Dental Research Journal

Original Article

Evaluation of serum C-reactive protein levels in subjects with aggressive and chronic periodontitis and comparison with healthy controls

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ABSTRACT

Background: Periodontal subgingival pathogens affect local and systemic immune responses and initiate an acute phase systemic inflammatory response characterized by the release of C-reactive proteins (CRPs).This study has been carried out to evaluate the serum concentration of CRPs, which can be used as a marker of periodontal disease as well as a risk indicator for cardiovascular diseases.
Materials and Methods: In a retrospective study a total number of 45 subjects were selected from the outpatient department of periodontics a mean age of 40 years. Based on the periodontal status, the subjects were divided into 3 groups of 15 subjects each. Group I: Control group [with attachment loss (AL) ≤ 2 mm and pocket depth (PD) < 3 mm], Group II: Generalized aggressive periodontitis (AL ≤ 5 mm), Group III: chronic periodontitis (AL ≥ 2 mm, PD ≥ 5 mm), which includes moderate and severe periodontitis. The clinical parameters recorded were plaque index,gingival index, bleeding index, probing PD, and clinical attachment levels and scoring was done on 6 surfaces of all teeth. For the CRP assessment, blood samples were collected from subjects at the time of clinical examination. Analysis of covariance was used for comparison of mean values between the groups to adjust the ages (P value < 0.05).
Results: Overall, the mean CRP levels were high in subjects with generalized aggressive and chronic periodontitis compared with controls. This was found to be statistically significant. A statistically significant difference (P = 0.012) was found in the CRP level between groups I and II and between groups II and III, and between groups I and III.
Conclusion: The results of the present study indicated an increase in serum CRP levels in subjects with generalized aggressive periodontitis and chronic periodontitis as compared with the controls.

Key Words: Aggressive periodontitis, chronic periodontitis, C-reactive proteins, serum concentration

Received: June 2011
Accepted: March 2012

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INTRODUCTION

Periodontitis is a local inflammatory process mediating destruction of periodontal tissues triggered by bacterial insults[1] Periodontal subgingival pathogens affect local and systemic immune and inflammatory response. Local inflammatory response to these gram-negative bacteria and bacterial products is characterized by the infiltration of periodontal tissues of the inflammatory cells, including polymorphonuclear leucocytes, macrophages, lymphocytes, and plasma cells. Activated macrophages release cytokines and some individuals respond to microbial challenge with an abnormally high delivery of such mediators as PGE2, IL-1, and TNF-α.[2]

These cytokines are involved in the destruction of periodontal connective tissue and alveolar bone[3] They can also initiate a systemic acute phase

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response. During the acute phase of many diseases, a characteristic group of changes occur in the plasma cells and of blood termed acute phase response and the substances undergoing characteristic alteration of serum levels are termed acute phase reactants.[4]

Systemic acute phase response is characterized by features, such as fever, neutrophilia, changes in lipid metabolism, and induction of various acute phase proteins, such as C-reactive protein (CRP), fibrinogen, and serum amyloid.[5] CRP is a type I acute phase protein that is produced by the liver in response to diverse inflammatory stimuli.[6] These stimuli include heat, trauma, infection, and hypoxia. In healthy individuals CRP levels are found in trace amounts, that is, <0.3 mg/L serum of CRP could exceed 100 mg/L in the presence of overwhelming systemic infection, which provides a useful marker for tracking the course of infection.[7]

Recent investigations suggested that even a moderate increase in CRP levels, such as those found in periodontitis patients, may predict a risk for atherosclerosis and cardiovascular disease(CVD)[8,9] The mechanism by which CRP participates in CVD is not clear; however, CRP may activate the complement system and be involved in foam cell formation in atheromas. Recent studies showed that CRP is a strong predictor of future coronary artery disease in healthy men and women[7] The purpose of the present study is to quantitatively evaluate the serum levels of CRP in both male and female subjects with various degrees of periodontitis (chronic and aggressive form) and compare them with controls who have a clinically healthy periodontium.

