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To evaluate the serum cortisol, salivary cortisol, and serum interleukin-1 B level in patients of chronic periodontitis with smoking and stress and without smoking and stress

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Abstract

The role of cognitive, social and biological factors in the etiology of chronic periodontitis has been reported.

The aim of this study was to evaluate the salivary cortisol level and interleukin-1 B level in patients of Chronic periodontitis in smokers and stress and nonsmokers without stress.

The design of study randomized, prospective, double-blinded, and prospective study.

The total sample size was comprised of 600 subjects between the ages of 20 and 50 years. The sample size was divided into 300 males and 300 females. Out of 600 subjects, 200 subjects comprised of subjects with chronic periodontitis with positive depression level with a history of smoking (Group I), 200 subjects comprised of subjects with chronic periodontitis without depression and without smoking (Group II), and 200 subjects who were taken as the control group comprised of healthy subjects without chronic periodontitis, without depression level, and no smoking history (Group III). Salivary cortisol levels were determined by enzyme-linked immunosorbent assay (ELISA).

The result showed that there was a positive correlation between morning and evening salivary cortisol level in all the groups with correlation coefficient. There was significant higher value of salivary cortisol in Group I patients when compared with Group II and Group III. However, when the comparison of salivary cortisol levels was done between the Group II and Control group, the result showed nonsignificant *P* value.

It is suggested that stress is positively correlated with the salivary cortisol levels in smokers and nonsmokers.

Abbreviations: ACTH = Adrenocorticotropic hormone, CAL = Clinical Attachment Level, CI = Confidence Interval, CM = Childhood Abuse, CP = Chronic Periodontitis, CRH = Corticotrophin-releasing hormone, ELISA = Enzyme-linked immunosorbent assay, GI = Gingival Index, HPA axis = Hypothalamic-Pituitary-Adrenal Axis, IL-1, B, 8 = Interleukin-1, B and 8, NSSI = Non-Suicidal Self-Injury, PD = Pocket Depth, PGs = Prostaglandins, PI = Periodontal Index, PPD = Probing Pocket Depth, SCL-90 = Symptom Checklist 90.

Keywords: chronic periodontitis, interleukin B, psychological factors, salivary cortisol, smoking

1. Introduction

Chronic periodontitis (CP) has been considered as a multifactorial disease, where the main etiology of this is the microbial dental biofilms, which is the initiator for the inflammation process.[1,2] The authors revealed that the degree of periodontitis corresponds to the quantity of the biofilm.[1,2] It has been already proved that the local, systemic, and environmental factors such as socioeconomic status, diabetes mellitus, oral hygiene, and smoking has been associated with chronic periodontitis. The smokers have been associated with severe bone loss as compared to nonsmokers.[3]

Biopsychosocial models emphasize the multifactorial nature of CP. The role of cognitive, social, and biological factors in the etiology of CP has been reported.[4] Future research on CP etiology should emphasize on both local and psychological factors and the relationship between them. There have been several previous attempts to link depression and the hypothalamic-pituitary-adrenal (HPA) axis response in CP patients.[4,5,6] Stress resulted in the increased level of neuroendocrine hormones such as immunosuppressive hormones, which further reduce the formation of T cell lymphocytes and also macrophages.[5,6]

Smoking has been considered as the second main etiological factor for the CP. Smokers have been more likely to have more periodontal pathogens, which further leads to more and severe attachment loss and bone loss as compared with nonsmokers.[5,6]

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Ethical approval had been taken from the ethical cum research committee of the university regarding this study under the vide letter no XI'AN:IMC /2017/N-41 dated on 2November 26, 2017, and written informed consent/assent form had been obtained from all the participants of the study.

The authors declare no conflicts of interest.

The datasets generated during and/or analyzed during the current study are publicly available.

