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RESEARCH ARTICLE

ASSOCIATION OF PERIODONTITIS, ELEVATED C REACTIVE PROTEIN LEVELS AND ACUTE MYOCARDIAL INFARCTION – A CASE CONTROL STUDY

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ABSTRACT

Background & Objectives: Destructive periodontal diseases (PD) have been associated with increased risk of atherosclerotic complications, including acute myocardial infarction (AMI) and stroke. The ability of Periodontitis to produce systemic C-reactive protein (CRP) level elevations may represent the link with cardiovascular events. Hence, the aim of this study was to compare the serum levels of CRP in AMI patients (with and without periodontitis) and a control group. This study also explored the possibility of using CRP levels in patients with periodontitis as a possible risk marker and a screening tool for predicting future cardiovascular disease independent of the conventional risk factors.

Methodology: 40 cases of AMI were taken as cases and 40 age and sex matched healthy individuals were taken as controls. Community Periodontal Index (CPI) score and Loss of Attachment (LOA) score were determined, as well as CRP level estimated from blood for every individual examined.

Results: It was noted that CRP levels were higher in the individuals with PD both in cases and controls. CRP levels in the AMI patients with PD were much higher than the CRP levels in healthy individuals with a positive correlation of CPI, LOA and CRP. A cut off value for CRP level was determined using the ROC curve and noted that values above 0.45mg/L are at a higher risk.

Conclusion: The assessment of CRP levels in the individuals with PD would therefore work as a screening tool and help us in educating the patient about the adverse effects of periodontal ill health.

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INTRODUCTION

Periodontitis is an inflammatory reaction of the supportive tissues surrounding the tooth, including the periodontal ligament, cementum, and alveolar and supporting bone (Beck *et al.*, 1999). It is chronic in nature, progresses slowly, and usually there are no symptoms. Periodontitis is measured clinically as attachment loss, pocket formation and radiographic bone loss and affects 7% to 15% of adults, with varying amounts of severity (Deliargyris, 2004). Periodontal disease and cardiovascular disease (CVD) appear to have a number of characteristics in common because they are more likely to occur in persons who are older, male, who smoke, are diabetics and in both cases might lead to systemic inflammation. Periodontal diseases and oral infections themselves may be risk factors for systemic diseases, including CVD (Beck, 1999). C-reactive protein (CRP), an acute-phase reactant produced mainly in the liver, belongs to the pentraxin family of proteins.

Its plasma concentration can increase rapidly in response to a wide range of inflammatory stimuli (Casula *et al.*, 2000). The ability of Periodontitis to produce systemic CRP level elevations may represent a possible mechanism underlying the link with cardiovascular events. Studies have shown that cytokines (interleukin-6 and interleukin-1) and acute-phase protein CRP in systemic circulation can be used as serum markers for future cardiac and vascular events (Widener, 2007). Destructive periodontal diseases have been associated with increased risk of atherosclerotic complications, including myocardial infarction (MI) and stroke. The finding comes at a time when the understanding of atherosclerotic complications are changing from a focus on the occlusion of arteries due to the buildup of plaque deposits, to an increased awareness of the role of inflammation played in plaque rupture and thrombus formation (Craig, 2004). With this background the aim of this study is to compare the serum levels of CRP in patients with acute myocardial infarction (AMI) (with and without periodontitis) and a control group (with and without periodontitis). This study will also explore the possibility of using CRP levels in patients with periodontitis as a possible risk marker and a screening tool for predicting future cardiovascular disease independent of the conventional risk factors.

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MATERIALS AND METHODS

Study population - In the present case control study, 40 cases of Acute myocardial infarction admitted in the ICU of cardiac wing, were taken as cases and 40 age and sex matched healthy individuals who visited the OPD of our institute were taken as controls. Inclusion criteria were-40 Patients with Acute myocardial infarction (20 patients with periodontal disease, and 20 patients without periodontal disease) and the Control group- 40 age and sex matched healthy individuals with and without periodontitis. Individuals with ongoing infection, recent history of antibiotic use(<4weeks), current corticosteroid therapy, needing emergency coronary artery bypass surgery or cardiac valve operations, currently on NSAIDs, on oral contraceptive pills were excluded from the study.