MATERIALS AND METHODS

This was a retrospective clinical study conducted in the Department of Periodontics, Peoples Dental College, Bhopal, India. A total number of 45 subjects were selected from the outpatient department of periodontics. The nature and purpose of the study was explained to the patients and an informed consent was obtained. A detailed case history was recorded in a specially prepared form, which included information regarding the patients' overall medical status/general health and wellbeing.

Materials

Mouth mirror, Williams periodontal probe, Explorer, Tweezer, Disposable 5cc syringe, Spirit cotton swab, Handcuff, and EDTA-coated glass test tube.

Inclusion criteria

Patients aged between 25 and 50 years, they should not have received any antibiotic therapy in the previous 3 months. They should not have undergone any extractions or periodontal therapy in the previous 3 months.[10,11]

Exclusion criteria

Patients with known systemic diseases and presence of other chronic infections, patients taking contraceptive pills, pregnant or lactating females.[10,12]

Based on the periodontal status, the subjects were divided into 3 groups.

Group I: (Control group) 15 subjects with attachment loss (AL) £ 2 mm and pocket depth (PD) < 3 mm were included.[1,7]

Group II: (Generalized aggressive periodontitis) 15 subjects with generalized pattern of severe periodontal destruction with AL of at least 5 mm on 8 or more teeth.[7]

Group III: (Chronic periodontitis) 15 subjects diagnosed with moderate and severe forms of chronic periodontitis were included.[1,13]

Moderate periodontitis: Subjects with a minimum of 20 natural teeth, at least 1 molar tooth in each quadrant and at least 4 sites with AL > 2 mm and <4mm and PD > 5 mm and < 7 mm.

Severe periodontitis: subjects with a minimum of 20 natural teeth, at least, 1 molar tooth in each quadrant and at least 4 sites with AL > 5 mm and PD > 7 mm.

Clinical procedure and study design

After the selection of subjects a detailed case history was taken and the following clinical parameters were recorded. Clinical parameters for the study were Plaque index, Gingival index, Bleeding index, Probing PD, and Clinical attachment level.

These parameters were assessed for subjects in all the 3 groups. For the CRP assessment, blood samples were collected from subjects at the time of clinical examination.

Plaque index (Silness and Loe) Scoring was done for 6 surfaces of all the teeth distobuccal, buccal, mesiobuccal, mesiolingual, lingual, and distolingual.

Criteria for the plaque index:

0: No plaque in the gingival area.

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 surface.
2: Moderate accumulation of soft deposits within the gingival pocket and on the gingival margin and/or on the adjacent tooth surface that can be seen by the naked eye.
3: Abundance of soft matter within the gingival pocket and/or on the gingival margin and adjacent tooth surface.

Bleeding index (Ainamo and Bay):
0: Absence of bleeding.
1: Presence of bleeding.

Gingival index (Loe and Silness);
0: Normal gingiva.
1: Mild inflammation, slight change in color, slight edema, and no bleeding on palpation.
2: Moderate inflammation, redness and edema, ulceration, and tendency to spontaneous bleeding.
3: Severe inflammation, marked redness and edema, ulceration, and tendency to spontaneous bleeding.

Probing PD was measured from the gingival margin to the probable PD at the mesiobuccal, midbuccal, distobuccal, mesiolingual, midlingual, and distolingual surface of all the teeth and clinical attachment level was measured from the cementoenamel junction, to the probable PD of all the teeth on the same surfaces, using the Williams periodontal probe to the nearest millimeter.

Blood sample collection and storage

About 4–5 mL of blood sample was collected from each of the subjects from the brachial vein, by aseptic technique using a 5 cc syringe and transferred to an appropriately labeled tube and allowed to clot, centrifuged, and the smear layer removed carefully. The serum thus obtained was stored at −20°C for the analyses at a later date.

C-reactive protein quantification

Serum CRP levels were assessed by means of a commercially available high-sensitivity CRP (hs-CRP) enzyme immunoassay. (Diagnostics Biochem Canada Inc–ELISA Kit…The EiAsy™ Way)

Statistical analysis

Mean and standard deviation are calculated for all the groups and periodontal parameters. Mean values of each parameter were compared between the groups using one-way analysis of variance with post hoc test of least Significant difference method. Pearson's correlation was used to assess the correlation between severity of periodontitis and serum CRP levels. In the present study, *P* value of 0.05 was considered as significant. Statistical package for social science (SPSS) version 15 was used for statistical analysis. Analysis of covariance was used for comparison of mean values between the groups to adjust the age.

