

Assessment of C-Reactive Protein Level in Patients with Symptomatic Apical Periodontitis and Periodontal Diseases

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Abstract

Introduction: C-reactive protein (CRP) is a homopentameric acute-phase inflammatory protein, a highly conserved plasma protein. Objective of this study is to investigate the potential association between apical periodontitis and chronic generalized periodontitis and inflammatory serum markers indicative of cardiovascular risk. **Methodology:** In this cross-sectional study, 90 patients were divided in three groups: Group 1 consists of patient affected by chronic generalized periodontitis, Group 2 consists of patient affected by chronic apical periodontitis and Group 3 consists of healthy controls. All the patients were checked for body mass index, periodontal status (CPI) and caries status (DMFT). Blood sample was collected for high-sensitivity-CRP and values were calculated with fully automated latex agglutination – Beckman coulter method for all the groups. **Results:** CRP was significantly expressed in apical periodontitis (1.94 ± 0.86) and chronic generalized periodontitis (1.92 ± 0.81) compared with healthy controls (0.87 ± 0.61) ($P < 0.001$). This suggests that individuals with periodontitis (both types) have elevated levels of CRP, indicating a potential systemic inflammatory response. **Conclusion:** This study shows that CRP is unregulated during apical periodontitis and chronic generalized periodontitis. Still, the regulatory mechanisms and functional significance in apical periodontitis and chronic generalized periodontitis and their potentially associated systemic effects remain to be elucidated.

Keywords: Apical periodontitis, C-reactive protein, Periodontal disease.

INTRODUCTION

C-reactive protein (CRP) is a homopentameric acute-phase inflammatory protein, a highly conserved plasma protein.^[1] At locations of infection or inflammation, CRP can increase up to 1,000-fold.^[2] Elevated serum levels of CRP, a clinical marker of inflammation, are a powerful independent predictor of cardiovascular disease (CVD) in those who do not exhibit any symptoms.^[3] Increased levels of inflammatory cytokines, particularly interleukin-6 (IL-6), cause the CRP gene to be transcriptionally induced primarily in hepatocytes in the liver.^[4] An individual has a higher risk of coronary heart disease if their CRP level is >3 mg/L, and this risk rises in individuals who have Type 2 diabetes.^[5]

Bacterial infection raises the levels of CRP, a sign for inflammation.^[6] Apical periodontitis typically arises as a consequence of pulpal infection caused by bacterial biofilm inside the root canal system of teeth. An immunoinflammatory response is elicited by endodontic offenders and their by-

products, which attempt to localize the infection and prevent further dissemination at the expense of apical periodontal tissue breakdown.^[7]

Apical periodontitis is “an acute or chronic inflammatory lesion around the apex of a tooth caused by bacterial infection of the pulp canal system”.^[8] Typically, it follows the presence of deep caries lesions or dental fractures. This condition can manifest as either acute and painful or chronic and asymptomatic. While root canal therapy serves as a viable treatment option for eliminating bacteria and preventing recurrence, apical periodontitis may persist or reoccur following treatment completion. Histologically, it is characterized by a periapical

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inflammatory reaction subsequent to bone resorption and local infiltration of inflammatory cells. Clinical diagnosis relies on patient symptoms, clinical indicators, and radiographic findings, with chronic apical periodontitis specifically identified by the presence of periradicular radiolucencies on affected teeth.^[9]

Periodontal diseases encompass conditions that impact the supportive tissues surrounding the tooth, including the alveolar bone, periodontal ligament, cementum, and gingiva. The onset of periodontal infection is instigated by particular invasive oral pathogens, comprising both aerobic and anaerobic bacteria, which colonize dental plaque biofilms on the tooth's root surface.^[10]

