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Research Article

Correlation of Chronic Periodontitis and Stress Hormone: A Correlative Study

Sital Jain[1,2], Nischal Das[3], Anupam Deka[4], Swarga Jyoti Das[5]*

[1]*Department of Periodontics, Regional Dental College, Guwahati, Assam, India*

[2]*Private Practitioner, Guwahati- 781006, Assam, India*

[3]*Fellowship Trainee, Department of Medicine, Gauhati Medical College, Guwahati-781032*

[4]*Reader, Department of Periodontics, Regional Dental College, Guwahati-781032*

[5]*Former Professor, Department of Periodontics, Regional Dental Clinic, Guwahati-781005, Assam, India*

***Corresponding Author:** Swarga Jyoti Das, Principal and Head of the Department in Periodontics and Oral Implantology, Kalka Dental College, Patapur By-pass Road, Meerut-250103, UP, India, Tel: (+91)70023-91651; Fax: (+91) (121) 2440817
E-mail: swargajyoti_das2@rediffmail.com

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Abstract

Introduction and Purpose: Psychological stress affects the host immune inflammatory response negatively through release of glucocorticoids, predominantly cortisol via the Hypothalamic Pituitary Adrenal (HPA) axis. Thus, it may play an important role in the pathogenesis and progression of chronic periodontitis, which is the result of host-microbial interaction. This study was conducted to evaluate the correlation of stress with generalized chronic periodontitis, if any, by estimating the level of serum cortisol.

Materials and Methods: The subjects (n = 60) were divided into two groups: control (n = 20) and case (n = 40). Control group comprises of the subjects with healthy periodontium, while the case group comprises of subjects with generalized chronic periodontitis. The periodontal parameters considered were plaque index, gingival index, probing pocket depth and clinical attachment level. Serum cortisol level was estimated in venous blood using electrochemiluminescence method. Correlation between the periodontal health and Serum cortisol level was evaluated applying Pearson's Correlation Co-efficient, using Independent sample 't' test considering 0.05 as significance level.

Results: Serum cortisol level was found to be higher in the subjects with chronic periodontitis compared to that of the subjects with healthy periodontium. A statistically significant correlation was observed between Serum cortisol level and probing pocket depth, whereas a positive though weak correlation was observed with the other periodontal parameters.

Conclusion: A positive correlation between chronic periodontitis and stress hormone is suggested.

Keywords: *Chronic Periodontitis; Hypothalamic Pituitary Adrenal (HPA) Axis; Probing Pocket Depth; Serum Cortisol; Clinical Attachment Level*

Abbreviations

HPA: Hypothalamic-Pituitary-Adrenal; CRF: Corticotropin-Releasing Factor; ACTH: Adrenocorticotropic Hormone; ROS: Reactive Oxygen Species; MMPs: Matrix Metalloproteinases; ECLIA: Electrochemiluminescence Immunoassay; ECL: Electrochemiluminescence; TH: T Helper; SPSS: Statistical Package for Social Sciences; RIA: Radioimmuno Assay; EIA: Enzyme Immunoassay

Introduction

Stress is defined as any stimulus that disrupts the body's internal balance. The principal effectors of the stress response are localized in the paraventricular nucleus of the hypothalamus, the anterior lobe of the pituitary gland, and the adrenal gland. This triad is referred to as the hypothalamic-pituitary-adrenal (HPA) axis [1,2] (Figure 1). The principal regulator of this axis is corticotropin-releasing factor (CRF), synthesized and secreted by hypophysiotropic neurons localized in the medial parvocellular subdivision of the paraventricular nucleus [3,4]. In stress, CRF is released into hypophysial portal vessels that access the anterior pituitary gland. Binding of CRF to its receptor on pituitary corticotropes induces the release of adrenocorticotropic hormone (ACTH) into the systemic circulation [5]. The circulating ACTH stimulates the adrenal cortex to synthesize and release glucocorticoids (predominately cortisol, regarded as stress hormone) that impairs the host defense, particularly the cellular immune response [6].

