and TNF-α were effective in improving chronic periodontitis and reducing tissue destruction [11], Few studies reported the effect of scaling and root planning on the levels of inflammatory cytokines in Gingival Crevicular Fluid (GCF) in patients with chronic periodontitis [12,13]. IL-33 is an effective and pro-inflammatory cytokine in the expression of RANKL (Receptor Activator Of Nuclear Factor Kappa-B Ligand) and bone resorption. IL-33 can induce osteoclasts and bone resorption via RANKL. This cytokine is secreted from damaged cells and stimulates degrading signals of the host immune system during infection [10].

Increased levels of IL-33 have been reported in the Gingival Crevicular Fluid (GCF) of patients with invasive periodontitis compared to healthy subjects. A positive correlation has been found between the IL-33 level and the Gingival Index (GI), Periodontal Index (PI), and Bleeding on Probing (BOP). High levels of IL-33 expression and its ST2 receptor have been reported in the gingiva of patients with chronic periodontitis [14]. Mendonca, et al. found that increased IL-33 levels in the saliva of patients with lupus erythematosus and chronic periodontitis indicating the progression of the inflammatory line of the disease [15]. It is now possible to use some salivary biomarkers for disease screening. It seems that nonspecific inflammatory salivary markers may not be used for diagnosis of any specific diseases but it has been reported that the levels of these markers increase in systemic inflammatory diseases [15,16].

It seems that the use of the saliva for measuring the IL-33 level is an easy, inexpensive, and non-invasive method [13]. The saliva contains inflammatory mediators that play a major role in oral health [17].

Therefore, the aim of this study was to evaluate IL-33 levels in saliva samples before and after non-surgical periodontal treatment and to compare its levels with healthy subjects.

Materials and Methods

Subjects

This case-control study was conducted in two groups of subjects, one with Moderate Chronic Periodontitis (MCP) and the other without the disease as control group, who presented to the School of Dentistry from April to October 2018. The case group included 24 subjects with MCP based on definition presented by the American Academy of Periodontology [18]. The control group included 24 healthy subjects without MCP who had no systemic diseases, did not receive any medications, and had healthy gingiva. Individuals with a history of smoking, pregnancy, systemic diseases such as diabetes, rheumatoid arthritis, chronic inflammatory diseases, cardiovascular disease, multiple sclerosis, systemic bacterial and viral diseases and subjects that used antibiotics, anti inflammatory agents or immunosuppressant drugs within the past 6 months were excluded due to their possible roles in the immune or inflammatory response. In addition, individuals with a history of invasive periodontal surgery who underwent periodontal treatment and antibiotic therapy or used Non-Steroid Anti-Inflammatory Drugs (NSAID) in the last 6 months were also excluded from the study. The subjects in the control and case groups were matched in terms of age and sex. The Research Ethics Committee of Babol University of Medical Science approved this study according to the Declaration of Helsinki.

Periodontal examination

The entire protocol was explained to the patients at the beginning of the treatment and informed consent was obtained from all of them. Periodontal probing (CP11; ASA Dental, Bozzano Massarosa, Italy) was performed and a periodontal chart was prepared. The probe was used parallel to the long axis of the teeth at six sites per tooth for each patient (mesiobuccal, buccal, distobuccal, mesiolingual, lingual, and distolingual). The periodontal status was evaluated by measuring periodontal indices such as the Gingival Index (GI), Clinical Attachment Loss (CAL), bleeding on probing (BOP), and plaque index (PI) [12,19]. Clinical examination was performed by an experienced examiner. Individuals with chronic periodontal disease had at least 20 teeth. The control group consisted of healthy subjects with a BOP value of less than 20%, a probing depth of less than 3 mm, and no clinical attachment loss. The case group included patients with chronic periodontitis, clinical attachment loss of 3-4 mm, and BOP value of more than 80%. BOP positivity was considered as an objective sign of gingival inflammation. CAL was measured using a graduated probe as the distance (mm) between the cemento-enamel junction and gingival margin [12].

Treatment through scaling and root planning and saliva collection.