RESULTS

A total number of 45 male and female subjects with the age range between 25 and 50 years participated in the study. All the patients who participated in the study were systemically healthy and were adjusted for factors known to elevate CRP levels. Subjects were classified into 3 groups based on their PD and AL.

Group I: (n = 15) Control group.

Group II: (n = 15) Generalized aggressive periodontitis.

Group III: (n = 15) Chronic periodontitis.

The mean CRP concentration in the groups I, II, and III were calculated. A statistically significant difference (P = 0.012) was found in the CRP level between groups I and II and between groups II and III and between groups I and III [Table 1].

The results of the present study indicated an increase in serum CRP levels in subjects with generalized aggressive periodontitis and chronic periodontitis compared with controls. Clinical parameters, such as bleeding on probing, showed a positive correlation with CRP levels in aggressive periodontitis group and a positive correlation was also seen for probing PD, clinical attachment level, and CRP in chronic periodontitis group of subjects. Of particular concern could be the elevation in CRP levels in younger individuals as represented by aggressive periodontitis patients that may contribute to an early CVD in susceptible patients.

DISCUSSION

Periodontitis is an inflammatory disease of the supporting tissues surrounding the teeth. Earlier it was considered simply as a chronic localized infection; however, a growing body of evidence suggests that the pathology of periodontitis may affect the outcome of several systemic diseases, such as myocardial infarction, stroke, or preterm low birth weight babies[5] Gram-negative anaerobes present in large numbers in subgingival dental plaque in periodontal pockets affect the local and systemic inflammatory response. Endotoxins derived from gram-negative

Table 1: Comparison of C-reactive protein levels among all the groups

	Group I	Group II	Group III	*P* value
Mean	1.0180	4.5453	6.0671	0.012
SD	0.94069	2.88116	3.15639	

microorganisms interact with toll-like receptors expressed on the surface of neutrophils, macrophages, lymphocytes, and plasma cell, which are abundant in periodontal inflammation. Toll-like receptors-ligand complexes activate single transduction pathways in both the innate and adaptive immune systems leading to the production of cytokines, which coordinate the local and systemic inflammatory responses. Some individuals respond to microbial challenge with an abnormally high delivery of such inflammatory mediators as PGE-2, IL-1, and TNF.[2,14,15]

CRP is a very strong acute phase protein. In healthy young subjects and resting situations the serum concentration is < 1.5 mg/L. Plasma CRP is produced only by hepatocytes, predominantly under transcriptional control by the cytokine IL - 6, although other sites of local CRP synthesis and possibly secretions have been suggested. CRP has been known to be present in monocyte-derived macrophages, in atherosclerotic plaques, lymphocytes, and alveolar macrophages. Acute phase proteins not only appear in acute and severe disease processes, but also in longstanding, chronic conditions. For example, CRP has often been found at relatively low levels (range, 0.3–3.0 mg/L) in subjects with chronic stomach ulcers associated with *Helicobacter pylori*, in persons with chronic lung infections, such as *Chlamydia pneumonia*, and in individuals with a chronic cytomegalovirus infection. Simultaneously, it has been established that CRP in particular showed a strong association with CVD. Slightly elevated (>0.3–3 mg/L) and chronically present levels of CRP were determined to have a predictive value for the occurrence of a cardiovascular event. Both periodontal and CVDs share several risk factors, including smoking, diabetes mellitus, age, socioeconomic status, obesity, and psychologic stress. The epidemiologic evidence to date show a significant but modest relationship between periodontitis and CVD.[9]

CRP production is part of the nonspecific acute phase response to most forms of inflammation, infection, and tissue damage and was therefore considered to provide clinically useful information. A high sensitivity assay for measuring CRP levels has been developed to detect the levels of CRP below what was previously considered the normal range.