Despite several distinctions between chronic inflammatory diseases originating from periodontal and endodontic sources, significant similarities exist, primarily characterized by: (1) The presence of a common microbiota often associated with Gram-negative anaerobic bacteria in both conditions,^[11] and (2) the observation of heightened systemic cytokine levels in association with both disease processes. For instance, increased concentrations of inflammatory mediators have been detected in both the gingival crevicular fluid of individuals with periodontal disease and the periapical tissues of teeth affected by endodontic pathology.^[9]

The inflammatory response within the oral connective tissue, triggered by microorganisms, initiates symptomatic vasodilation, leading to heightened permeability of the endothelium. This phenomenon facilitates the migration of leukocytes into the perivascular region and allows for bacterial invasion.^[12]

Overall, low-grade chronic dental infections have been linked to various systemic conditions to varying extents.^[13]

From a mechanistic perspective, it is widely acknowledged that an increased systemic inflammatory burden significantly impacts the onset and progression of CVDs.^[9] Elevated levels of inflammatory bioactive molecules, such as acute-phase proteins (high-sensitivity [hs] CRP), cytokines (including tumor necrosis factor alpha, IL-1, IL-6, IL-12, and IL-10), matrix metalloproteinases (MMPs [specifically MMP-8 and MMP-9]), and soluble adhesion molecules (soluble [s] E-selectin, vascular cellular adhesion molecule [VCAM]-1, and intercellular adhesion molecule [ICAM]-1), play integral roles across various stages of atherogenesis and exhibit predictive value for future vascular events.^[13]

Despite the observed epidemiological correlation, there remains a scarcity of evidence definitively establishing the biological plausibility linking apical periodontitis with cardiovascular risk. A recent meta-analysis revealed limited evidence suggesting elevated levels of serum immunoglobulins in connection with apical periodontitis, yet other pertinent inflammatory markers were not consistently supported.^[13] Our objective is to investigate the potential association between apical periodontitis and chronic generalized periodontitis and inflammatory serum markers indicative of cardiovascular risk.

MATERIALS AND METHODS

Patient coming to Government Dental College and Hospital, Ahmedabad fulfilling below mentioned study criteria were selected for the study. In the present cross-sectional study, the selected sample was divided in three groups: Group 1 consists of patient affected by chronic generalized periodontitis, Group 2 consists of patient affected by chronic apical periodontitis and Group 3 consists of healthy controls. Each group consists of 30 patients.

- Inclusion criteria for Group 1 was the following:
 1. Age 20–40 patients
 2. Presence of at least 25 teeth
 3. Presence of localized or diffuse periodontal disease
 4. Absence of any endodontic lesion.
- Inclusion criteria for Group 2 was the following:
 1. Age 20–40 patients
 2. Presence of at least 25 teeth
 3. Presence of at least one radiographically assessed endodontic lesion
 4. Absence of chronic periodontal disease.
- Inclusion criteria for Group 3 was the following:
 1. Age 20–40 patients
 2. Presence of at least 25 teeth
 3. Absence of periodontal and endodontic lesion.
- Exclusion criteria was the following:
 1. Presence of CV risk factors (arterial hypertension, dyslipidemia, diabetes mellitus, obesity, and history of smoking)
 2. Presence of chronic inflammatory condition involving systemic health
 3. Presence of non-endodontic lesions.

Null hypothesis to be tested was that there is no association between chronic periodontitis, chronic apical periodontitis, and CRP levels.

Group 1 consisting of patients affected by chronic periodontitis, which was checked using CPI index, Group 2 consists of patients affected by chronic apical periodontitis which will be screened by OPG and IOPA and Group 3 consists of healthy controls. In addition, all the patients were checked for body mass index (BMI), periodontal status (CPI) and caries status (DMFT). Blood sample was collected for hs-CRP values calculated with fully automated latex agglutination – Beckman coulter method for all the groups.

The American Heart Association and U.S. Centers for Disease Control and Prevention have defined risk groups as follows:

- Low risk: <1.0 mg/L
- Average risk: 1.0 mg/L
- High risk: Above 3.0 mg/L.

