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Evaluation of Pentraxin-3 and Interleukin-6 Levels in Serum and Gingival Crevicular Fluid in Patients with Generalized Periodontitis and Periodontal Health Controls before and after Scaling and Root Planing

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A B S T R A C T

Objectives: Pentraxin-3 (PTX3) and interleukin-6 (IL-6) are two of the most important inflammatory cytokines produced by cells in periodontal tissues. The present study aims to evaluate the levels of PTX3 and IL-6 in serum and gingival crevicular fluid (GCF) in patients with generalized periodontitis stages II and III, grades A and B, and periodontal health individuals before and after scaling and root planing (SRP).

Materials and Methods: In this study, 22 patients with periodontitis (12 males and 10 females) and 22 periodontal health controls (11 males and 11 females) were selected. All patients underwent full-mouth SRP. Serum and GCF samples were collected before and one month after SRP. PTX3 and IL-6 levels in serum and GCF samples were evaluated by enzyme-linked immunosorbent assay. Data analysis was performed using Mann-Whitney U and Wilcoxon tests ($P<0.05$).

Results: Serum levels of PTX3 were significantly higher in the periodontitis group than the controls ($P<0.05$). GCF PTX3 levels and serum and GCF IL-6 levels were not significantly different between the groups. Furthermore, this study did not show any significant changes in the levels of these cytokines before and after SRP.

Conclusion: Among the studied cytokines and media, only serum PTX3 levels showed a significant difference between periodontitis patients and healthy controls and could serve as a diagnostic marker of periodontal inflammation. SRP did not affect the levels of these cytokines, suggesting that other inflammatory factors may be involved in disease process. However, additional longitudinal prospective studies are needed to confirm these results.

Keywords: Periodontitis; Interleukin-6; Pentraxin 3; Gingival Crevicular Fluid; Serum

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INTRODUCTION

Periodontitis is an infectious and inflammatory disease caused by microbial plaque, genetic and environmental factors, the main cause of which

is the presence of periodontal microorganisms. Host mediators secreted in response to periodontal pathogen-derived endotoxins are involved in destroying periodontal tissues, including cytokines, prostaglandins, matrix metalloproteinases, and acute-phase proteins [1]. Pentraxins are a type of acute-phase protein that have been conserved during evolution in different species and are considered inflammatory markers [2]. Pentraxin 3 (PTX3) is a long pentraxin that plays an important role in innate immunity, regulating inflammatory challenges, and clearing apoptotic cells. Cells in periodontal tissues, such as neutrophils, fibroblasts, monocytes/macrophages, dendritic cells, epithelial cells, endothelial cells, and vascular smooth muscle cells, produce it [3]. Rapid and significant increases in PTX3 blood levels, as an acute phase protein, have been reported under various infectious and inflammatory conditions such as endotoxic shock, sepsis [4], atherosclerotic lesions, coronary artery disease, small vessel vasculitis, rheumatoid arthritis, and chronic kidney disease [5]. Today, PTX3 is considered a potential marker for detecting the active stage of diseases due to the relationship between its serum level and the severity of some pathological conditions [6]. Due to the infectious and inflammatory nature of periodontitis, PTX3 may also play a role in the pathogenesis of this disease. In response to inflammatory cytokines (such as IL-1β and tumor necrosis factor α), PTX3 is produced by different cells of periodontium [7]. A recent study identified gingival crevicular fluid (GCF) levels of PTX-3 as a diagnostic marker of inflammatory activity in periodontitis [8].

Interleukin-6 (IL-6) is one of the cytokines that play an important role in initiating and maintaining inflammation and immune responses [9]. It is a multifunctional cytokine responsible for regulating acute phase protein synthesis and is extensively studied as a periodontal inflammatory marker [10]. This cytokine is produced by various cells such as monocytes [11], fibroblasts [12], osteoblasts [11], and vascular endothelial cells [13] in response to inflammatory challenges. It plays an important role in the differentiation of B cells and the proliferation of T cells [14]. Synergistically with IL-1β, it induces bone resorption [15]. IL-6 even appears to induce C-reactive protein synthesis [16]. On the other hand, it has been reported to increase the production of tissue matrix metalloproteinase inhibitors [17], suppress IL-1 expression, induction of IL-1Ra [18], and release of soluble tumor necrosis factor (TNF) receptors [19], which are some of its anti-inflammatory properties [20]. One study showed that periodontitis significantly affected the serum levels of systemic inflammatory markers and non-surgical periodontal treatment resulted in a decrease in the levels of these inflammatory markers [21]. Several studies have also suggested the essential role of IL-6 along with TNF-α in the progression and severity of periodontitis [22]. IL-6 has also been shown to increase even with mild periodontal attachment loss, making it a useful biomarker to detect active pockets. However, the use of cytokines for the differential diagnosis of periodontal disease is still controversial [23]. Considering the inflammatory potential of these cytokines and due to the minimal number of studies on PTX3 as a diagnostic biomarker for periodontitis, this study was designed to evaluate the levels of PTX3 and IL-6 in serum and GCF in patients with generalized periodontitis and periodontal health individuals before and after scaling and root planing (SRP). We assume that GCF and/or serum levels of IL-6 and PTX3 may help distinguish inflammatory conditions.