In healthy individuals, CRP levels are found in trace amounts with levels < 0.3 mg/L, in acute inflammation CRP could exceed 100 mg/L, and the level decreases in chronic inflammation. Consequently, CRP has been used as a marker of the course of infection. Accumulating evidence suggests that small elevation of serum CRP within the range of 1–10 mg/L is a significant indicator of risk of atherosclerosis, CVD,[9] and type 2 diabetes. Positive CRP may indicate any of a number of possibilities,[11] Rheumatoid arthritis, Rheumatic fever, Cancer, Tuberculosis, Pneumococcal pneumonia, Myocardial infarction, Systemic lupus erythematosus.

Positive CRP results also occur during the last half of pregnancy or with the use of oral contraceptive pills, increase with aging, obesity, high blood pressure, alcohol use, smoking, low levels of physical activity, chronic fatigue, coffee consumption, elevated triglycerides, insulin resistance and diabetes, a high protein diet, suffering sleep disturbances, and depression. Alcohol can cause inflammation and raise CRP.[11]

The best way we know to reduce CRP levels are exercise and a diet that includes omega-3 fatty acids as statins appear to protect against inflammation as well as cholesterol.[11] CRP levels decrease with the resolution of inflammation or trauma.[7]

Recent studies have indicated that serum CRP of patients with periodontal diseases is elevated with deep periodontal pockets, severe attachments loss, subgingival microflora,[1] and alveolar bone loss.[6]

Treatment of periodontal infection, whether by intensive mechanical therapy, drug therapy, or extraction significantly lowers the serum CRP levels.[16]

There are very few studies that have evaluated CRP levels in aggressive periodontitis subjects. However, one study be Salzburg *et al*.[7] reported an increase in CRP levels even in generalized aggressive periodontitis patients (3.72 mg/L), which is similar to the findings of the present study (4.54 mg/L).

In the present study, although the CRP levels were found to be elevated in aggressive periodontitis group of subjects, the mean levels were found to be lower than in the chronic periodontitis group. The reason for this difference in CRP levels between aggressive and chronic periodontitis groups is not exactly understood

at this point in time but could be attributable to the longstanding nature and chronic course of the disease process of chronic periodontitis, thus exerting its systemic influence over a long period of time compared with aggressive periodontitis, which runs a shorter course.[1,6]

Also the mean age values of chronic periodontitis subjects and aggressive periodontitis subjects in the present study were in accordance with the prevalence studies of aggressive periodontitis and chronic periodontitis, which have shown an increased prevalence for the occurrence of aggressive periodontitis in younger age groups and occurrence of chronic periodontitis in older age groups.

In the present study, clinical parameters such as bleeding on probing showed a positive correlation with CRP level in aggressive periodontitis group and a positive correlation was also seen for probing PD, clinical attachment level, and CRP in chronic periodontitis group of subjects. This is similar to the results of earlier studies, which revealed increased bleeding on probing depth and AL to be significantly associated with elevated CRP concentrations.[1,7]

CONCLUSIONS

The results of the present study indicated an increase in serum CRP levels in subjects with generalized aggressive periodontitis and chronic periodontitis as compared with controls, which was statistically significant. Clinical parameters such as bleeding on probing showed a positive correlation with CRP levels in aggressive periodontitis group and a positive correlation was also seen for probing PD, clinical attachment level, and CRP in chronic periodontitis group subjects.

However, the result of the present study cannot be used to determine the causality of the associations between periodontitis and CRP due to some limitations, one being the small sample size and the other is that the study is only cross-sectional. Moreover, the subjects might have undiagnosed systemic factors that could influence the CRP levels. But keeping in view the results of the earlier studies and that of the present study, it would be appropriate if large sample based, well-controlled, longitudinal trials are performed to determine the relationship between periodontitis and elevated CRP levels and the effect of periodontal therapy on serum CRP concentration.

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How to cite this article: Kanaparthy A, Kanaparthy R, Niranjan N. Evaluation of serum C-reactive protein levels in subjects with aggressive and chronic periodontitis and comparison with healthy controls. Dent Res J 2012;9:261-5.

Source of Support: Nil. **Conflict of Interest:** None declared.