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The recent studies revealed that stress and depression could negatively influence the sign and symptoms of CP and further help in the progression of CP. Chronic stress and depression affects the systemic conditions and probably stimulates the HPA axis. When the HPA axis will be stimulated, it will increase the serum and salivary level of cortisol.[6,7] Cortisol is considered as stress hormone, which has been produced by the adrenal cortex. When the cortisol has been stimulated, it will activate the antistress and anti-inflammatory response.[6,7] Some of the literature suggests that the relationship between the CP and stress seems to be linked together, as depressive patients showed lack of oral hygiene maintenance, which further proceed for the periodontitis.[7,8] The association between the smoking associated stress on the production of salivary cortisol has been uncleared till date.

Some of the researches showed that child abuse could be a major risk factor for the depression in the age group between 18 and 30 years, which further could be associated with chronic periodontitis. Serafini et al [9]in 2017 have found that the increasing risk of nonsuicidal self-injury (NSSI) and suicidal behavior has been connected with childhood abuse (CM). Maltreats were also connected with an increased risk of suicide conduct among adolescents, especially girls.[10] Recent data show specificity for CM as well as adolescent harm behavior.[11] The history of physical/sexual abuse is connected with a higher risk of depression, which further increases the ratio of suicide attempts and a history of neglect and an increased risk of NSSI. So, childhood traumatic experiences need to be considered a potential risk factor for the development of higher stress levels, depression as well as stress-related conditions, which enhances the risk of CP. The exact nature of the relationship between CM and NSSI is presently uncertain in adolescent and early adulthood.[12] Serafini et al[9] in 2017 found the positive association between CM and NSSI. This information may help to early detect and rapidly recognize those who experienced CM as a specific group at risk for NSSI and suicidal behaviors.[9] Kaplan et al [13]concluded that the relation between childhood emotional, physical, and sexual abuse and carrying out NSSI for automatic reasons was mediated by symptoms of depression and dissociation. The association between physical abuse and the social functions of NSSI was mediated by symptoms of anxiety and dissociation, which could be indirectly related to CP.

Serafini et al[14] in 2016 concluded that the persons with substantial affective disorders might experience continuous challenges in processing sensory input, which may have a severe impact on their quality of life. Childhood trauma may also be highly correlated with excessive sensory processing patterns that have an interesting function in emotional patient quality of life. However, this link must be better understood in order to discover targeted areas of intervention and to improve their overall well-being.[14] Serafini et al[14] also quoted the involvement of individual factors such as perceptual processes, alexithymia, and childhood traumatic experiences in the pathophysiology of major affective disorders, although the constellation of these possible contributors in differentiating between bipolar and unipolar forms and their effect on quality of life have not been still investigated and integrated in a complex model. Existing studies suggested that traumatic childhood experiences and, in particular, childhood maltreatment may enhance the risk of lifetime depression and are able to exacerbate the course of the illness in a dose-response manner.[15]

Interleukin 1B has been considered as the inflammatory cytokine, which further plays a major role in the inflammation and further resorption of the bone. Therefore, interleukin B has been taken as very important marker in the periodontal pathology. Interleukin B stimulates the resorption of the bone and further precipitates the bone loss.[16]

Depression in particular has been shown to influence the expression of periodontitis sign and symptoms, but the relationship between these psychological variables and physiological parameters, such as cortisol levels, was not established in CP patients.[16]

It has been further realized that there was very limited literature about the combined effect of stress and smoking on the periodontitis. With this is mind, the aim and objective of the study to evaluate the salivary cortisol level and interleukin-1 B level in patients of CP in smokers with stress and nonsmokers and without stress.

2. Material and methodology

Ethical approval has been obtained from the XI'AN international medical hospital Ethics and Research Board (approval XI'AN: IMC /2017/N-41) and written informed consent/assent form had been obtained from all the participants of the study. Not a single patient refuses to participate in the study. The design of study was prospective and double-blinded. The duration of the study was 2 years 6 months. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice (GCP) guidelines.

2.1. Sample size estimation

The sample-size calculation was based on a reliable regression model, which suggested at least 100 samples per parameter. Assuming that a 10% dropout rate might occur, it was calculated that 200 patients would need to be enrolled in each group. However, taking 5% CI and maximum drop out of 30%, we have considered that 200 patients will give statistical sound results, so total of 600 patients had been taken.