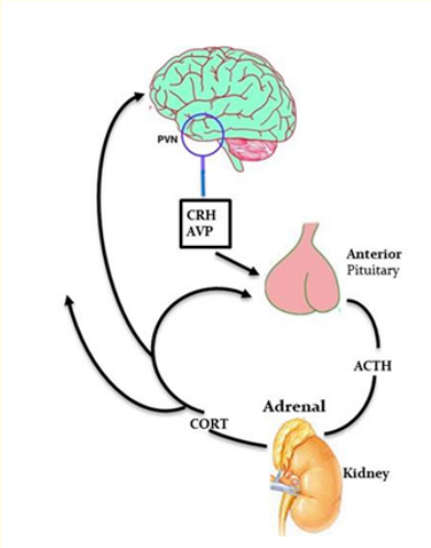

Figure 1: *Schematic diagram of the hypothalamic-pituitary-adrenal (HPA) Axis.*

Prolonged stress, whether physical or emotional, results in high levels of cortisol, which stimulates TH2 cells to produce proinflammatory cytokines and mediators, namely IL-1 and PGE2 that further increases the secretion of IL-17, reactive oxygen species (ROS), Matrix metalloproteinases (MMPs) and factors that influence the osteoclast differentiation [7,8]. Since periodontitis is an inflammatory disease of the supporting tissues of teeth primarily caused by microorganisms, modified by environmental and stress-related behavioural factors (namely alcohol consumption, smoking, depression and neglect of oral hygiene) and stress affects the inflammatory and hormonal profiles, a close correlation is anticipated between these two i.e. periodontitis and stress. The existing observations on the effect of psychological stress and serum cortisol on the onset of periodontal disease is contradictory [9-14]. Considering this, the present study was conducted to compare the serum cortisol level in healthy periodontium and chronic periodontitis and also correlate the association between periodontal health and stress in terms of serum cortisol level.

Materials and Methods

The subjects (n = 60) were selected from the Out Patient Department of Periodontics and Oral Implantology. Ethical clearance was obtained from the Institutional Ethical Committee. The subjects excluded from the study were the patients on corticosteroid therapy, im-

munosuppressive drugs and patients under antibiotic treatment and patients who have undergone periodontal treatment during the last 6 months before initiation of study, smokers and lactating mothers.

The subjects were divided into 2 groups:

- Control group (n = 20): Subjects with healthy periodontium, showing no sign of gingival inflammation.
- Case group (n = 40): Subjects with moderate to severe clinical attachment loss (CAL) (> 3 mm) and having minimum 20 teeth with the involvement of > 30% sites as per International Workshop for Classification of Periodontal Diseases and Conditions (1999).

Clinical parameters

A full mouth clinical examination was carried out in all the participants. The clinical parameters considered were:

- Plaque index
- Gingival index
- Probing pocket depth
- Clinical attachment level.

Plaque index (Silness and Loe, 1964)

Teeth were air dried and examined visually using A ≠ 17 Shepherds hook to evaluate the tooth surfaces. Six index teeth (16, 12, 24, 36, 32, 44) were explored in the cervical third, near the entrance to the gingival sulcus. If any one of the six index teeth were missing then the scoring was done on the entire dentition. The scoring criteria are as follows:

- Score 0: No plaque in the gingival area.
- Score 1: A film of plaque adhering to the free gingival margin and adjacent area of the tooth. The plaque may be recognized only by running a probe across the tooth surface.
- Score 2: Moderate accumulation of soft deposits within the gingival pocket and on the gingival margin and/or adjacent tooth surface that can be seen by the naked eye.
- Score 3: Abundance of soft matter within the gingival pocket and/or on the gingival margin and adjacent tooth surface.

Scores from all the surfaces of a tooth were added and divided by the number of teeth examined to obtain the score for specific tooth. Plaque index for an individual was obtained by dividing the sum of all the individual scores by the total number of surfaces recorded.

Gingival index (Loe and Silness, 1963)

The gingival health status was assessed using a mouth mirror and a periodontal probe. It was scored on a numerical scale, according to the following criteria:

- Score 0: Normal gingiva.
- Score 1: Mild inflammation, slight change in color, slight edema, no bleeding on probing.
- Score 2: Moderate inflammation, redness, edema, and glazing; bleeding on probing.
- Score 3: Severe inflammation, marked redness and edema, ulceration; tendency to spontaneous bleeding.

The gingival score for a tooth was obtained by dividing the sum of scores obtained at four areas by four. Then scores of each tooth are added and divided by the number of teeth examined to acquire gingival index scores for an individual.

Probing pocket depth

It was measured using the UNC -15 periodontal probe. The working end of this probe is 15 mm long probe with markings at each mm and color coding at 5th, 10th and 15th mm. The probe was inserted with a firm, gentle pressure (0.75 N) to the bottom of the pocket aligning the shank with the long axis of the tooth surface to be probed. Pocket depth was measured from gingival margin to the base of the pocket, at four specific points in relation to a tooth: distofacial and mesiofacial line angle, and middle of the buccal and lingual surfaces.