Sample collection

One milliliter of un-stimulated saliva was collected from healthy subjects and patients before treatment during early hours between 8-10 am. The subjects were advised to avoid eating, drinking, and oral hygiene for two hours prior to saliva collection. Standard non-surgical treatment including gingival scaling was performed to remove biofilms, dental plaques, periodontal pathogens and debris using the Cavitron Plus Ultrasonic Scaler (woodpecker, DTE-D5, China) at 50 KHz. The subjects were then educated for dental health and saliva samples were collected again after eight weeks [12].

Cytokine assay

The saliva samples were centrifuged at 2000 g for 10 minutes at 4°C and the supernatant was used to measure the IL-33 level. The level of IL-33 was measured in the salivary samples using the human IL-33 ELISA kit (Shanghai Crystal Day Biotech Co., Ltd, China) according to the manufacturer's instructions. The intra-assay and inter-assay CV (%) of the IL-33 ELISA kit was < 8% and < 10%, respectively.

Statistical analysis

The data were analyzed using the GraphPad Prism v 6.07 (GraphPad Software Inc., La Jolla, CA, USA). The two groups were adjusted with respect to age and gender, so that these two factors would not affect the results. The results are expressed as the mean ± SEM. Mann-Whitney, Wilcoxon, and chi-square tests were used to compare different parameters between the two groups. In addition, Pearson correlation test was applied to investigate correlations was evaluated. P values less than 0.05 were considered significant.

Table 1: Demographic data of control (healthy) and case (MCP) groups.

Groups	Case (MCP)	Control	P value
Number	24	24	-
Sex (Male/Famale)	13 (%54/2)/ 11 (%45/8)	11 (%45/8)/ 13 (%54/2)	0.56
Age (Mean±SD)	38.6 ± 11.2	37.6 ± 15.2	0.2

Results

Demographic information of subjects

Of 48 subjects who were studied in this research, 24 subjects with MCP and a mean age of 38.6 ± 11.2 years (13 males and 11 females) constituted the case group and 24 subjects without MCP and a mean age of 37.6 ± 15.2 years (11 males and 13 females) comprised the control group. The study population was adjusted in terms of age and gender. The demographic characteristics of the subjects are presented in Table 1.

Significant decrease of IL-33 following treatment with scaling and root planning

There was a significant difference (p = 0.008) in the level of IL-33 between the control (467.1 ± 43.7 Pg/ml) and case group (600.4 ± 44.6 ng/ml). As shown in Figure 1, scaling and root planning significantly (p = 0.02) decreased the IL-3 level to 479.4 ± 44.6 Pg/ml.

Significant difference in PI, GI, BOP, and CAL before and after treatment in MCP group

There was a significant difference in PI, GI, BOP, and CAL before and after treatment in the MCP group (p<0.001) (Table 2).

Table 2: Mean values (±SD) of Plaque Index (PI), Gingival Index (GI), Bleeding On Probing (BOP), attachment loss level (AL), and total amount of IL-33 in MCP group. *Significant difference was observed before and after treatment (P<0.001).

	Before treatment (n=24)	After treatment (n=24)
PI	2.4±0.5	1.1± 0.3
GI	2.1±0.4	0.9±0.5
BOP	3.1±2.2	1.8±1.6
AL	7.2±3.1	4.1±1.1
IL33	600.4±44.6	479.4±44.6 Pg/ml

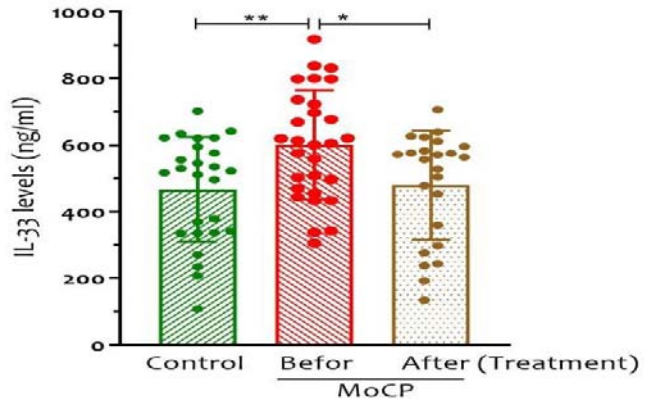

Figure 1: Comparison of salivary IL-33 levels before and after treatment in MCP group and IL-33 level in control group. * P < 0.05. IL-33 level was higher in MCP than control group. (p=0.03) IL-33 level decreased after non-surgical periodontal treatment (p=0.02).