The total sample size was comprised of 600 subjects between the ages of 20 and 50 years. The sample size was divided into 300 males and 300 females. Out of 600 subjects, 200 subjects comprised of subjects with CP with positive depression level with smoking history (Group I), 200 subjects comprised of subjects with CP without depression and without smoking (Group II), and 200 subjects who were taken as the control group comprised of healthy subjects without CP and without depression level (Group III). The control subjects were randomly selected who were coming to the department for any dental treatment. Only those controls were enrolled in the study who revealed negative history of any systemic diseases and on questionnaire categorized under negative depression. The study was taken as double-blinded protocol, as the lab investigator and patients were unaware of the groups which they have been allotted.

Parallel random assignment to treatment arms was performed and simple type randomization was used without any restriction. Automated computerized system has been used for the random allocation sequence.

2.1.1. Inclusion criteria. The diagnosis in respect of periodontology was based on the basis of International Workshop Classification of Periodontal Disease and Conditions 1999.[16]

In all the patients, following parameters has been taken to conform of chronic periodontitis case: clinical attachment level,

depth of probing; mobility; bleeding on probing. The measurements of 6 sides of each tooth have been recorded. The same measurement has been taken by 2 different periodontist designated at the rank of professor.

The Gingival Index (GI) and Periodontal Index (PI) were determined and recorded at 4 gingival sites per tooth. Pocket depth (PD) measurements were obtained using a Williams periodontal probe. The PD was measured from the free gingival margin to the base of the pocket. PD and Clinical Attachment level (CAL) were measured for each tooth at 6 sites, namely the mesiobuccal, midbuccal, distobuccal, mesiolingual, midlingual, and distolingual. The severity of disease was classified on the basis of the amount of attachment loss (i.e., slight, 1–2 mm; moderate, 3–4 mm; and severe, >5 mm).

Division of Groups:

(1) Group I: Patients with CP with probing pocket depth (PPD) ≥5 mm, clinical attachment loss ≥5 mm, more than 30% teeth involved, and further radiographic evidence of loss of bone. Patients with smoking habit 10 cigarette per day minimum since 5 years.
(2) Group II: Patients with CP with PPD ≥5 mm, clinical attachment loss ≥5 mm, more than 30% teeth involved, and further radiographic evidence of loss of bone.
(3) Group III: Control Group. Periodontally healthy patients and further No history of smoking

2.1.2. Exclusion criteria. Any systemic disease and ingestion of any other type of medication, which can increase the level of salivary/blood cortisol such as hyperpituitarism (overactive pituitary gland), benign pituitary tumors including adenomas, cancerous pituitary tumors, benign, and malignant adrenal gland tumors, Cushing syndrome, long-term and high dose of corticosteroid medications used to treat asthma, arthritis, certain cancers, pregnancy was used as exclusion criteria for all the groups.

All the subjects were asked to fill another questionnaire regarding the Graded Chronic Pain Scale and Depression so that they could be subjectively assessed for the severity of disease and depression. The depression was assessed by the standard questionnaire used for the depression, The SCL-90 developed by Derogatis is a self-report instrument containing 90 items and designed to measure nine current psychiatric symptoms, as well as psychological depression.

2.1.3. Saliva collection. The subjects were provided with plain plastic tubes to collect the saliva samples at home, twice a day, between 7:00 and 8:00 hours on awakening and then again between 20:00 and 22:00 hours because of the circadian rhythm of cortisol. The subjects were asked to abstain from food and drinks one hour before the collection of saliva. However, water consumption was allowed before the collection of the saliva. They also asked to refrain from smoking, heavy exercise, and brushing their teeth before collection of saliva. The morning post-awakening salivary cortisol samples were immediately handed to the laboratory, whereas for evening samples, the samples were kept in the refrigerator overnight and handed to the laboratory by the next day.