After the cases and controls were selected based on the above criteria, written informed consent from each individual was obtained. A detailed case history was recorded along with questionnaire concerning medical history, life style and habits practised. The study was approved by the ethical committee of the institution.

Oral examination

Patients with AMI and control subjects underwent oral examination. The Community periodontal index (CPI) and Loss of Attachment (LOA) values were used to assess the periodontal status. Patients with AMI were examined once stabilized and within 48 hours of the episode, whereas control subjects were examined during their visit to the OPD of Vydehi institute of Dental Sciences. Periodontitis was considered to be a potential systemic exposure when attachment loss >3mm was present (code 3 and above in CPITN index). The loss of attachment values were collected from index teeth in order to obtain an estimate of the lifetime accumulated destruction of the periodontal attachment. The mean values of the CPI score and LOA were determined for every individual examined.

CRP level estimation

2ml of peripheral blood was collected from the cases as well as the controls for the estimation of C Reactive Protein levels. The Blood collected in an anti-coagulant tube, was centrifuged and stored between +2 to +8 degrees Celsius until assayed. CRP was measured using the Beckman Coulter Synchron CX Systems CRP test kit. Level Interpretation- 0-3 mg/L - Normal; 3-10 mg/L- Low level of infection predictive of cardiac and vascular disease;>10 mg/L-High level of chronic inflammation. Increase 5 to 10 times chronic level- Acute change: surgery, infection, or injury. Therefore values above 3mg/L were considered predictive for the cardiac and vascular diseases.

Statistics

Student's T test was done to evaluate the mean value between the two groups. The mean values of CRP, CPI, LOA were compared between the cases and controls and also between the subgroups. Chi-square/ Fisher Exact test was used to find the

significance of study parameters on categorical scale between two or more groups. Pearsons correlation was done to know the association between CPI scores & CRP levels and also LOA scores & CRP levels. The diagnostic statistics were applied to evaluate the sensitivity, specificity of the test. The values based on the diagnostic statistics are depicted as the area under the curve in the ROC (Receiver operating characteristics) curve.

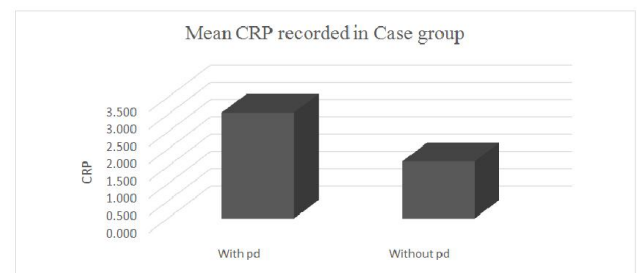
RESULTS

Among the 40 cases of AMI that were evaluated, higher mean CRP(3.066) was recorded in the group with Periodontal Disease (PD) compared to the group without PD (1.651) and the difference between them was statistically significant ($P<0.05$). (Table 1 & Graph 1).

Table 1. Comparison of CRP levels in Case group higher mean CRP(3.066) was recorded in the group with Periodontal Disease (PD) compared to the group without PD (1.651) and the difference between them was statistically significant ($P<0.05$)

Periodontal disease (PD)	Mean	Std Dev	SE of Mean	t	P-value
With PD	3.066	1.687	0.377	2.348	0.024*
Without PD	1.651	2.100	0.470		

(* statistically significant)



Graph 1. Comparison of CRP levels in Case group- CRP was higher in PD sub group

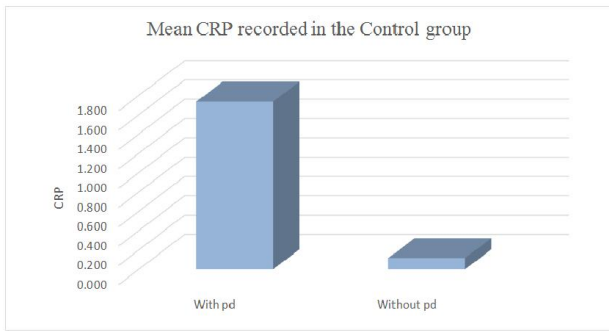
Among the 40 controls that were assessed it was noted that higher mean CRP was recorded in the group with PD compared to the group without PD and the difference between them was statistically significant ($P<0.001$). (Table 2 & Graph 2).