Significant association of IL-33 with MCP development

As shown in (Figure 2A), linear regression analysis showed a significant increase in CAL (p = 0.001) with an increase in the IL-33 concentration in the MCP group. Although BOP (Figure 2B) and PI (Figure 2C) increased with an increase in IL-33 level, the difference was not statistically significant (p = 0.29 and p = 0.47, respectively).

Discussion

The results of this study showed that the pre- and post-treatment IL-33 levels were higher in moderate chronic periodontitis patients compared to the healthy subjects, indicating that IL-33 could intensify bone resorption. It might be possible in the future to prevent the progression of periodontal disease by preventing its function. IL-33 is a multifunctional pleiotropic cytokine that induces osteoclast activity and prompts NF-kB ligand (RANKL). It has a positive role in controlling osteoclastogenesis. Previous studies found that the IL-33 levels were higher in patients with rheumatoid arthritis compared to control the group and reported that it had a positive correlation with bone erosions [20,21]. The results of the present study were consistent the findings regarding rheumatoid arthritis [20].

The present study found that non-surgical periodontal treatment reduced the IL-33 level. It is suggested that non-surgical periodontal treatment may be effective in preventing and/or controlling periodontal diseases; however, this treatment may not completely eliminate all of the pathogenic microorganisms [22]. In the present study, the IL-33 level reduces 8 weeks after Scaling and Root Planning (SRP). The results of previous studies are conflicting; some studies found a decrease in pro-inflammatory cytokines in the saliva after SRP or GCF [23,24] while some other studies found that SRP did not significantly reduce the levels of pro-inflammatory cytokines [25,26].

SRP is a straightforward and noninvasive technique. Periodontal indices are invariable and thus indicate the disease history rather than the present disease activity. Measurement of pro-inflammatory cytokines using ELISA can identify and assess the response to periodontal treatment [27]. Oh, et al. found that PPD and BOP improved significantly 2 and 4 months after SRP and named PPD and BOP gingival inflammation markers. In the present study, SRP reduced PI, GI, BOP, and gingival recession but the periodontal index was higher in MCP patients before and after SRP compared to healthy controls.

Although SRP treatment is effective in decreasing the clinical parameters, it is insufficient in treatment for patients who are highly susceptible to periodontitis and suffer from systemic inflammatory diseases related to periodontitis. It is suggested that some adjuvant therapies such as well-developed cytokine-targeted therapies have irreplaceable effects [22].

The present study found a positive correlation between the IL-33 level and CAL. Although BOP and PI increased with an increase in the IL-33 level, the differences were not statistically significant. A larger sample size may produce more accurate results. Wilton, et al. found no significant correlation between the IL-1β level, GCF volume, and the clinical characteristics [28].

Saglam, et al. comparatively investigated the IL-33 level in the saliva, plasma and gingival crevicular fluids of patients in three groups