Upon receipt at the laboratory, saliva samples were centrifuged and the clear fluid stored at -70° C until analysis. Cortisol biochemical parameters were analyzed by commercially available reagent kits. The cortisol saliva enzyme-linked immunosorbent assay (ELISA) kit was supplied by dbc, Diagnostic Biochem (Canada). The instructions manuals that were included with the kits for the procedures were followed strictly. All saliva samples were analyzed at the Biochemistry Laboratory. All the samples were analyzed by the expert faculty in the Biochemistry Department for the Cortisol Assessment and Interleukin Assessment.

The obtained results of all samples of cortisol were further subjected to statistical analysis. Statistical analysis was done by a highly expert statistician.

2.2. Statistical analysis

The collected data was put to statistical analysis using Statistical Package for Social Sciences software (SPSS inc., Chicago, IL, version 23.0 for Windows). Mean, median, range, and standard deviation (SD) for all variables in all the groups were calculated. A paired *t* test was used to calculate the value of difference in ratio between the Group I, II, and III. The Pearson correlation was performed to see the relationship between mean value of cortisol in the morning and in the evening. Analysis of variance (ANOVA) was used to assess the means of salivary cortisol level between various groups. A linear multi-regression between and psychosocial factors in both groups was performed as well as a linear correlation with associated values between cortisol levels and psychosocial factors. The P value $< .05$ was considered significant. Measurements were recorded by single examiner. All patients completed the study and fully complied with the recall program.

3. Results

The Pearson correlation was performed to see the relationship between mean value of cortisol in the morning and in the evening. The result obtained showed that there was a positive correlation between the morning and evening salivary cortisol level between the three groups. The correlation coefficient was 0.70. The correlation was highly significant in the groups with a P value less than .0001. Thus, it shows that salivary cortisol level is higher in the morning as compared to the evening (Tables 1 and 2).

The highest mean value was of salivary cortisol level was observed in CP patients with smoking and depression in the morning group (Group I) with statistically significant P value of less than .05 (Table 3). According to ANOVA test, when the means of morning salivary cortisol level in Group I, Group II, and

Table 1

Salivary cortisol statics related to the morning and evening time.

Paired Samples Statistics					
		Mean	N	Std. deviation	Std. error mean
Pair 1	Cortisol Morning	62.177	600	21.12	5.1291
	Cortisol evening	28.1290	600	11.22	3.2356

Table 2

Pearson correlation between morning and evening salivary cortisol level.

Paired Samples Correlations		N	Correlation	Sig.
Pair 1	Cortisol morning and Cortisol evening	600	.070	<.0001

with control group were correlated, the results obtained showed that there was statistically significant higher value of salivary cortisol in Group I when compared with Group II with a *P* value of .0001. There was also statistically significant higher value of cortisol in Group I when compared with control group with a *P* value less than .0001. However, when the comparison of salivary cortisol levels was done between the Group II and Control group, the result showed nonsignificant *P* value (Tables 3 and 4).

When the means of evening salivary cortisol level in Group I, II, and with control group were correlated, the results obtained showed that there was statistically significant higher value of salivary cortisol in Group I when compared with Group II with a *P* value of less than .0001. There was also statistically significant higher value of cortisol in Group I when compared with control group with a *P* value less than .0001. However, when the comparison of salivary cortisol levels was done between the Group II and Control group, the result showed nonsignificant *P* value (Table 4).

Linear regression analysis was applied on depression, smoking, chronic periodontitis, chronic pain scale, disability score, and disability point with cortisol as dependent variable. It was observed that the main predictor variable was positive depression level, smoking, and CP with statically significant *P* value of < .0001. Other variables such as chronic pain scale, disability point, and disability score came out to be nonsignificant with cortisol as dependent variable (Table 5).

When the means of interleukin B level in Group I, II, and with control group were correlated, the results obtained showed that there was statistically significant higher value of interleukin B level in Group I when compared with Group II and Group III with a *P* value of less than .0001 (Table 6).

4. Discussion

The outcome of this study showed that the highest mean value was of salivary cortisol level was observed in CP patients with smoking and depression in the morning group (Group I) with statistically significant *P* value of less than .05. However, salivary cortisol levels in Group II when compared with the salivary

Table 4

ANOVA test - Correlation of the salivary cortisol level Group I, II, and Group III.

