



RESEARCH ARTICLE

A QUANTITATIVE DETERMINATION OF C- REACTIVE PROTEIN IN PERIODONTAL AND CARDIOVASCULAR DISEASE : A COMPARATIVE STUDY

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ABSTRACT:

The aim of present study is to compare levels of serum C-reactive protein (CRP) in the subjects which manifest cardiovascular disease and / or periodontal disease or neither of disease and implication of periodontal disease as a risk factor for the development of cardiovascular diseases. **PATIENTS AND METHODS;** Study population included 60 patients with Chronic Periodontitis, cardiovascular diseases and controls. Both males and female patents between age group of 35-55 years were selected for the study.

RESULTS. The results of the study showed significantly elevated levels of CRP in cardiovascular patients with periodontal disease as compared to those with healthy periodontium. Hence the present study proves a possible relationship between Chronic Periodontitis and cardiovascular disease. Further studies should be considered making use of other markers of inflammation to prove the possible relationship.

Keywords: C-reactive protein, Periodontitis, cardiovascular diseases, inflammation

INTRODUCTION

A theory of focal infection, which proposed that local “foci” of infection were responsible for the initiation and progression of various inflammatory conditions, such as arthritis, appendicitis and peptic ulcers. A focal infection is a chronic, localized infection that can disseminate microorganisms or toxic microbial products to contiguous or distant tissue and can adversely affect the distant target organs. There is substantial evidence that the relationship between periodontal diseases and systemic diseases may be bi-directional. That is, not only the systemic conditions have oral manifestations, but periodontal diseases can also affect certain systemic conditions. Emerging evidence suggests that Chronic Periodontitis increases the risk for certain systemic diseases such as coronary artery disease, preterm low birth weight babies, respiratory diseases and possibly other conditions. This could occur via the host’s immunoinflammatory mediators which are elicited in response to bacteria, bacterial toxins or local tissue response to cytokines.



Cardiovascular diseases represents wide spectrum of diseases including Coronary Artery Disease (CAD), syndromes, Ischemic Heart Disease (IHD)) i.e., Myocardial Infarction (MI), stroke and angina. One of the chief causes for ischemic heart disease is atherosclerosis. Atherosclerosis is a result of injury to endothelial lining. Proliferation of arterial medial smooth muscle cells with accumulation of lipid occurs. This injury is mediated by cytokines and growth factors.¹ infections (including periodontal, H. pylori and C. pneumoniae infections), smoking, hypertension, hyperlipidemia, homocysteinemia and stress. Chronic Periodontitis and atherosclerosis have complex etiologies, genetic and gender predispositions, and potentially share many risk factors. These diseases also have many pathogenic mechanisms in common. C-reactive protein (CRP) is the first of the acute phase reactant proteins to increase during states of acute inflammation and is largely produced in the liver and to a certain extent in fat of the abdominal cavity, smooth muscle cells and macrophage in atheromatous plaque. It is normally present in ng/ml quantities but may increase dramatically to hundreds of mg/ml within 72 hours following tissue injury.² several parameters of inflammation have been identified as markers of cardiovascular diseases. C - reactive protein has recently gained special attention as a risk factor for cardiac and cerebrovascular events. Recent investigations suggested that even a moderate increase in CRP levels may predict risk for atherogenesis and cardiovascular disorders. It has been proposed that elevated CRP in patients with cardiovascular diseases may be the results of chronic infection and inflammatory process. Periodontitis is a common chronic infection of supporting tissues of the teeth. The Periodontal disease could cause oral bacterial byproducts to enter the bloodstream and trigger the liver to make proteins such as CRP that inflame arteries and in addition these effects may cause blood clots that contribute to clogged arteries leading to heart attacks or strokes.^{3,4,5} The aim of the present study is to compare levels of serum C-reactive protein (CRP) in the subjects which manifest Cardiovascular disease and/or periodontal disease or neither disease and Implication of periodontal disease as a risk factor for the development of Cardiovascular diseases.

MATERIALS AND METHODS

A cross-sectional case controlled study was designed and conducted at the Department of Oral Medicine and Radiology. M.A.Rangoonwala College of Dental sciences and research center, pune, India. The study included 60 subjects. Patients with Chronic Periodontitis, Cardiovascular diseases and Healthy control were distributed in three groups. Both males and females between age group of 35-55 years were included for the study. Verbal and written informed consent was obtained from all subjects prior to their enrollment in the study. This project was reviewed by the board of ethical committee M.C.E. Society's for the dental college and the project was envisaged after the clearance was obtained. Participation of the subjects in this study did not affect any treatment decisions regarding medical care.

**Periodontal condition criteria:**

Patients with Chronic Periodontitis should have Oral clinical features which includes bleeding on probing, periodontal pockets >4mm or clinical loss of attachment 3 mm. And moderate to severe radiographically evident interproximal bone loss. Patient included in this group should have at least eight teeth meeting these disease criteria. In addition, each patient should have at least two premolar or molar teeth in at least two quadrants meeting the disease criteria.