Table 2. Comparison of CRP levels in Control group - higher mean CRP was recorded in the group with PD compared to the group without PD and the difference between them was statistically significant ($P<0.001$)

Periodontal disease (PD)	Mean	Std Dev	SE of Mean	t	P-value
With PD	1.736	1.271	0.284	5.676	<0.001
Without PD	0.116	0.112	0.025		*

Higher mean CRP was recorded in the Case group with PD compared to the Control group with PD and the difference between them was statistically significant ($P<0.01$).

The values of the CRP levels of the 20 cases without PD and 20 controls without PD were analysed and higher mean CRP was recorded in the Case group without PD compared to the Control group without PD and the difference between them was statistically significant ($P<0.01$).



Graph 2. Comparison of CRP levels in Control group- crp level was higher in PD sub group

CPI score by 0.260, the CRP level increased by 1mg/L. Therefore, a positive correlation was noted between the CPI and CRP levels but it was not statistically significant as the P value was 0.268 (Table 4). When the correlation of the mean LOA score and CRP levels was done in the cases with PD, it was noted that for every increase in the mean LOA score by 0.098, the CRP level increased by 1mg/L. Therefore, a positive correlation was noted between the LOA scores and CRP levels but it was not statistically significant as the P value was 0.681 (Table 4). The correlation between the mean CPI scores and CRP levels was done in the cases without PD, it was noted that for every decrease in the mean CPI score by 0.182, the CRP level increased by 1mg/L.

Table 3. Association between different parameters/habits and PD in cases

Parameter		With Pd (N=20)		Without Pd (N=20)		χ^2	P-Value
		n	%	n	%		
Diabetes	Present	10	50%	9	45%	0.100	0.752
	Absent	10	50%	11	55%		
Hypertension	Present	9	45%	11	55%	0.400	0.527
	Absent	11	55%	9	45%		
Hyperlipideamia	Present	11	55%	8	40%	0.902	0.342
	Absent	9	45%	12	60%		
Smoking	Present	13	65%	12	60%	0.107	0.744
	Absent	7	35%	8	40%		

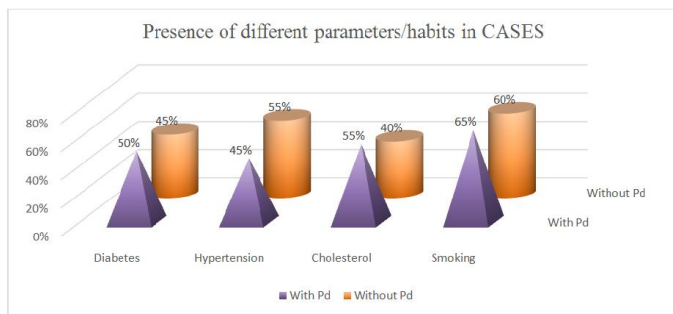
Table 4. Correlation between CPI scores & CRP levels and LOA scores & CRP levels

	CRP level (mg/L)	Mean CPI score	Mean LOA
Pearson correlation in cases with PD (N=20)	1	0.260	0.098
Pearson correlation in cases without PD (N=20)	1	-0.182	*
Pearson correlation in controls with PD (N=20)	1	0.480	*
Pearson correlation in controls without PD (N=20)	*	*	*

*. Cannot be computed because at least one of the variables is constant

Table 5. Determining the cut-off for CRP level to determine the risk of AMI: (Method – ROC Curve Analysis) Area Under the curve:

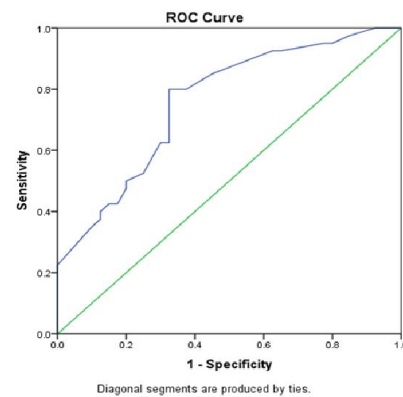
Area Under the Curve	Std. Error	P-Value	95% CI for AUC		Optimal Cut-Off	Sensitivity at Cut-Off	1-Specificity at Cut-Off
			Lower Bound	Upper Bound			
0.7584	0.0534	<0.001*	0.6538	0.8631	0.45	0.8000	0.3250



Graph 3. Association between different parameters/habits and PD in cases

In cases, no significant association was observed between diabetes & PD ($P > 0.05$), hypertension & PD ($P > 0.05$), hyperlipideamia & PD ($P > 0.05$) as well as between smoking & PD ($P > 0.05$) (Table 3 & Graph 3). When the correlation between the mean CPI scores and CRP levels was done in the cases with PD, it was noted that for every increase in the mean

Therefore, a negative correlation was noted between the CPI and CRP levels but it was not statistically significant as the P value was 0.442 (Table 4).



Graph 4. ROC Curve

The correlation of mean LOA scores and CRP levels in cases without PD could not be done as the variable for LOA

was “0”. When the correlation between the mean CPI scores and CRP levels was done in the controls with PD, it was noted that for every increase in the mean CPI score by 0.480, the CRP level increased by 1mg/L. Therefore, a positive correlation was noted between the CPI and CRP levels and it was statistically significant as the P value was 0.032 (Table 4). The diagnostic statistics were applied to evaluate the sensitivity, specificity of the test. The values based on the diagnostic statistics are depicted as the area under the curve in the ROC (Receiver operating characteristics) curve. With the values obtained from the ROC curve, it can be said that the optimal cut-off value for CRP (above which a person has risk of AMI) in determining AMI is 0.45mg/L. The sensitivity (True positives) at this cut-off value is 0.80 (80%) and 1-specificity (False Positives) is 0.3250 (32.5%) (Table 5 & Graph 4).

DISCUSSION

In our case control study, the CRP levels were assessed in 40 cases of AMI and 40 healthy individuals devoid of systemic diseases. Amongst the cases which comprised of 20 AMI patients with PD and 20 AMI patients without PD, it was noted that the mean CRP levels in cases with PD (3.066mg/L) was more when compared to the mean CRP levels in 20 Cases without PD(1.651mg/L) and the values were statistically significant ($P<0.05$). Similar results were obtained by the studies done by Ajwani (2000) *et al*, where they used the CPITN scores to define their cases of periodontal disease. Similarly, in a review conducted by Dietrich (2013) *et al*, it was noted that the CRP levels were elevated in the individuals with atherosclerotic vascular disease and PD (Deliargyris *et al.*, 2004; Latronico *et al.*, 2007; Karnoutsos *et al.*, 2008; Alonso-González *et al.*, 2011; Thomopoulos *et al.*, 2011 and Dietrich *et al.*, 2013).

Experiments with animal models demonstrate that specific infections with periodontal pathogens can actually accelerate atherogenesis. For example, in studies done by Chi *et al* and Gibson *et al*, inbred heterozygous and homozygous apolipoprotein E (apoE)-deficient mice exhibit increased aortic atherosclerosis when challenged orally or intravenously with invasive strains of *P. gingivalis* (Chi *et al.*, 2004 and Gibson *et al.*, 2004). Among the 40 controls that were assessed it was noted that higher mean CRP was recorded in the group with PD (1.736mg/L) compared to the group without PD(0.116mg/L) and the difference between them was statistically significant ($P<0.001$). This is in accordance with the study done by Stein *et al*, where they found elevated CRP levels in periodontal disease patients when compared to controls (Stein *et al.*, 2009).