Sample size estimation

To calculate the sample size for this study, a pilot study was conducted among 20 subjects having CGP and AP. The results of CRP value obtained for AP group, and CRP group is

1.80 ± 1.06 mg/dL and 1.20 ± 0.56 mg/dL, respectively. The mean difference obtained was 0.60 mg/dL using the formula sample size was calculated for each group is 30; hence, the estimated sample size is 90.

Statistical analysis

After collection of data, the data were coded and entered in Microsoft Excel 2019. The data were presented as mean ± standard deviation. The normality of data was checked using Shapiro–Wilk test, showing the data is normally distributed having $P > 0.05$. Hence, parametric test was applied. The mean difference among the groups was compared using one-ANOVA test. If the result is statistically significant than *post hoc* Tukey test was used to compared difference between two groups. Statistical Package for the Social Science (SPSS version 23, IBM Chicago) was used for analysis. The level of significance was set at 5%.

RESULTS

The study volunteers were composed of 47 males and 43 females. The average age for apical periodontitis was 30.70 ± 4.80 years, for chronic generalized periodontitis was 34.50 ± 4.93 years and for the control group, 24.97 ± 1.33 years ($P < 0.001$) (Table 1).

The $P < 0.001$ indicates highly significant differences in BMI among all three groups (apical periodontitis, chronic generalized periodontitis, and control). This suggests that BMI varies significantly between individuals with apical periodontitis, chronic generalized periodontitis, and those without these conditions (control group) (Table 2).

Mean CPI of apical periodontitis and chronic generalized periodontitis is 1.68 ± 0.55 and 4.51 ± 0.55, respectively, which is significantly higher ($P < 0.001$) than the control group (1.20 ± 0.25) (Table 3).

DMFT scores are significantly higher ($P < 0.001$) in both the apical periodontitis (2.40 ± 1.04) and chronic generalized periodontitis (3.73 ± 1.01) groups compared to the control group (2.20 ± 1.09) (Table 3).

The comparisons show significant differences ($P < 0.001$) in CPI scores between all groups. Chronic generalized periodontitis consistently has higher CPI scores compared to both apical periodontitis and control groups; while the control group has the lowest CPI scores (Table 4).

There are significant differences in DMFT scores between groups, except between apical periodontitis and control groups where the difference is not statistically significant ($P = 0.74$). Chronic generalized periodontitis group consistently shows higher DMFT scores compared to both apical periodontitis and control groups (Table 4).

CRP was significantly expressed in apical periodontitis (1.94 ± 0.86) and chronic generalized periodontitis (1.92 ± 0.81) compared with healthy controls (0.87 ± 0.61) ($P < 0.001$). This suggests that individuals with periodontitis (both types)

Table 1: Comparison of age among groups

Groups	Mean ± standard deviation (in years)	P value
Apical periodontitis (n=30)	30.70±4.80	<0.001**
Chronic generalized periodontitis (n=30)	34.50±4.93	
Control (n=30)	24.97±1.33	

** $P < 0.001$ highly significant

Table 2: Comparison of BMI among groups

Groups	Mean ± standard deviation (kg/m ²)	P value
Apical periodontitis (n=30)	25.11±1.58	<0.001**
Chronic generalized periodontitis (n=30)	24.54±1.49	
Control (n=30)	26.77±1.99	

** $P < 0.001$ highly significant. BMI: Body mass index

Table 3: Comparison of clinical parameters among groups

Groups	Periodontal status (CPI)	Caries status (DMFT)
Apical periodontitis (n=30)	1.68±0.55	2.40±1.04
Chronic generalized periodontitis (n=30)	4.51±0.55	3.73±1.01
Control (n=30)	1.20±0.25	2.20±1.09
P value	<0.001**	<0.001**

** $P < 0.001$ highly significant

have elevated levels of CRP, indicating a potential systemic inflammatory response (Table 5).

