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ORIGINAL RESEARCH

Assessment of C-reactive Proteins, Cytokines, and Plasma Protein Levels in Hypertensive Patients with Apical Periodontitis

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ABSTRACT

Introduction: Chronic apical periodontitis (CAP) manifests mostly as periapical radiolucency. Various inflammatory mediators play a significant role in the pathogenesis of apical periodontitis. In acute inflammatory conditions, C-reactive proteins (CRP) and fibrinogen show a rise in their concentrations. In chronic diseases with high inflammatory components, an increased prevalence of hypertension has been observed. Hence, we assessed the association of CAP and plasma levels of various inflammatory markers (CRP, interleukin 6 [IL-6], and fibrinogen) in severely hypertensive patients.

Materials and methods: This study was conducted in the conservative wing of the institute and included assessment of 250 hypertensive patients with apical periodontitis. With the help of periapical radiographs and clinical examination, the assessment of following parameters was done: Amount of teeth present, visible plaque index, periodontal pocket probing depth, clinical attachment level, bleeding on probing, presence/absence of carious lesions, which included assessment of caries in crown portion, in the root portion, and residual tooth roots (RR), presence of CAP from each patient; 8 mm of venous blood was collected in the morning for the assessment of plasma levels of IL-6, CRP, and fibrinogen levels. Immediate collection and processing of the samples were done in the hospital laboratory. All the results were analyzed by Statistical Package for the Social Sciences software.

Results: Out of 250, 155 patients were females. Mean plasma levels of CRP observed in our study were 0.8 mg/dL. Mean plasma levels of IL-6 and fibrinogen were found to be 3.3 and 337.1 mg/dL respectively. A significant correlation was observed while comparing mean body mass index (BMI), RR, and CAP in hypertensive patients. While comparing the mean plasma IL-6 levels, mean BMI, and CAP in the patients, significant results were obtained. Significant correlation was observed while comparing the mean BMI and CAP in hypertensive patients.

Conclusion: Systemic levels of CRP, IL-6, and fibrinogen levels are influenced by the presence of CAP in hypertensive patients.

Clinical significance: In hypertensive patients, CAP alters the systemic levels of various inflammatory markers.

Keywords: Apical periodontitis, C-reactive proteins, Fibrinogen, Inflammatory markers.

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INTRODUCTION

Manifesting commonly as periapical radiolucency, chronic apical periodontitis (CAP) is an inflammatory disease of the periradicular tissues. Microbial floras of the pulp canals of the teeth are responsible for the occurrence of these inflammatory lesions.[1,2] The root canal system acts

as a rich reservoir of the microorganism, which plays an important role in the etiopathogenesis of the periodontal diseases. Various antigens are released by these microorganisms in the periradicular areas, which result in propagation of inflammatory reactions, subsequently resulting in resorption of bone and periodontal ligament destruction.[3,4] Various cells involved in the immune system of the body secrete proinflammatory cytokines, such as interleukin-1β (IL-1β), IL-6, and IL-11. These mediators play a significant role in the pathogenesis of apical periodontitis.[5] Under the category of acute phase reactants, C-reactive protein (CRP) and fibrinogen are included since a rise in their concentrations has been observed in various acute inflammatory conditions.[6,7] In chronic diseases with high inflammatory components, an increased prevalence of hypertension has been observed. Diagnosis of refractory hypertension is done when blood pressure levels remain above 140/90 mm Hg even in cases where the patients are undergoing treatment therapy. Association between apical periodontitis and endodontic therapy in patients with cardiovascular pathologies has been explored in the last few studies.[8] Hence, we assessed the association of CAP and plasma levels of various inflammatory markers (CRP, IL-6, and fibrinogen) in severely hypertensive patients. Nonassociation between these inflammatory markers and CAP was taken as initial null hypothesis.

