Original Article

Association Between Psychological Stress and Stimulation of Inflammatory Responses in Periodontal Disease

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Abstract

Objective: Based on the evidence regarding the relationship between inflammatory processes and stress responses, the present study investigated the association between psychological stress and elevation of inflammatory mediators related to periodontal disease in adult patients.

Materials and Methods: The study consisted of 50 patients including 25 patients with chronic periodontitis and 25 cases with aggressive periodontitis. Twenty-five healthy subjects without any evidence of periodontal disorder were also randomly selected as the control group. The clinical parameters including plaque index (PI), bleeding on probing (BOP), probing depth (PPD) and clinical attachment loss (CAL) were recorded and GCF samples were collected for analysis of GCF contents of IL-6 and IL-1β levels. The Kettle stress questionnaire was also used to determine stress severity.

Results: IL-1β was significantly higher, but IL-6 was only slightly higher(marginal p-value=0.058)The median score of stress was higher in aggressive periodontitis than the chronic disorder and also in the two periodontal disease groups than the healthy subjects. Among studied clinical parameters, CAL and PPD were positively correlated with the GCF IL-1β level. No significant correlations were found between clinical parameters and GCF IL-6 level. There were strong positive relationships between stress severity and in both aggressive and chronic periodontitis; however stress did not influence GCF contents of IL-6.

Conclusion: Psychological stress has a pivotal role in the stimulation of inflammatory processes via IL-1β increase in aggressive and chronic periodontitis.

Key Words: Periodontitis; Stress; Cytokines; Interleukin-1α

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INTRODUCTION

It has been well known that periodontal diseases may be commonly accompanied with some clinical events including soft tissue inflammation and bone loss. Some recent investigations have shown that the inflammatory process of cytokines released by monocytes and macrophages in response to bacterial

products such as lipopolysaccaride and endotoxin are responsible for the breakdown of the periodontium in periodontitis [1- 2].

The role of some inflammatory mediators has been more highlighted as elevation of the interleukin-1b (IL-1β) level in the gingival crevicular fluid (GCF) and in the periodontal pocket tissue [3].

Besides, the relationship between the inflammatory process and psychological stress has been shown.

A review of published articles shows a strong positive relationship between periodontal diseases and psychological factors such as stress, distress, anxiety, depression and loneliness [4].

In response to psychological or certain physiological stressors, an inflammatory reaction occurs through the release of neuropeptides and inflammatory mediators from the sensory nerves and activation of mast cells or other inflammatory cells [5].

It has been shown that stress can effectively increase serum IL-1β, IL-6, and IL-10 and decrease IFN-γ production, suggesting that there is an interaction between endocrine and immune systems in response to a physiological stress [7].

Furthermore, the patients with mood disorders were also found to have an exaggerated inflammatory response to psychological stress compared to healthy individuals [6]. Based on the evidence about the relationship between the inflammatory process and stress responses, the present study investigated the association between psychological stress and elevation of inflammatory mediators related to periodontal disease in adult patients.

MATERIALS AND METHODS

Study population: In a case control study, 50 adult patients admitted to periodontal clinics of the Faculty of Dentistry at Tehran University of Medical Sciences, consecutively entered the study.

The study was approved by the Research and Ethics Committee of the Faculty of Dentistry and all individuals signed an informed consent before taking part in the study. Case subjects were enrolled as two groups, aggressive periodontitis and chronic periodontitis.

Table 1. Demographic and socioeconomic variables in cases and control groups

Characteristics	Aggressive Periodontitis (n=25)	Chronic Periodontitis (n=25)	Control group (n=25)	p-value
Age (yr)	41.0 (37.0, 44.5)	44.0 (37.5, 54.0)	24.0 (23.0, 24.0)	<0.001
Gender:				
Male	13 (52.0)	13 (52.0)	17.0 (68.0)	0.418
Female	12 (48.0)	12 (48.0)	8 (32.0)	
Marital status:				
Single	3 (12.0)	3 (12.0)	19 (76.0)	<0.001
Married	22 (88.0)	22 (88.0)	6 (24.0)	
Education level:				
Elementary school	2 (8.0)	1 (4.0)	0 (0.0)	
High school	20 (80.0)	18 (72.0)	2 (8.0)	<0.001
College	3 (12.0)	6 (24.0)	23 (92.0)	
Cigarette smoking (+)	4 (16.0)	5 (20.0)	2 (8.0)	0.474

Data are presented as median (1^{st}, 3^{rd} quartiles) or number (percentages)

Aggressive periodontitis was defined as having advanced periodontal disease, characterized as a clinical attachment level (CAL) greater than 5mm in at least 14 permanent teeth, existence of bone loss evidence in dental radiography and absence of a consistency between bone loss severity and local factors. Chronic periodontitis was defined as having severe periodontal disease, characterized as a clinical attachment loss (CAL) greater than 5mm in at least eight study sites, existence of bone loss evidence in dental radiography, and existence of periodontal destruction level and local factors such as dental plaque.