There is no significant difference in CRP levels between individuals with apical periodontitis and those with chronic generalized periodontitis. However, both the apical periodontitis and chronic generalized periodontitis groups show significantly higher CRP levels compared to the control group ($P < 0.001$) (Table 6).

DISCUSSION

Given the prevalence of Gram-negative anaerobic microbes linked to endodontic infections, which are also present in periodontal lesions and atherosclerotic plaques, links between endodontic inflammation and cardiovascular consequences appear biologically plausible.^[14]

The anatomic relation of apical periodontitis origins with the bloodstream can lead to the release of inflammatory mediators, bacterial products (i.e., lipopolysaccharide) and/or bacteria, resulting in low-grade systemic inflammation and/or direct vascular damage. There is no epithelial barrier separating the highly vascular connective tissue from apical granulomas and cysts from the necrotic root canal, in contrast to marginal periodontal diseases. In addition, extraradicular infection denotes the introduction of endodontic germs directly into the bloodstream.^[15,16]

Elevated levels of both IL-6 and CRP are associated not only with subsequent atherosclerosis but also with the development

Table 4: Multiple comparison of clinical parameters between groups

Groups	Mean difference CPI	P value	Mean difference DMFT	P value
Apical periodontitis versus chronic generalized periodontitis	-2.83	<0.001**	-1.33	<0.001**
Apical periodontitis versus Control	0.48	<0.001**	0.20	0.74
Chronic generalized periodontitis versus control	3.31	<0.001**	1.53	<0.001**

**P<0.001 highly significant

Table 5: Comparison of biomarkers among groups

Groups	CRP Mg/L
Apical periodontitis (n=30)	1.94±0.86
Chronic generalized periodontitis (n=30)	1.92±0.81
Control (n=30)	0.87±0.61
P value	<0.001**

**P<0.001 highly significant. CRP: C-reactive protein

Table 6: Multiple comparison of CRP between groups

Groups	Mean difference	P value
Apical periodontitis versus chronic generalized periodontitis	0.02	0.99
Apical periodontitis versus Control	1.07	<0.001**
Chronic generalized periodontitis versus Control	1.05	<0.001**

**P<0.001 highly significant. CRP: C-reactive protein

of Type II diabetes, even among individuals with no current evidence of insulin resistance.^[17]

Emerging reports propose that extrahepatic sources of CRP production may explain the lower and more sustained CRP concentrations that appear to predict cardiovascular risk. Recently, the literature reported that periodontal fibroblasts have low responsiveness to IL-6,^[18] whereas enhanced CRP synthesis to IL-6 can be seen in apical periodontitis through trans-signaling, acting as a potential reservoir of IL-6 and CRP for sustaining a low systemic inflammatory response.^[19,20] In the line of these studies, our study also shows that CRP is significantly up-regulated in apical periodontitis and chronic generalized periodontitis. Although there is no directional association between these entities, experimentally induced apical periodontitis in a rat model supports the hypothesis that apical periodontitis can induce systemic inflammation and functional impairment in remote organs.^[21]

CRP is involved in every step of vascular disease by enhancing inflammation, oxidative stress, and coagulation.^[22] These effects are mediated by several properties of CRP, including its ability to activate complement and up-regulate vascular adhesion molecules, monocyte recruitment into the arterial wall, proinflammatory cytokines (tumor necrosis factor alpha and IL-1), superoxide, myeloperoxidase, and MMPs; it also impairs endothelial vasoreactivity and mediates low-density lipoprotein uptake by endothelial macrophages to form foam cells, among other effects.^[22-24]

Both specific and non-specific immune responses are significantly influenced by the cytokine network. Many studies have demonstrated the production of cytokines in periapical lesions.^[25] IL-6 is considered both a pro- and anti-inflammatory cytokine; it is produced during inflammation and after tumor necrosis factor-alpha (TNF-a) and IL-1 secretion.