In our study, when the CRP levels of the cases and controls with PD were evaluated, it was noted that higher mean CRP was recorded in the Case group with PD(3.066mg/L) compared to the Control group with PD(1.736mg/L) and the difference between them was statistically significant ($P<0.01$). When we compare values of the CRP levels of the 20 cases without PD and 20 controls without PD, higher mean CRP was recorded in the Case group without PD (1.651mg/L) compared

to the Control group without PD (0.116mg/L) and the difference between them was statistically significant ($P<0.01$). The above results strategically point out to the correlation between the periodontal disease, elevated CRP levels and atherosclerotic disease. As we saw in the results, the value of the CRP levels in blood were elevated in the case group in general but higher values were observed particularly in those with the periodontal disease.

The studies done by Deliargyris *et al.* (2004), Latronico *et al* (2007), Rai *et al.* (2009), Inaba *et al.* (2010), just to name a few, have all found the similar correlations in their studies too [2,6,7,14,15]. In their studies also they found a strong correlation between the periodontal status, elevated CRP levels in blood and atherosclerotic diseases. The mean CPI score and Mean LOA score had a positive correlation with the CRP levels in cases with PD, that is, for every increase in the mean CPI score by 0.260 & mean LOA score by 0.098, the CRP score increased by 1/mL. But it was not statistically significant. The studies done by Cates (2009), Rakshit *et al* (2014), have found similar results in their study that is, with the increase in the severity of the periodontal disease the CRP level was increased in the coronary heart disease patients (Rai *et al.*, 2009; Cates *et al.*, 2009 and Rakshit *et al.*, 2014). To assess if there was any association between various parameters/habits and periodontal disease in cases and controls, the Chi square test was employed. In cases, no significant association was noted between the parameters Diabetes Mellitus, Hypertension, Hyperlipidemia, Smoking and Periodontal Disease.

Though in various studies in the past the detrimental effects of diabetes mellitus and smoking on periodontal tissues have been proven, in our study no significant association could be found. It could probably be due to the fact that, all the parameters were not present in every case, that is, if the case was a diabetic, it did not necessarily mean he was a hypertensive and smoker too. Similarly in controls as they were devoid of systemic diseases, the association between smoking and periodontal disease was done and no significant correlation was noted, as only 3(15%) of the controls had a habit of smoking. Our study had one more objective, that is, to explore the possibility of using CRP levels in patients with periodontal disease as a possible risk marker and a screening tool for predicting future cardiovascular disease independent of the conventional risk factors.

It was evaluated by assessing the CRP levels of the cases and controls with periodontal disease and subjecting it diagnostic statistics. The values based on the diagnostic statistics are depicted as the area under the curve in the ROC curve. The cut off value was evaluated from the ROC curve. The sensitivity (True positives), that is, the possibility that a person might be at a risk of developing AMI at this cut-off value is 0.80 (80%) and specificity (False Positives) is 0.3250 (32.5%). The optimal cut-off value for CRP (above which a person has risk of AMI) in determining AMI was found to be 0.45mg/L. With the above results it can be said that CRP is not only a risk factor but also a risk predictor too. This is in accordance with the study done by Bursi *et al*, who prospectively followed up patients with Major Adverse Cardiac Events (MACE) and

noted that persistent increase in CRP was associated death in those individuals (Bursi *et al.*, 2007; Manolov *et al.*, 2003; Hirschfield *et al.*, 2003 and Li *et al.*, 2004). Joshipura *et al.*, stated that periodontal disease with elevated CRP levels in the presence of confounders like age, smoking etc, are at an increased risk for developing a cardiovascular accident. They also stated that, improvement in the endothelial function of the susceptible individuals were noted after initiation of periodontal therapy (Joshipura *et al.*, 2004; O'brien *et al.*, 2006 and Alley *et al.*, 2006).

Conclusion

Therefore, with the results we gathered from this study, we got to know that there is definitely an association between periodontitis, elevated CRP levels and AMI. It is clearly evident that elevated CRP levels are noted in the cases with PD. Longitudinal follow up studies are definitely required to assess, if periodontal intervention in such individuals will decrease their CRP levels and decrease their incidence of future atherosclerotic accidents.

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