In addition, 25 healthy subjects without any evidence of periodontal disorders, tissue inflammation and bone loss in radiography were randomly selected to form the control group. All cases who had received previous periodontal treatment (within the last year) and patients under antibiotic, anti-inflammatory and antidepressive medication (within the last month) as well as those presenting systemic conditions were excluded.

Furthermore, pregnant women, patients in need of antibiotic prophylaxis and those wearing orthodontic appliances were not included.

Clinical measurement: Indices of PI (modified plaque index), PPD (probing pocket depth), CAL (clinical attachment loss) and BOP (bleeding on probing) were assessed at six sites per tooth (mesiobuccal, buccal, distobuccal, mesiolingual, lingual and distolingual) of all erupted teeth using a manual periodontal probe (Williams probe).

GCF sampling and cytokine production analysis: The gingival crevicular fluid was collected from the periodontal pocket of each quadrant in each patient by Whatmann means of durapore filter membranes. After isolation of the test sites from saliva, Durapore strips were consecutively inserted 1mm into the pocket and left in place for 60s.

Then, the strips were placed into a microcentrifuge tube and immediately frozen at -70°C until the day of the analysis. After centrifugal elution, the amount of IL-1b and IL-6 in the GCF was determined by using enzyme linked immunoadsorbent assays (ELISAs) specific for each cytokine.

Psychosocial measurements: In order to assess stress in all patients, Kettle stress questionnaire was used.

This questionnaire is a self report tool, consist-

Table 2. Clinical parameters in cases and control groups

Parameters	Aggressive Periodontitis (n=25)	Chronic periodontitis (n=25)	Control group (n=25)
Number of teeth	24.0 (22.0, 26.0)	26.0 (22.0, 28.0)	28.0 (28.0, 30.0)
Probing pocket depth (mm)	7.0 (6.0, 7.8)	5.5 (5.0, 6.8)	0.0 (0.0, 0.0)
Clinical attachment level (mm)	8.5 (8.0, 9.0)	7.0 (6.0, 8.3)	0.0 (0.0, 0.0)
Bleeding on probing	24 (96.0)	24 (96.0)	0.0 (0.0, 0.0)
Plaque index:			
0	1 (4.0)	0 (0.0)	22 (88.0)
1	6 (24.0)	3 (12.0)	3 (12.0)
2	15 (60.0)	17 (68.0)	0 (0.0)
3	3 (12.0)	5 (20.0)	0 (0.0)

Data are presented as median (1^{st}, 3^{rd} quartiles) or number (percentages)

ing of 40 scales and each scale consists of three items that describes the subjects' statements of stress and anxiety symptoms and their reactions towards these statements. The total score allows a classification of stress intensity levels: 0-3, normal; 4-6, mild; 7 and 8, moderate; and 9 and 10, severe.

Statistical analysis: Results were expressed as the median ± 1st and 3rd quartiles for quantitative variables and percentages for categorical variables. Categorical variables between the groups were compared using χ^2 test and continuous variables were compared by using one-way analysis of variance (ANOVA) for variables with normal distributions, and the Kruskal-Wallis test for variables with non-normal distributions. The Pearson's correlation was also used to find correlations between clinical periodontal parameters and the amount of GCF cytokines.

Individual characteristics (gender, age, history of cigarette smoking, education level, marital status and also the stress score) were first considered in a simple linear regression analysis to estimate the strength of association between these factors and cytokine levels. In the subsequent analysis, all risk factors were simultaneously considered in a multiple linear regression analysis to screen for independent significant factors. P values of 0.05 or less were considered statistically significant. All statistical analyses were performed using SPSS version 15.0 for Windows (SPSS Inc.,.Chicago, Illinois, USA).