It has been shown that macrophages present in periapical lesions can also produce IL-6 *in vitro*. Macrophages are often stimulated by primary endodontic contents to release a broad range of cytokines. These cytokines establish various network interrelationships that are linked to the development of distinct patterns of clinical and radiographic aspects for endodontic illnesses.^[26] The overproduction of IL-6 that was found is particularly supportive of hyper-reactivity of macrophages to stimulation by endodontic contents.^[26]

Four research looked at the connection between the level of IL-6 produced *in vitro* and the extent of the periapical lesion.^[26,27] They concluded that larger periapical lesions have higher IL-6 levels, and they showed that IL-6 can induce osteoclast formation and bone resorption^[28] thus confirming its role in bone resorption in chronic inflammatory periodontitis.

IL-6 was present in periapical lesions *in vivo* and also in *in vitro* models,^[29] indicating its pro-inflammatory role. Nevertheless, another study found that IL-6 knockout mice had increased periapical lesion development. According to the authors, it indicates that this group of mice developed lesions in the early phase of infection.^[28] Considering these findings, IL-6 has been hypothesized to be a critical downstream factor in the cytokine cascade determining bone resorption.^[30] The depletion of IL-6 may therefore affect the activation of osteoclasts, which is required for bone resorption. Therefore, a localized increase in IL-6 in response to infection during the formation of periapical lesions may cause both the activation of pre-existing osteoclasts and the production of new osteoclasts from hematopoietic progenitor cells. However, their data indicate that the depletion of IL-6, similar to the depletion of IL-1 and TNF responses,^[30] does not prevent periapical bone resorption, suggesting that other factors are more directly involved in regulating bone resorption. Perhaps other cytokines are involved in bone resorption in the absence of IL-6.

Cytokines are multifunctional. One cytokine may act on several target cells, and several cytokines may have an effect on one target cell. Furthermore, depending on the tissue, cytokines can have an antagonistic or synergistic effect. Previous studies support our hypothesis showing that after its secretion, IL-6 subsequently inhibits the secretion of TNF-a

and IL-1, pro-inflammatory cytokines involved in periapical bone resorption.^[26,31] It is important to note that TNF- α , IL-1 β and IL-6 stimulate osteoclast differentiation in a synergic fashion.^[32] Therefore, the interaction between IL-6, TNF- α , IL-1, and RANKL may enhance bone resorption.^[33]

In the present study, both the apical periodontitis and chronic generalized periodontitis groups show significantly higher CRP levels compared to the control group ($P < 0.001$). This indicates that both types of periodontitis are associated with elevated CRP levels, suggesting a systemic inflammatory response. These findings underscore the potential systemic implications of periodontitis, regardless of its type, in contributing to elevated CRP levels.

The elevated levels of CRP and IL-6 in periodontitis patients may occur when bacteria and bacterial products, such as lipopolysaccharide, as well as locally produced pro-inflammatory cytokines enter the circulation. The correlations between chronic infections and CVD that have been reported may be partially explained by CRP and IL-6. CRP may activate complement in damaged vessel walls whereas IL-6 has proinflammatory properties and a pro-coagulant effect. These characteristics might have a role in the development of coronary syndromes. Furthermore, IL-6 stimulates the production of CRP by hepatocytes.^[34]

CRP acts locally and systemically by enhancing inflammation, oxidative stress, and a procoagulant state. Overall, the current results sustain that apical periodontitis and chronic generalized periodontitis might act as a continuous reservoir of potent proinflammatory mediators, such as IL-6 and CRP, that besides inducing local tissue destruction might also contribute to systemic inflammation. These potential implications become even more relevant in AAP due to its lack of clinical symptoms and unawareness of the patients.

CONCLUSION

Our study shows that CRP is upregulated during apical periodontitis and chronic generalized periodontitis. Still, the regulatory mechanisms and functional significance in apical periodontitis and chronic generalized periodontitis and their potentially associated systemic effects remain to be elucidated.

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