MATERIALS AND METHODS

This prospective cohort study was conducted between October 2018 and February 2019 on patients attending the Periodontology Department of Tehran University of Medical Sciences. Thirty-two subjects with untreated generalized periodontitis stage II and III grades A and B (according to the American Academy of Periodontology/European Federation of Periodontology 2018 classification system) [24] and 27 periodontally healthy subjects, were included. In the 2018 classification of periodontal disease, a multidimensional

staging and grading system was introduced to sub-classify periodontitis disease entities. The severity of periodontal disease at the time of presentation and the complexity of disease management dictates the staging, while grading offers additional information, including the rate of past disease progression and the risk of future progression. A comprehensive medical history was taken and individuals with a history of certain diseases or conditions including diabetes mellitus, heart disease, hepatitis, immunological diseases, taking corticosteroids, receiving periodontal treatment, or treatment with broad-spectrum antibiotics in the past three months, smoking, alcoholism, pregnancy, and breast-feeding were excluded from the study [25]. Finally, the study included a total of 44 cases, with 22 cases in each group.

Periodontitis patients were defined by periodontal pocket depth (PPD)>4mm with bleeding on probing (BOP) or PPD≥6mm [24]. PPD was measured from the free gingival margin to the base of the probable pocket. BOP is supposed positive if it occurred within 15 seconds after periodontal probing. The periodontal health cases had no inflammation (BOP<10%) and no evidence of clinical attachment and bone loss (CAL).

This study was approved by the Ethics Committee of the Dental Research Center of Tehran University of Medical Sciences (code: IR.TUMS.DENTISTRY.REC.1397.090). Informed consent was obtained from all participants before inclusion in the study.

GCF Sampling:

In this study, three sampling sites were chosen for each patient. For patients with periodontal disease, the periodontal pockets with the highest attachment loss were selected. In the control group, the sites were selected randomly. To minimize the risk of contamination of GCF samples, teeth were carefully cleaned with a cotton pellet and the intended area was isolated using cotton rolls and air-dried. A sterile paper strip (Proflow Inc., Amityville, NY, USA) was placed inside the sulcus until minimal resistance was felt and left there for 30 seconds. Three GCF samples were collected from each area. Paper strips contaminated with blood or saliva were excluded. The samples were then transferred to microtubes containing 500µl phosphate-buffered saline and 0.1% bovine serum albumin. Afterward, the tubes were centrifuged at 8,000rpm for 5 minutes. The collected samples were then transported to the laboratory at -15°C and stored at -80°C.

Serum Sampling:

Blood samples (5cc) were collected from the antecubital vein using a 20-gauge needle. The isolated serum was obtained by blood centrifuge at 1,000rpm for 15 minutes and immediately transferred to a plastic vial and stored at -80°C.

Supra- and sub-gingival scaling and root planing (SRP) were performed in a single session by a periodontist. Oral hygiene instructions were given to all patients. One month after completing SRP (according to Mathew's study [26]), patients were asked to come back for recall. GCF and blood samples were taken and centrifuged again with the same method and prepared for storage.

Measurement of PTX3 and IL-6 in GCF and Serum Samples:

Serum and GCF PTX3 and IL-6 levels were measured using an enzyme-linked immunosorbent assay (ELISA) kit (Human PTX3 ELISA Kit, RK02168, ZellBio GmbH, Germany and Human IL-6 ELISA Kit, RK00004, ZellBio GmbH, Germany).

Standard samples were added to the well according to the manufacturer's protocol and a biotin-conjugated anti-cytokine antibody was added. The wells were covered and incubated at room temperature (18-25°C) for 2 hours. Afterward, the wells were washed six times with buffer and streptavidin-HRP solution was added to all wells and incubated for 1 hour at room temperature. The solution was drained and washed six times with a buffer. Then TMB (3,3',5,5'-Tetramethylbenzidine) color-developing solution was added and the microplate was incubated for 10 minutes at room temperature and in a dark place. Finally, a stop solution was added, and the Elisa Reader read the optical absorption of all wells at 450nm. The assays were performed in triplicate.

Calculation of sample size and statistical analysis:

The minimum sample size was calculated to be 10 patients for each group (n=10 in control and test groups) according to a previous study by Fujita et al. [25] by assuming alpha=0.05, beta=0.197. A total of 44 cases (n=22 for each group) were included in this study.