RESULT

Demographic and socioeconomic variables in the patient groups and control group are shown in Table 1. There were statistically significant differences in some parameters such as age, marital status and education level between the three study groups. The healthy subjects were younger and had a higher education level than the patient groups (p<0.001). However, there were no statistically significant differences in smoking and sex ratio between the three groups (both p<0.001). Regarding clinical parameters (Table 2), the indices of PPD (p=0.002), CAL (p=0.002) and PT (p=0.001) were higher in aggressive periodontitis than the chronic group, but there were no statistical difference in BOP (P=0.999), types of

Table 3. Serum levels of cytokines and stress severity in cases and control groups

Parameters	Aggressive Periodontitis (n=25)	Chronic Periodontitis (n=25)	Control group (n=25)	p-value
Cytokines levels:				
IL-1β	226.0 (177.0, 259.0)	90.0 (51.0, 182.0)	52.0 (24.5, 68.0)	<0.001
IL6	2.4 (1.8, 3.4)	1.5 (1.2, 2.4)	1.7 (1.2, 2.6)	0.058
Stress severity:				
Normal	0 (0.0)	1 (4.0)	8 (32.0)	
Mild	9 (36.0)	19 (76.0)	15 (60.0)	<0.001
Moderate	16 (64.0)	5 (20.0)	2 (8.0)	
Severe	0 (0.0)	0 (0.0)	0 (0.0)	
Median stress score	7.0 (6.0, 7.5)	5.0 (4.0, 6.0)	4.0 (3.0, 5.5)	<0.001

Data are presented as median (1st, 3rd quartiles) or number (percentages)

periodontal bone defects (P=0.978) and PI (P=0.149) between the groups. Regarding cytokine levels, a higher level of IL-1β was found in aggressive periodontitis than the other groups and the level of IL-6 was slightly higher in the aggressive group.

As for the severity of stress, the median score of stress was higher in aggressive periodontitis than the chronic disorder and also in the two groups with periodontal disease than the healthy subjects (Table 3). However, severe stress situation was not observed in any of the study groups. Among the studied clinical parameters, CAL and PPD were positively correlated with the GCF level of IL-1β; whereas, no significant correlations were found between any of the parameters and the GCF level of IL-6 (Table 4). Multivariate linear regression analysis was performed controlling for gender, age, educational level, marital status and smoking status. In the aggressive group (Table 5), there was a strong positive relationship between stress severity and the GCF level of serum IL-1β (β=58.138, p<0.001) in the presence of confounders, but the correlation between stress severity and the level of IL-6 was poor in this group (p=0.716).

In addition, in chronic periodontitis (Table 6), a strong positive relationship was found between the stress score and the GCF level of IL-1β (β=28.536, p<0.001); whereas, the correlation between stress severity and IL-6 in this group was not significant either (p=0.153).

DISCUSSION

In the present study, we first assessed the changes of clinical parameters related to inflammatory mediators and then tried to study the relationship between the changes of these mediators and stress severity in the two groups of patients suffering from aggressive and chronic periodontitis and healthy subjects. It is difficult to measure GCF biochemical contents due to very small amounts of them, so the overall amount, assessed by the strip that was placed in the pockets for 1 minute was reported (pg/60s). According to the literature for periodontal disease, this scale is more suitable than the density scale [8-10]. In our study, the mean value of IL-1β in the aggressive periodontitis group (208pg/60s) was observed to be almost 2 times higher than the other patient group (112pg/60s) and nearly 4 times higher than the healthy group (58pg/60s).

Table 4. Correlation between clinical parameters and GCF cytokine levels

Parameters	IL-1β		IL-6	
	Correlation coefficient	p-value	Correlation coefficient	p-value
CAL	0.452	0.001	-0.193	0.183
PPD	0.504	<0.001	-0.213	0.142
BOP	0.058	0.690	-0.180	0.215
PI	-0.068	0.643	0.060	0.684
PT	0.352	0.013	0.034	0.816

CAL: Clinical attachment loss
PPD: Probing pocket depth
BOP: Bleeding on probing
PI: Plaque index
PT: bone loss

This is in agreement with other studies [11]. The level of IL-6 amount in GCF was also observed for every sample and the mean IL-6 of the aggressive group was statistically significantly higher than the chronic and healthy group, but the difference between the chronic and healthy group was not statistically significant.