MATERIALS AND METHODS

This study was conducted in the conservative wing of the institute and included assessment of 250 hypertensive patients that reported with the chief complaint of apical periodontitis from 2010 to 2012. Ethical approval was taken from the Institutional Ethical Committee, and written consent was obtained from all the patients after explaining in detail the entire research protocol. Patients diagnosed with refractory hypertension were included in this study. These included those subjects in which values of blood pressure remained >140/90 mm Hg, even in those cases where patients were undergoing treatment protocol.[9] Sociodemographic data were collected from the data records of the patients. Assessment of the smoking history of the patients was also done during the initial phase of the study. Diagnosis of the patients was done based on the criteria defined by the American Heart Association.[10] A certified cardiologist was appointed to supervise the patients during the entire treatment protocol.

Clinical Assessment

Collection of the medical and dental records and data was done from the record files of the patients during their appointment with the doctor. Single certified examiner was appointed to examine the dental, periodontal, and radiographic profile of the patients. With the help of periapical radiographs and clinical examination, the assessment of following parameters was done:

- Amount of teeth present,
- Visible plaque index (VI),
- Periodontal pocket probing depth (PD),
- Clinical attachment level (CAL),
- Bleeding on probing (BP),
- Presence/absence of carious lesions, which included assessment of caries in crown portion, in the root portion, and residual tooth roots (RR),
- Presence of CAP.

Dental mirrors and probes were used for the assessment of VI. North Carolina 15 mm periodontal probe was used for the evaluation of PD and CAL. PD, CAL, and caries were assessed on radiographs based on criteria described by Vidal et al.[11] All those lesions that were considered as positive for the presence of periapical lesion in which radiolucency was present on radiographic examination along with evidence of pulp necrosis clinically. Same experienced examiner was used for the assessment of clinical and radiographic data.

Inclusion Criteria

- Antihypertensive therapy in patients for a minimum of 3 years,
- Patients <45 years of age,
- Patients in which no current dental treatment was carried out,
- Patients with negative history of any other system illness,
- Patients with negative history of any known drug allergy,
- Patients who had not undergone any major or minor surgical procedure in the last 6 months,
- Patients who had not undergone any antibiotic or anti-inflammatory drug therapy in the last 8 months.

From each patient, 8 mm of venous blood was collected in the morning for the assessment of plasma levels of IL-6, CRP, and fibrinogen levels. Immediate collection and processing of the samples were done in the hospital laboratory. Kits and system as used by Vidal et al[11] were used for the assessment of plasma levels of inflammatory markers. Following were the lower limits used for the detection of the inflammatory parameters.

- *IL-6 levels*: 0.1 mg/dL.
- *CRR levels*: 0.016 mg/dL.
- *Fibrinogen levels*: 50.0 mg/dL.

All the results were analyzed by Statistical Package for the Social Sciences software. Multiple regression coefficient and Chi-square test were used for the assessment of the level of significance.