Probing pocket depth of each tooth was obtained by dividing the sum of depth obtained at four areas by four. Then pocket depth of each tooth were added and divided by the number of teeth examined to acquire pocket depth for an individual subject.

Clinical attachment level

It was measured from the cementoenamel junction of a tooth to the base of the pocket in mm using UNC -15 periodontal probe, as described before. It was measured at four points in relation to a tooth: distofacial and mesiofacial line angle, and middle of the buccal and lingual surfaces. Clinical attachment level for each subject was determined by adding all the individual scores and then dividing this by the total number of surfaces recorded.

Biochemical parameters

Estimation of serum cortisol

All the participants were instructed to abstain from unusual physical activities for at least 2 hours before blood collection and were called between 8.00 to 9.00 am. 2 (Two) ml of venous blood was drawn from the median cubital vein under strict aseptic conditions and was transferred to the vacutainer containing sodium fluoride. Blood Sample was then centrifuged for 10 minutes at 1300g at room temperature. The supernatant was transferred to tubes using a disposable pipette, which were stored immediately below -80°C and were utilized later on for estimation of cortisol by electrochemiluminescence immunoassay (ECLIA).

Electrochemiluminescence (ECL) refers to a chemical reaction that produces light via electrical stimulation. It is known to occur with numerous molecules including compounds of ruthenium, osmium, rhenium or other elements. The development of ECLIA is based on the use of a ruthenium chelate as the complex for the development of light following application of a voltage to the immunological complexes attached to Streptavidin-coated micro particles. Thus, ECLIA can be regarded as a quantitative method for measurement of antigen or antibody based on the change in electrochemiluminescence signal before and after immunoreaction. The amount of light produced is indirectly proportional to the amount of cortisol concentration in the sample. The steps of the reactions involved are schematically shown in figure 2.

Serum cortisol was measured using the cortisol assay (Roche diagnostics) following the manufacturer's instruction:

- 10 µL of serum sample was incubated with a ruthenium pyridine-labeled primary antibody to which Biotinylated monoclonal anti-cortisol antibody and Streptavidin-coated paramagnetic micro particles were added to form a complex comprising an antigen, an antibody and a magnetic particle, which then adsorbed onto the surface of an electrode through the magnetic particle.
- A dibutyl ethanolamine solution was added to initiate the ECL reaction by applying voltage and scanned optical signal is recorded by an optical detector and measured with a photomultiplier, namely Electrochemiluminescence immunoassay analyzer Vitros 200 (USA).
- Evaluation and calculation of the concentration of the serum cortisol was carried out by means of a calibration curve that was established using standards of known concentration of synthetic cortisol labelled with ruthenium complex and expressed in nmol/L.

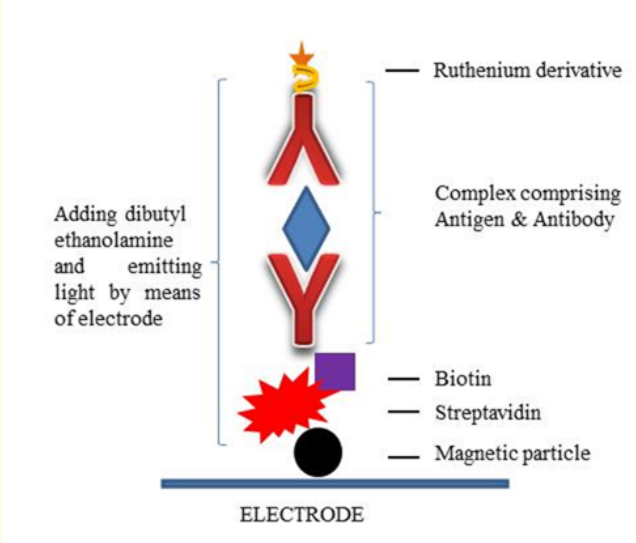

Figure 2: *Schematic representation of an Electrochemiluminescence immunoassay (ECLIA).*

The collected data were analyzed using statistical package for social sciences (SPSS) version 20 (IBM). Correlation analysis was done to evaluate the association between the clinical parameters and serum cortisol level applying Pearson's correlation co-efficient, using independent sample 't' test considering 0.05 as significance level.