Dependent variable	(q) depression	(j) depression	Mean difference (q-j)	sig.
Cortisol morning	Group I	Group II	42.10	.000
		Group III	49.49	.000
	Group II	Group I	-42.10	.000
		Group III	5.67	.145
Cortisol evening	Group I	Group II	20.80	.000
		Group III	29.81	.000
	Group II	Group I	-20.80	.000
		Group III	3.45	.789

cortisol levels in the control group showed a nonsignificant *P* value of .154. It was also observed that the main predictor variable was positive depression level, and smoking in CP with statically significant *P* value of < .0001. Other variables such as chronic pain scale, disability point, and disability score came out to be nonsignificant with cortisol as the dependent variable.

Although the underlying cause of CP remains poorly understood, it is widely recognized to be multifactorial, involving physiological, behavioral, psychological, and environmental factors.[17]

The authors believe that both physical and psychological factors contribute to the onset and maintenance of CP. Psychometric tests, as well as endocrine measurements, have been used to evaluate some of psychological factors.[17,18] Any differences in these respects between diagnostic categories of CP might have implications for the understanding and treatment of the condition.

The HPA axis system is the primary endocrine depression axis in humans. When stimulated, the hypothalamus secretes corticotrophin-releasing hormone (CRH) in response to which the pituitary gland secretes adrenocorticotropic hormone (ACTH). This in turn stimulates the secretion of cortisol from the cortex of the adrenal glands. It is possible that facial pain represents greater stimulus to HPA-axis activation than pain elsewhere in the body.[19,20]

In our study, the results show that in all the 3 groups namely, Group I, II, and III were significantly higher in the morning as compared with the evening, with a *P* value < .0001. The results were in consistence with the study conducted by Badrick et al[21]; they revealed that the level of salivary cortisol was increased in the smokers as compared with nonsmokers, thus further suggesting smoking has a short-term effect on the neuroendocrine system. However, Handa et al[22] reveled opposite results and

Table 3

Mean values of morning and evening salivary cortisol in Group I, Group II, and Group III.

Dependent variable	Category	N	Mean	Std. Deviation	Minimum	Maximum
Cortisol level in morning	Group I	200	62.15	21.22	23.11	98.23
	Group II	200	23.11	14.58	14.12	58.12
	Group III	200	20.85	6.78	7.75	25.16
	Total	600	27.81	20.98	7.75	98.23
Cortisol level in evening	Group I	200	52.12	24.12	19.10	88.13
	Group II	200	26.90	16.28	11.21	48.11
	Group III	200	15.75	5.18	3.75	22.16
	Total	600	22.31	18.11	3.75	88.13

Table 5

Linear regression.

Model	Unstandardized coefficients		Standardized coefficient		
	B	Std error	Beta	T	Sig
Depression	−37.01	8.11	714	−5.11	.000
Smoking	17.13	5.4	720	4.219	.000
Chronic periodontitis	35.14	7.1	2.11	5.375	.000
Chronic pain scale	.789	.480	.550	3.14	.333
Disability score	−.543	.514	−.514	−3.15	.089
Disability point	4.567	3.11	−2.01	−.310	.777

A. Dependent variable: Cortisol.

showed that serum cortisol level was lower in the smokers as compared with nonsmokers.

The outcome of our study showed that Group I presented higher cortisol levels in the morning and in the evening than Group II and the control group, with a significant *P* value of < .0001. However, salivary cortisol levels in Group II when compared with the salivary cortisol levels in the control group showed a nonsignificant *P* value of .154. The results were similar to the study conducted by George et al.[23] They assessed salivary cortisol response to psychological depression and its relationship to psychological variables. They subjected a modified version of the Trier Social Stress Test to all patients, which lasted for 20 minutes. The CP group showed significantly higher cortisol response to experimental depression than the control group.[23]

The experience of depression full life events is a major risk factor for depression, and understanding vulnerability to depression is the key to understanding depression. The results of the current study demonstrated that the Graded Chronic Pain Scale was higher in group I patients who had higher depression score as compared to Group II. Thus, it was considered possible that the pain interference in daily, recreational/social/family, and work-related activities could account for the higher cortisol levels seen in CP patients with depression. Many authors have concluded that the biological processes can translate psychological depression into the sensation of pain and can contribute to the development of CP.[24]

The results of the study showed that the saliva has been more efficient and accurate for the local changes in the microbial periodontal environment as compared to the serum. Further, salivary cortisol level corresponds to the biologically active unbound level of cortisol. So, this level has not been affected by the corticosteroid globulin, which may confuse with serum cortisol levels.