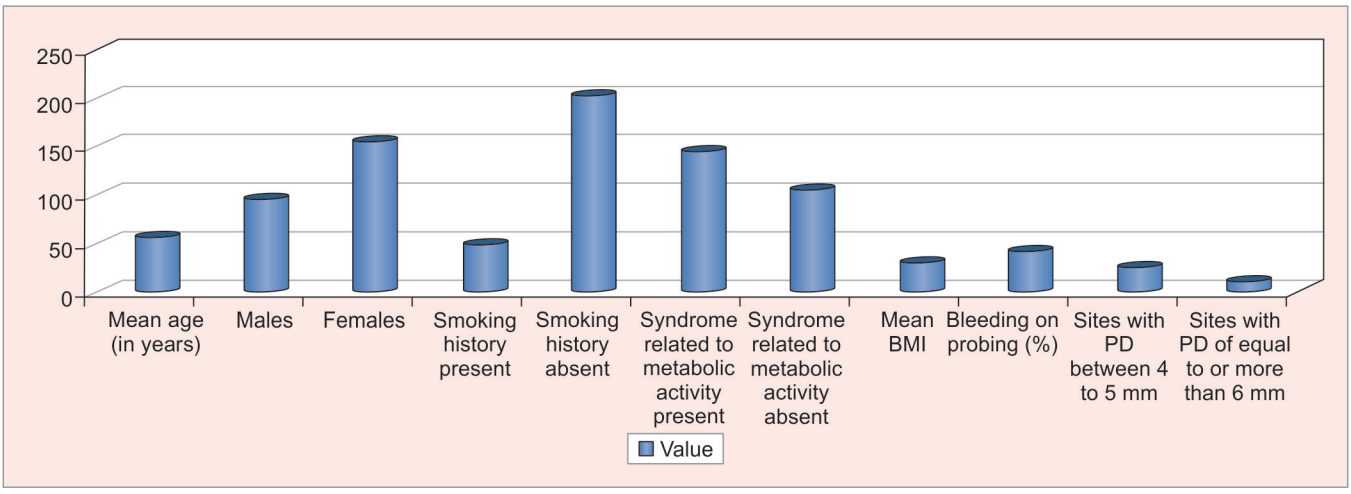
RESULTS

Mean age of the patients in this study was 55.2 years (Graph 1). Out of 250, 155 patients were females while remaining were males. In this study, 202 patients showed a negative smoking history. The presence of metabolic syndrome was observed in 145 patients. Mean body mass index (BMI) of the patients in this study was 30.5. Blood pressure was present in 42.1% of the patients. Mean plasma levels of CRP observed in our study were 0.8 mg/dL (Graph 2). Mean plasma levels of IL-6 and fibrinogen were found to be 3.3 and 337.1 mg/dL respectively. Table 1 shows the association of CRP levels in patients with CAP with various clinical and independent parameters. A significant correlation was observed while comparing mean BMI, RR, and CAP in hypertensive patients. Table 2 highlights the association of IL-6 levels in patients with CAP with various clinical and independent parameters. While comparing the mean plasma IL-6 levels, mean BMI and CAP in the patients, significant results were obtained. Table 3 shows the association of fibrinogen levels in patients with CAP with various clinical and independent parameters. Significant correlation was observed while comparing the mean BMI and CAP in hypertensive patients.