Results

The mean values of plaque index, gingival index, probing pocket depth, clinical attachment level in group A was observed to be 0.61 (± 0.33), 0.65 (± 0.35), 1.36 mm (± 0.36 mm) and 1.40 mm (± 0.28 mm), respectively. The mean values of plaque index, gingival index, probing pocket depth, clinical attachment level in group B was observed to be 1.56 (± 0.23), 1.29 (± 0.26), 3.74 mm (± 0.59 mm) and 4.00 mm (± 0.92 mm), respectively. The mean plaque index, gingival index, probing pocket depth, clinical attachment level were higher in group B than that of the group A. The difference in the mean values of plaque index, gingival index, probing pocket depth, clinical attachment level between the groups was tested for statistical significance using Independent Samples 't' test at 0.05 significance level and found very highly significant ($p < 0.001$).

The mean serum cortisol level in group A and group B was observed to be 10.58 µg/dl (± 2.86 µg/dl) and 11.85 µg/dl (± 5.08 µg/dl), respectively. The difference between the mean values of two groups is 1.26 µg/dl. It was tested for statistical significance using independent samples 't' test at 0.05 significance level and found statistically not significant ($p = 0.223$).

The Pearson correlation co-efficient with respect to plaque index, gingival index, probing pocket depth, clinical attachment level with serum cortisol level in group A was found to be (-) 0.01, (-) 0.03, (+) 0.03 and (+) 0.10, respectively. This correlation was tested statistically at 0.05 significance level and found a positive though weak correlation of probing pocket depth and clinical attachment level with serum cortisol, while the correlation of plaque index and gingival index with Serum cortisol was observed to be a negative and non-significant (Table 1).

		Group A (Healthy Periodontium) (n = 20)				Group B (Chronic Periodontitis) (n = 40)			
Serum Cortisol level	Pearson Correlation Coefficient (r value)	Plaque Index	Gingival Index	Probing Pocket Depth	Clinical Attachment Level	Plaque Index	Gingival Index	Probing Pocket Depth	Clinical Attachment Level
		- 0.01	- 0.03	0.03	0.10	0.05	0.31	0.17	0.13
	p value	0.94^{ns}	0.88^{ns}	0.88^{ns}	0.65^{ns}	0.73^{ns}	0.28^{ns}	0.04^{*}	0.41^{ns}

Table 1: *Correlation of clinical parameters with serum cortisol level. ns = Not Significant; ∗ = Statistically Significant.*

To determine the association of periodontitis and stress, correlation coefficient of Serum Cortisol levels and the periodontal parameters were plotted, where more the steepness of regression line towards right indicates stronger correlation. As shown in table 1, the 'r' values between Serum cortisol and plaque index, gingival index, probing pocket depth, clinical attachment level were found to be 0.05, 0.31, 0.17 and 0.13, respectively. On plotting, a positive but weak correlation between the Serum Cortisol levels and plaque index, gingival index and clinical attachment level is revealed. However, the correlation between the probing pocket depth and serum cortisol level is statistically significant (Figure 3).

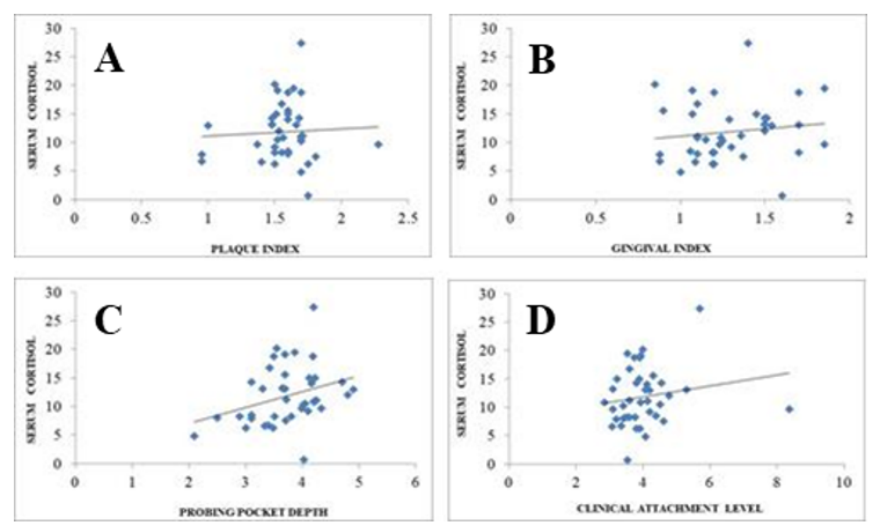

Figure 3: *Scatter diagram showing correlation between serum cortisol level and plaque index (A), serum cortisol level and gingival index (B), serum cortisol level and probing pocket depth (C), serum cortisol level and clinical attachment level (D). Note that steepness of regression line in C showing the positive and significant correlation between the probing pocket depth and serum cortisol level.*