The raised level of interleukin B in smokers and nonsmokers with CP showed similar results with study done by Ghurbi et al,[25] in which they found the significant elevation of IL-1, B, and IL-8 in smokers as compared with nonsmokers.

The reason of raised level of interleukin B in smokers may be due to nicotine in cigarette smoke, which may affect the inflammatory response to the microorganism by increasing the release of cytokines and PGs leading further to attachment and bone loss. The present study showed the SCL-90 questionnaire of depression was associated with poor periodontal status, as more periodontal destruction was seen in Group I as compared with Group II and Group III. This study proved that the any amount of stress could affect the periodontal issue. This study confirms the possible linkage of stress, cortisol, periodontitis, and smoking.

Besides the traditional psychotropic drugs (trycyclic antidepressants), introduction of psychological intervention, stress management, and change of habits as a part of the integral treatment of CP patients with depression can be effective in reduction of painful conditions and tension in various types of patients suffering from CP.

4.1. Limitations

A larger sample size and a long-term assessment in the form of a longitudinal study are needed to further corroborate the findings of the present study. The presence of stress or depression was assessed by a self-rating questionnaire system, which might be subjected to individual bias related to understanding of the gravity of the stated question and also ability to respond correctly according to the scale and the situation bias may also take place, that is, the condition of instability of the clinical phenomenon being evaluated. Also, it does not allow an assessment of the subjective and behavioral aspects of individuals. The analysis of the stress levels determined with self-report scales may be approached incongruously in epidemiological studies, for it is difficult to correlate facts of the present or recent past periodontal disease activity, especially due to the mean age of the onset of disease, its clinical course and chronicity.

Table 6

Comparison of Groups I, II, and III for the interleukin B levels.

Levels	Mean level of interleukin B	Comparison	*P*
Group I	327.91 ± 56.1	Group I Vs Group II	<.0001
		Group I vs Group III	<.0001
Group II	178.91 ± 72.1	Group II Vs Group I	<.0001
		Group II vs Group III	.123
Group III	102.23 ± 72.1	Group III vs Group I	<.0001
		Group III vs Group II	.123

5. Conclusion

Within the limits of this study, the present cross-sectional analysis establishes a strong and definite relationship between depression, smoking status, and CP. Smokers with CP demonstrate significantly high cortisol values in saliva as compared to those in serum. Similarly, serum IL-B values are higher in smokers as compared to nonsmokers with CP. Smokers exhibit higher stress levels as compared to nonsmokers. Considering that the diagnosis, assessment, and management of CP must include both physical and psychological factors, it is suggested that

salivary cortisol could be a promising tool in identifying underlying psychological factors that could be associated with CP with smoking. Furthermore, a long-term assessment in the form of a longitudinal study with a larger sample size would help to further corroborate the findings of the present study.

5.1. Practical implication of the study

The study concluded that people with high levels of cortisol have an increased risk of periodontitis. If a patient with choric periodontitis and with history of smoking is present, and there are no obvious identifiable etiologic factors, it is possible that evaluation of salivary cortisol level may point toward psychological etiologic factors that may be responsible for the CP. So, the clinicians could plan the treatment strategy according to the etiological factors.

Author contributions

Conceptualization: Ansheng Zhang.
Data curation: Bocheng Chen.
Formal analysis: Bocheng Chen.
Investigation: Haiou Zhang.
Methodology: Haiou Zhang.
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Software: Chenyu Pan.
Supervision: Ansheng Zhang.
Validation: Bocheng Chen.
Visualization: Chenyu Pan.
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