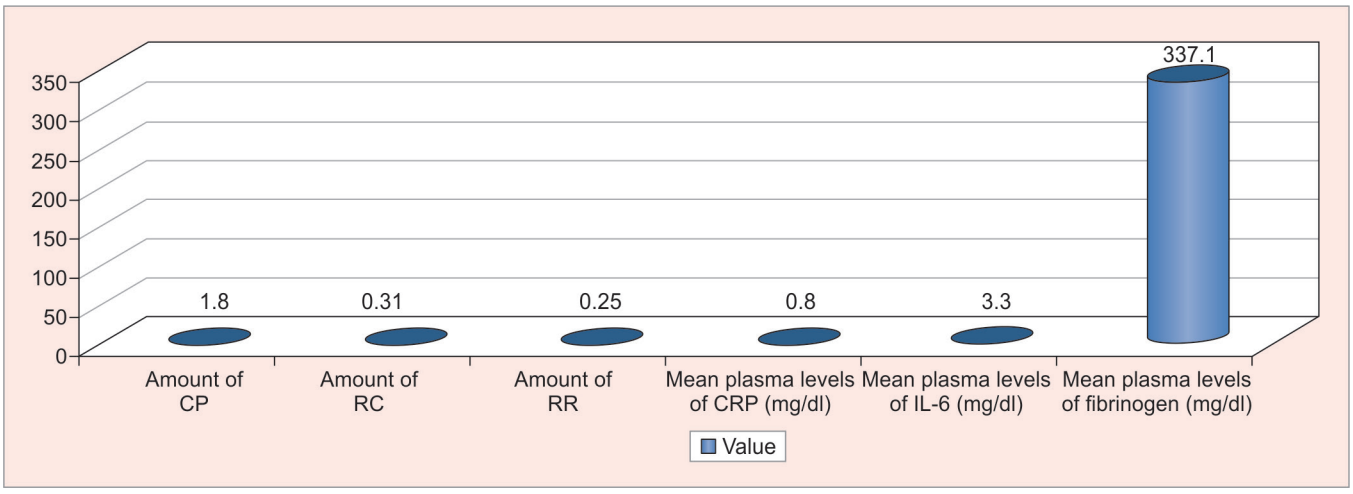
DISCUSSION

Polymicrobial infection of the root canal system is one of the most common factors for causation of apical periodontitis. Following the invasion of microorganisms, necrosis of pulp tissue occurs which subsequently leads to the formation of microbial biofilm. These changes are followed by initiation of inflammatory processes at the apical most portion of the tooth where direct communication between the microorganisms and the periapical tissues is formed. Resorption of bone follows which leads to invasion of inflammatory cells. It is after these changes that the apical periodontitis starts appearing on the radiograph.[12]

An increase in acute-phase reactants (CRP, fibrinogen) and inflammatory cytokines is seen in chronic



Graph 1: Clinical and demographic details of the patients



Graph 2: Plasma levels of inflammatory markers and caries in patients; CP: Chronic Periodontitis; RC: Root Caries

Table 1: Association of CRP levels in patients with CAP with various clinical and independent parameters

Parameters	*Adjusted regression coefficient*	*p-value*
Body mass index	0.262	0.02*
Association of metabolic syndrome	0.220	0.52
Smoking (%)	–0.069	0.31
Bleeding on probing	0.210	0.31
Periodontal pocket probing depth of 4–5 mm (n)	0.130	0.09
Periodontal pocket probing depth ≥6 mm (n)	0.220	0.18
Cavities in coronal tooth region (n)	0.295	0.82
Cavities in root region (n)	0.190	0.47
Residual tooth roots (n)	0.193	0.03*
Chronic apical periodontitis	0.252	0.01*

*Significant

Table 2: Association of IL-6 levels in patients with CAP with various clinical and independent parameters

Parameters	*Adjusted regression coefficient*	*p-value*
Body mass index	0.235	0.02*
Association of metabolic syndrome	0.080	0.03*
Smoking (%)	−0.112	0.15
Bleeding on probing	0.151	0.23
Periodontal pocket probing depth of 4–5 mm (n)	0.202	0.32
Periodontal pocket probing depth ≥6 mm (n)	0.180	0.52
Cavities in coronal tooth region (n)	0.090	0.58
Cavities in root region (n)	0.070	0.14
Residual tooth roots (n)	0.095	0.35
Chronic apical periodontitis	0.150	0.02*

*Significant

Table 3: Association of fibrinogen levels in patients with CAP with various clinical and independent parameters

Parameters	*Adjusted regression coefficient*	*p-value*
Body mass index	0.200	0.00*
Association of metabolic syndrome	0.170	0.21
Smoking (%)	0.050	0.41
Bleeding on probing	0.300	0.25
Periodontal pocket probing depth of 4–5 mm (n)	0.315	0.15
Periodontal pocket probing depth ≥6 mm (n)	0.270	0.34
Cavities in coronal tooth region (n)	0.289	0.55
Cavities in root region (n)	0.155	0.41
Residual tooth roots (n)	0.263	0.20
Chronic apical periodontitis	0.390	0.01*

*Significant

inflammatory diseases. All these inflammatory mediators are broadly categorized into two categories. First category comprises cytokines that play a role in cellular inflammation (IL-1, IL-2, IL-3, IL-4, IL-7, transforming growth factor, etc.), while the category includes mediators that play a role in humoral immunity (IL-3, IL-4, IL-5, IL-6, IL-7, etc.).[13] In patients with pulp necrosis, once the periapical lesion is established, various inflammatory mediators are released, among which IL-1, IL-6, IL-8, and IL-17 are the prominent in the development of apical periodontitis.[14] An alteration in CRP and other mediators has also been seen in various inflammatory lesions.[15] A relation between cardiovascular diseases and periodontal diseases has already been well established. In various observational and meta-analysis-based studies, a statistically significant elevated risk of cardiovascular diseases is seen in periodontitis patients.[16] Hence, we assessed the association of CAP and plasma levels of various inflammatory markers (CRP, IL-6, and fibrinogen) in severely hypertensive patients. Nonassociation between these inflammatory markers and CAP was taken as initial null hypothesis.