Discussion

The stress-induced responses either result in change in behavior or are transmitted to the HPA axis to release corticotrophic releasing hormone from the hypothalamus. As stated before, corticotrophic releasing hormone activates the pituitary gland to release ACTH, which

in turn induces the release of glucocorticosteroids (predominately cortisol) from the adrenal cortex [15,16]. The glucocorticoids then produce a myriad of effects throughout the body, such as suppressing the inflammatory response, modifying cytokine profiles, elevating blood glucose levels, and altering levels of growth factors [17,18]. Increased levels of plasma glucocorticoids may provoke an increased response of T helper (TH) 2 cells [19-21]. Marshall., *et al*. (1998) demonstrated an imbalance between TH1 and TH2 cells during stress situations like examinations, leading to increased secretion of cytokines which play an important role in the pathogenesis of periodontitis [22].

The mean serum cortisol levels in group B is more than that of group A. These findings are in accordance with the observations of Genco., *et al*. 1998; Kessler., *et al*. 1997 [23,24] in which the mean cortisol levels were higher in the case groups. This could be due to deregulation of the immune system, mediated through the hypothalamic-pituitary-adrenal and sympathetic-adrenal medullary axis [25].

Mean score of plaque index in group B is more than group A. These findings support the observation of Kurer., *et al*. 1995 and Rosania., *et al*. 2009 [26,27], who stated that students under academic stress show high plaque values and severe gingival inflammation. That may be due to infrequent or inefficient tooth brushing [28].

Mean gingival index was found to be more in group B than that of group A. These findings are in accordance with the observation by Klages., *et al*. 2005 and Johannsen., *et al*. 2006 [28,29]. Here, cortisol may act on gingival inflammation directly as well as indirectly. Direct influence might involve modulation of the HPA axis, leading to endocrine imbalance and consequently lowering of the host resistance [23], while indirect influence would involve behavioral changes [26,27].

Mean score of probing pocket depth and clinical attachment level were higher in group B compared to group A. These findings are in accordance with the observations made previously [11,23,30,31], who stated that psychosocial stress may influence behavioral changes, namely smoking, poor compliance, and poor oral hygiene. Again, stress leads to overeating, especially high fat diets that leads to cortisol release [23].

In Group B, a positive correlation was observed between plaque index, gingival index, probing pocket depth and clinical attachment level with serum cortisol level. This correlation was statistically significant for probing pocket depth ($p < 0.05$). This supports the findings of Genco., *et al*. 1998; Mannem and Chava, 2012, Mudrika., *et al*. 2014 [23,32,33] in a subsample of individuals with and without periodontitis. This could be endorsed to the reduced TH2-mediated immune responses via glucocorticoids, thereby enhancing the growth of pathogenic microorganisms [34].

An association between chronic periodontitis and stress was hypothesized by many authors over the years, but the role of stress hormones and the psycho-neuro-immunologic mechanism behind it was not very well understood due to limited data. In the present study, the relationship between stress and periodontal disease was investigated using serum cortisol. Venous blood samples were collected early in the morning since cortisol levels in the peripheral blood follow a circadian rhythm, showing highest titers in the early morning that declines gradually over the day with minimum titer reached near midnight. External factors such as inflammatory, physical, and psychosocial stresses are known to affect the cortisol release [25,35]. Therefore, it indicates the practicability of using serum cortisol level for monitoring the progression of periodontal diseases.

The procedure used here for detection of serum cortisol, namely ECLIA possesses excellent sensitivity, comparable to EIA and RIA with no use of radioisotopes. The method is simple, rapid (less than 8 minutes) and relatively inexpensive. Again, the reagents are stable and nontoxic. Since the chemiluminescent reaction is initiated electrically, the entire reaction can be precisely controlled.

These results encourage the prospect of a future trial or research with a larger sample size. Further studies are required to incorporate physiological measures which also would complement any psychological assessment of stress. However, this study did not address the effect or mechanisms through which stress could result in progressive periodontal disease in susceptible subjects.

Conclusion

In the light of the present study, we may conclude that serum cortisol level is higher in the subjects with chronic periodontitis compared to the subjects with healthy periodontium, suggesting a positive correlation between the serum cortisol level with plaque index, gingival index, pocket probing depth and clinical attachment level.

Conflict of Interest

Nil.

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