The results were presented as mean ± standard deviation (SD). For non-parametric variables, group comparisons were made using the Mann-Whitney U test. Additionally, the Wilcoxon test was used to conduct pairwise comparisons to identify the pair or pairs that were different. If the P-value was less than 0.05, it was considered statistically significant.

RESULTS

The mean±standard deviation and male to female ratio were 55±7 and 12/10 in the periodontitis group, and 49±5 and 11/11 in the controls, respectively. Clinical parameters and Elisa results of the study population are presented in Table 1.

PPD, CAL and, plaque index (PI) recordings were significantly higher in periodontitis patients than in the healthy group. Also, significant differences existed in these parameters before and after treatment.

Mann-Whitney U test for two independent samples showed that serum levels of PTX3 were significantly higher in the periodontitis group (P<0.001). However, there were no significant differences in GCF and serum IL-6 and GCF PTX3 levels between the two groups. Furthermore, no statistical differences were found in the levels of these cytokines before and after SRP.

DISCUSSION

The present study evaluated GCF and serum levels of PTX3 and IL-6 in patients with generalized periodontitis stage II, III grade A, B, and periodontal health individuals before and after SRP. Our study suggests that Serum PTX3 levels could serve as a valuable inflammatory biomarker for periodontitis. However, we found no statistically significant difference in GCF levels of PTX3 between periodontal patients and the control group. Similarly, there was no significant difference in serum and GCF levels of IL-6 between the two groups. Moreover, SRP did not have any impact on the levels of these cytokines. Changes in oral microflora, as seen in periodontitis, affect the inflammatory profile [27]. The plasma level of PTX3 rises during a wide range of pathological conditions from infections to autoimmune and degenerative disorders [8]. Measurement of GCF or plasma PTX3 levels might help identify patients at a higher risk of developing degenerative disease or even patients in the early stages of periodontitis [8]. Our study found a significant difference in PTX3 serum levels between periodontal health cases and patients with periodontitis.

Temelli et al. [28] also demonstrated a positive correlation between serum PTX3 levels and the periodontal inflamed surface area. Pradeep et al. [29] reported that the PTX3 levels in GCF were significantly higher in patients with chronic periodontitis compared to healthy controls. They suggested that GCF PTX3 levels could be an indicator of inflammatory activity in periodontitis. However, in the present study, the results

Table 1. Clinical periodontal measurements and ELISA results of the study groups (N=22 in each group)

Study groups		Periodontal parameters			Biomarkers			
					Serum		GCF	
		PPD (mm)	CAL (mm)	PI (%)	IL-6 (pg/L)	PTX3 (pg/L)	IL-6 (pg/L)	PTX3 (pg/L)
Periodontitis	Before treatment	5.6±2.01*	4.4±0.96*	80.92±6.6#	100.96±45.51	9.48±3.17$	18.02±8.61	0.32±0.17
	1 month after	3.8±2.15	3±1.88	60.3±8.2	80.46±22.86	5.33±5.66	17.88±9.32	0.25±0.14
Controls		1.7±0.45	0	45.5±5.27	76.31±24.57	1.73±0.45	30.49±18.61	0.36±0.37

PPD: periodontal pocket depth. CAL: clinical attachment and bone loss. PI: plaque index. PTX3: Pentraxin-3.
* P=0.02; # P=0.007; $ P≤ 0.05
All data are reported as mean±standard deviation.

indicated that the PTX3 levels in GCF were not significantly higher in diseased sites in periodontitis patients compared to periodontal health sites in healthy individuals. This difference in results could be attributed to the varying sample sizes and ages of the participants in the Pradeep study, which included 15 individuals with chronic periodontitis and 10 healthy controls between the ages of 23 and 50. As mentioned in a review study by Brüünsgaard [30], age is the determining factor in the status and fluctuations of inflammatory cytokines. In contrast to our study, Fujita et al. [25] concluded that the PTX3 levels in GCF were significantly higher in periodontitis sites than in periodontal health sites in patients with chronic periodontitis. The differences observed between the two studies may be due to the larger sample size in the Fujita study (50 healthy and periodontitis sites in 50 chronic periodontitis patients). On the other hand, in Fujita's study, both healthy and non-healthy samples were taken from one person. However, in the present study, healthy samples were taken from completely healthy individuals, and non-healthy samples were taken from a person diagnosed with periodontitis. According to Keles et al. [31] found that PTX3 levels in the gingival tissue of mice with induced periodontitis were significantly higher than in the healthy group. However, unlike our study, serum PTX3 levels were not significantly different between the patient and healthy models.