In this study, we observed a significant correlation of mean CRP levels with BMI, RR caries, and chronic periodontitis (Table 1). However, a significant finding regarding the association of IL-6 and fibrinogen was observed only with apical periodontitis and BMI of the patients (Tables 2 and 3). Our results were in correlation with the results of Marton and Kiss[17] and Cotti et al[18] who observed similar findings in their studies. These results favor the hypothesis, as suggested by the previous authors, that apical periodontitis plays a modifying role in altering the systemic levels of various inflammatory markers of the body.

We observed a significant correlation between periodontal pathologies and plasma fibrinogen levels. These results were in agreement with the findings of Wu et al[19] who observed similar results in their study. Gomes et al[20] systemically reviewed and investigated the evidences regarding the association of apical periodontitis and inflammatory markers. They conducted a systemic search in the Medline and PubMed database between 1948 and 2012 and meta-analyzed all the data on the serum assessment of inflammatory markers in apical periodontitis patients. They observed that among the 531 articles searched, only 20 were shortlisted for final assessment. Among various inflammatory markers, assessment of 31 different types of them was analyzed in those 20 articles. They observed an increase in the values of serum levels of immunoglobulin A (IgA), IgG, and IgM in patients with apical periodontitis. From the results, they concluded that some amount of correlation exists between the increase levels of IL-1, IL-2, and IL-6 in patients with apical periodontitis. Baser et al[21] conducted a cross-sectional study to evaluate the serum levels of high sensitive CRP (hs-CRP) and gingival crevicular fluid (GCF) levels of hs-CRP, prostaglandin E2 (PGE2), and IL-1β in patients with apical periodontal lesions. They analyzed 60 chronic periodontitis patients and divided into two study groups. First group with 30 patients

comprised cases with mild apical periodontitis and 30 cases with severe apical periodontitis. They observed that in patients with severe periodontitis, periodontal parameters showed a significant increase. Furthermore, a significant increase in the values of GCF, IL-1β, and PGE2 levels in patients with severe periodontitis was seen in comparison with mild periodontitis. From the results, they concluded that in assessing the severity of disease, IL-1β in GCF could be used as a significant marker. Vidal et al[22] assessed the impact of nonsurgical treatment on the plasma levels of inflammatory markers in periodontitis patients' refractory arterial hypertension. They analyzed 22 patients and divided them into two study groups. First group consisted of 11 patients who received periodontal treatment, while the remaining 11 patients comprised the control group. All the demographic, clinical, and plasma details of the patients were recorded and analyzed. They observed a significant reduction in the inflammatory and periodontal markers in the patient group. However, they did not observe any significant difference between the baseline data and records after 3 months in the control group. From the results, they concluded that in hypertensive patients with severe periodontitis, nonsurgical periodontal therapy was equally effective. Garrido et al[23] assessed the expression of coiled coil-rich proteins in patients with apical lesions of endodontic origin. They included patients with asymptomatic apical periodontitis and healthy controls and evaluated their IL-6 and CRP levels. They observed that in apical lesions of endodontic origin, IL-6 and CRP were synthesized. From the result, they concluded that in periodontal ligament, constitutive expression of IL-6 and CRP messenger RNA occurs.

CONCLUSION

Keeping in view the above results, the authors conclude that systemic levels of CRP, IL-6, and fibrinogen levels are influenced by the presence of CAP in hypertensive patients. However, further studies in future are required for better exploration and understanding these areas of dental medicine.

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