It is worth noticing that IL-6 is a mediator with small values and a very narrow range; for instance, in our samples, the IL-1β range was 2-302 pg, but the IL-6 range was only 0.18-5.4 pg. In addition, it was shown that the measures of CAL and PT were positively correlated with the level of IL-1β.

In several previous studies, this correlation was also reported so that the total levels of IL-1β, IL-6 and IL-8 were significantly elevated in subjects with periodontal disease as compared to healthy subjects and this elevation was associated with sites showing periodontal destruction [11].

Especially, the changes of IL-1β in GCF were confirmed in active periodontitis as compared to inactive sites, suggesting that this cytokine can serve as a possible indicator of disease activity in refractory periodontitis [12-18].

Furthermore, in some trials, significant reductions in the level of IL-1β were observed in patients undergoing periodontal therapy [19-20]. Some other studies showed a strong relationship between the ratio of IL-1β in tissue biopsies of periodontitis patients and the severity of periodontitis [21]. Higher tissue concentration of IL-1β in periodontitis according to increasing clinical parameters can suggest that IL-1β plays a major role in the pathogenic mechanisms of periodontal tissue destruction, so measurement of tissue IL-1β would be a valuable diagnostic marker of the severity of the periodontal disease [22]. We also found that the severity of stress had a strong relationship with the amount of IL-1β in both groups of patients with aggressive and chronic periodontitis. Giannopoulou et al. found that IL-1β measured in GCF was in association with stress [11]. In a study by Deinzer et al., a significantly higher amount of GCF IL-1β level in stress situations was observed and it was concluded that stress might affect periodontal health by increasing local IL-1β levels [23]. Besides, some other studies could not show any relationship between the inflammatory process and the stress situation.

Table 5. Multivariate linear regression analysis expressing the association between stress score and IL-1β level in the presence of confounders in aggressive periodontitis group

Variables	Univariate p-value	Multivariate p-value	Beta coefficient	95% Confidence Interval for Beta	
Stress score	<0.001	<0.001	58.138	37.105	79.171
Male gender	0.652	0.330	23.561	-25.866	72.987
Age	0.753	0.827	0.380	-3.208	3.967
Education level	0.221	0.739	-1.063	-7.668	5.542
Marriage	0.477	0.015	-91.719	-163.206	-20.231
Cigarette smoking	0.545	0.352	-26.897	-86.022	32.228

R Square: 0.692

In a study by Castro et al., although a positive association of periodontitis with age, male gender, smoking and educational level was confirmed, no significant association was found between psychosocial factors and periodontal disease [24].

In another study by Solis et al., no evidence was found for an association between depression, hopelessness, psychiatric symptoms and established periodontitis [25].

Some mechanisms have been known to explain the relation between inflammatory process causing periodontitis and stress disorders. Firstly, it is hypothesized that the stress has immunostimulatory properties so that activation of the acute phase response of the immune system may be induced by repeated acute or chronic psychological stressful states which elicit the elaboration of stress hormones such as norepinephrine, epinephrine, cortisol and glucagon, together with activation of the renin-angiotensin system [26-29].

Interestingly, depressive mood states can induce hypothalamic pituitary adrenal axis hypersensitivity and the products of this system released by emotional stress may influence immune activities by immune cells via alterations in the production of cytokines [30-32]. According to the changes of inflammatory indices due to stressful satiation, treatment protocols of periodontal disorders should focus not only on medications, but also on the control of the stress situation and psychological support.

Therefore, further studies for determination of the influence of psychological supportive approaches as therapeutic protocols in periodontal diseases can be recommended. It is worth mentioning that this cross-sectional study is prone to potential temporal bias, as the variables are measured simultaneously and a temporal cause and effect relation is not presumable. Further investigation, perhaps based on a cohort study is suggested.

Table 6. Multivariate linear regression analysis expressing the association between stress score and IL-1β level in the presence of confounders in chronic periodontitis group

Variables	Univariate p-value	Multivariate p-value	Beta coefficient	95% Confidence Interval for Beta	
Stress score	<0.001	<0.001	28.536	17.470	39.602
Male gender	0.244	0.370	19.956	-25.655	65.567
Age	0.382	0.328	-1.098	-3.394	1.198
Education level	0.002	0.005	-12.780	-21.069	-4.491
Marriage	0.261	0.114	72.983	-19.186	165.152
Cigarette smoking	0.333	0.265	37.796	-31.256	106.848

R Square: 0.762

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