Folwaczny et al. [32] showed that the PTX3 gene expression was significantly lower in periodontitis patients compared to healthy subjects. However, their study evaluated the PTX3 gene expression using real-time PCR in biopsies of gingival tissues, while the present study evaluated protein expression in GCF and serum. PTX3 levels in saliva, according to Gümüş et al. [33], like PTX3 levels in GCF, according to ours, were similar in the periodontitis group and control groups.

In contrast to our study, Gheorghe et al. [34] demonstrated a decrease in GCF PTX3 levels three months after non-surgical periodontal treatment in 15 chronic hepatitis C patients with periodontitis and 17 patients with periodontitis. Similarly, Tasdemir et al. [35] found a significant reduction in GCF PTX3 levels three months after non-surgical periodontal treatment along with adjunctive ozone therapy. The study was conducted on 36 patients aged between 18 to 64 years, who had moderate to severe generalized periodontitis.

Periodontitis is episodic with destruction and remission periods. During the destruction period, host proinflammatory cytokines act as mediators of tissue degradation. This leads to an inflammatory response in the periodontium, which stimulates bone resorption and the induction of tissue-degrading proteases [36]. Elevated levels of PTX3 in some samples may be associated with destruction periods of the disease.

Keles et al.'s study [37], indicated a significant difference in serum and GCF levels of IL-6 between severe chronic periodontitis and healthy subjects. Each group consists of 15 patients aged 25 to 55 years. However, the present study did not find any significant differences in this factor. On the other hand, Yaghobee et al.'s study [38], found significant differences in the levels of IL-6 in GCF around implants with peri-implantitis compared to healthy implants and teeth.

Gani et al. [22] conducted a study which revealed that there were no significant differences in IL-6 levels between healthy subjects, those with generalized chronic periodontitis, and those with localized chronic periodontitis. This finding is consistent with the results of our study. The concentration of IL-6 does not seem to be a reliable indicator of periodontal degradation, as confirmed by Goutoudi et al. [39] study. A study conducted by Marcaccini et al. [40] revealed that early periodontal treatments were able to cause a significant decrease in IL-6 levels. however, some studies have not been able to confirm the existence of such a significant difference. [21] Likewise, there were no significant differences in the levels of this factor before and after treatment in the present study.

It has been observed that IL-6 has a dual role in the inflammation process, with both inflammatory and anti-inflammatory

properties. This cytokine plays an important role in inflammatory processes synergistically with IL-1β. On the other hand, it has been reported that it can increase the production of anti-inflammatory mediators such as tissue inhibitors of matrix metalloproteinases (TIMP) and interleukin 1 receptor antagonists (IL-1Ra). Therefore, there may be differences in the results of studies conducted at a particular time on specimens, as changes in the level of IL-6 during the process of inflammation and repair are normal. As a result, it is difficult to accurately interpret the findings of the present study and similar studies, which are cross-sectional.

There were some limitations and shortcomings in this study, including a small sample size which, although slightly higher than estimated from previous studies, did not reveal any significant differences between some parameters. The one-month follow-up period, based on previous studies, may not be sufficient to improve the inflammatory profile of patients. It is important to note that the study has a cross-sectional design, which may pose a limitation. It is recommended to collect samples from both healthy and periodontitis-infected areas within the same patient. various factors including smoking, systemic disease, oral hygiene, age, sample size, periodontal disease severity, and study duration can impact the outcomes.

CONCLUSION

According to our study, Serum PTX3 levels were significantly higher in patients with periodontitis. However, there was no significant difference in the levels of PTX3 in GCF between patients with periodontitis and healthy individuals. Therefore, serum PTX3 levels might be a more useful diagnostic marker for periodontal disease than GCF PTX3 levels, particularly as an early diagnostic marker of inflammation in clinically healthy tissues. Levels of IL-6 in both serum and GCF were not significantly different between the two groups. Moreover, the levels of these cytokines were not affected by non-surgical periodontal treatment. Periodontal disease can alter the inflammatory profile of GCF and serum, although these changes may not always be consistent with the extent of destruction, and the differences in levels of inflammatory factors between healthy and diseased individuals may not always be statistically significant. Early periodontal treatment can help to reduce the inflammatory profile of the GCF and serum by reducing local factors, leading to a decrease in the clinical signs of periodontal disease, although these changes in the level of inflammatory factors may not necessarily be significant.

It is necessary to conduct additional studies with larger sample sizes, more follow-up sessions, and matched sampling between healthy and periodontitis groups in terms of age and sex. Systematic review studies and meta-analyses should also be conducted to summarize the results of previous studies. These efforts will help us achieve definitive results that can be generalized to a wider range of patients.

CONFLICT OF INTEREST STATEMENT

The authors have no commercial association (e.g., consultancies, stock ownership, equity interests or patent licensing arrangements) that might pose a conflict of interest in connection with the submitted article.

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