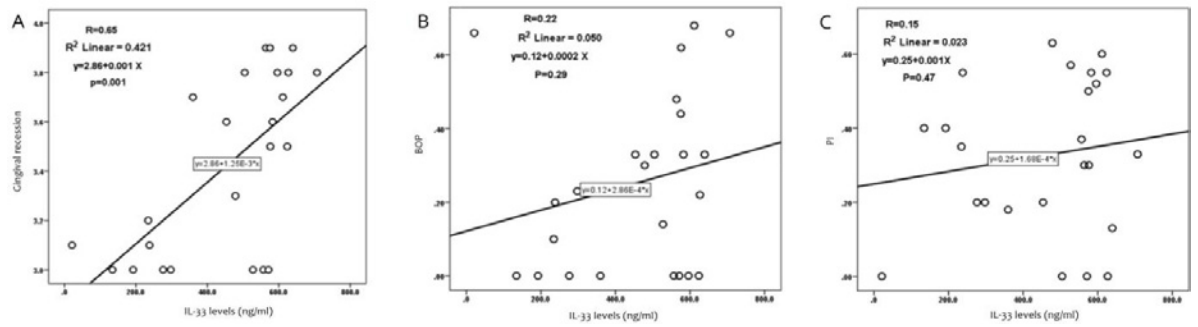

Figure 2: Analysis of IL-33 levels of MCP patients with (A) gingival recession, (B) BOP and PI. There was a significant correlation between IL-33 levels and gingival recession (CAL), whereas no significant correlation was observed between IL-33 and BOP and PI.

including chronic periodontitis (n=20), gingivitis (n=20), and healthy controls (n=20). They found higher levels of total amount of GCF IL-33 in gingivitis and CP groups compared to the control group. The level of IL-33 in the GCF also had a positive correlation with BOP, GI, and PI [29]. None of the previous studies measured the IL-33 level before and after non-surgical periodontal treatment, and it seems that the results of the study by Saglam, et al. [29] support the findings of the present study. This study only found a positive correlation between IL-33 level and CAL. Laperine, et al. found a positive correlation between the IL-33 level and RANKL in moderate chronic periodontitis and suggested that IL-33 level could be considered an extracellular alarming signal that reveals pro-inflammatory properties of bone resorption induced by Porphyromonas gingivalis [10].

In line with the results of this study, da luz, et al. [30] and Malcolm, et al. [31] also reported the role of IL-33 in bone homeostasis, osteoclastogenesis, and bone resorption in periodontitis. However, Buduneh, et al. found no difference in the plasma or salivary levels IL-33 between healthy subjects and MCP while the IL-33 level was lower in GC of the patients with chronic periodontal disease [9]. The reduction in the IL-33 level in the present study, which was observed after non-surgical periodontal treatment in chronic moderate periodontitis group, seems to be associated with a decrease in the activity of microorganisms leading to decreased activity of the immune system and defense reactions of the host.

IL-33 plays two roles in inflammation depending on the disease and the model. IL-33 is a pro-inflammatory cytokine in periodontitis and an anti-inflammatory cytokine in cardiovascular diseases such as atherosclerosis, obesity, and type 2 diabetes [32].

Kursunlu, et al. reported that IL-33 levels were similar in chronic and invasive periodontitis, gingivitis, and healthy gingiva. They discussed that IL-33 was not effective in the pathogenesis of periodontal disease [2].

The differences between the results of the present study and the findings of other studies may stem from the differences in the type and severity of periodontal disease, age, sample type (salivary, gingival, crevicular fluid), the temperature at which the samples were stored, applied methods, geographic region, genetic factors, time of sample collection, and sample size.

We measured the IL-33 level eight weeks after non-surgical periodontal treatment. Cardoso, et al. investigated the cytokine levels 10 to 14 weeks after treatment [33]. Reis, et al. collected saliva specimens eight weeks after non-surgical treatment of periodontitis [12]. The time of sample collection is the present study was similar to the study by Reis, et al. [12] and different from the study performed by Cardoso, et al. [32]. Oh, et al. measured the IL1 level in the GCF 2 and 4 months after SRP [27]. Pro-inflammatory cytokine such as IL-1, TNF, IL-6, and IL-33 are necessary for the initiation of the inflammatory immune reaction [34]. Therefore, it is suggested that measurements of these cytokines are more accurate eight weeks after non-surgical periodontal treatment.

The limitations of the present study were its small sample size and not investigating other cytokines and other parameters. Further human studies with larger sample sizes are required to investigate the correlation between other cytokines and IL-33 in MCP.

Conclusion

It seems that the IL-33 level decreases after non-surgical periodontal treatment. IL-33 is associated with the degree of success in nonsurgical periodontal treatment. IL-33 may be a promising therapeutic target in chronic moderate periodontitis. Blocking the activity of pro-inflammatory cytokines may play a role in stopping inflammatory bone resorption.

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