The control group could exhibit mild to moderate gingivitis, and probing depths less than 4mm or clinical loss of attachment < 3 mm and radiographically < 2mm of bone loss and no Cardiovascular disorders (CVD) was included in the study .

Cardiovascular criteria:

The diagnosis of Cardiovascular disorders (CVD) was based on chest pain associated with typical electrocardiogram (ECG) changes (ST elevation, and/or non ST elevation and T-wave inversion), combined with a typical serial pattern of cardiac markers (i.e. creatinine kinase isoenzyme and troponin T) as assessed according to local laboratory standards. The initial ECG was considered diagnostic for Cardiovascular disorders if there was ST segment elevation of 2 mm or more in a chest lead. Or ST segment elevation of 1 mm or more in a limb lead. Non-ST elevation and T-wave inversion changes combined with typical serial pattern of cardiac markers were also considered diagnostic purposes for cardiovascular disorders. Left bundle block was considered diagnostic for Myocardial Infarction if chest pain combined with typical serial pattern of cardiac markers were present. All subjects were clinically examined by a cardiologist. And there after they received a periodontal examination. The study excluded Pregnant women, Individuals with acute and chronic medical disorders, Diabetes, Viral, fungal or bacterial infection, Patients with abnormal blood chemistries and Patient on drugs that would significantly affect the immune system & Smokers

METHODS

Panoramic radiography was performed on all the subjects followed by full mouth direct digital periapical radiographs with informed consent. The periodontal examination was carried out with mouth mirror and with a William's graduated periodontal probe. Loe and Silness. Gingival index (GI) were utilized to determine inflammatory components in patients. Probing Depths (PD) and gingival recession was measured with William's graduated periodontal probe. C- reactive protein was estimated by CRP-Turbilatex agglutination assay. (CRP) Turbilatex Quantitative Determination Cat. No. 101-0468 Size 1x45 ml/1x5 ml was used. This is a quantitative turbidimetry assay for measurement of CRP in human serum or plasma samples by means of particle enhanced immunoturbidimetry method. For comparing the average values (such as age, GI, CAL and CRP) across three study groups, we used One-way analysis of variance (ANOVA) procedure. For comparing the average values (such as age, GI, CAL and CRP) across two study groups, i.e. (between sub-group IIIA and sub-group IIIB) we used independent



sample 't' test. In order to compare the significance of difference of distribution of categorical variable between three study groups, we used Chi-square test for independence of attributes if cell frequencies are more than 5; else Fisher's exact test is used. A p-value less than 0.05 were considered to be statistically significant. The entire statistical analysis was done using Statistical Package for Social Sciences (SPSS version 12.0) for MS Windows.

RESULTS

The study included 60 samples which were divided into 3 Groups of 20 each. **Group- I:** Patients without periodontal and cardiovascular diseases (control Group) **Group- II:** Patients with periodontal disease and without cardiovascular diseases. **Group-III:** Patients with cardiovascular diseases and with/ or without periodontal disease.

Group III (Patients with cardiovascular diseases and with/without periodontal diseases) which was further sub-divided into **Group IIIA** and **Group IIIB** based on patients with Periodontitis or without Periodontitis.

Mean age for **Group- I** was 45.7 years, SD =6.5. **Group- II** was 44.7years, SD=5.6. **Group- III** was 45.6 years, SD=5.4. The study includes 31 male patients and 29 female patients. The sex wise distribution is approximately similar between three-study groups (50%). Gingival index (GI), mean Clinical attachment loss (CAL) and C-reactive protein (CRP) mean values was significantly less in **Group-I** (control group GI=0.57 mm, CAL= 1.42mm, and CRP=0.26 mg/dl) compare to **Group-II** which was significantly high (periodontal group GI=1.93 mm, CAL= 5.79mm, and CRP=0.85 mg/dl). The mean Gingival index (GI) and mean Clinical attachment loss is almost similar between **Group-II** and **Group-III** (**Group- III** CVD group GI=1.87 mm, CAL=5.09 mm, and CRP=2.07 mg/dl) But the mean C-reactive protein level is significantly high in **Group- III** compare to **Group- I** and **Group- III** that is CRP=2.07 mg/dl (Table 1) There is no statistical significance of age and sex between all the three groups. The GI Index, CAL and CRP level in **Groups II & III** compared to **Group I** are statistically significant. The GI and CAL in **Group II** compare to **Group III** are statistically non significant. CRP levels are statistically significant in **Group III** compare to **Group II** (Table 2).

Group III (Patients with cardiovascular diseases and with/without periodontal diseases) which was further sub-divided into **Group IIIA** and **Group IIIB** based on patients with Periodontitis or without Periodontitis. The average age is not significantly different across two- study sub Groups. The distribution of sex is approximately similar between two-study sub groups. Average GI Index, CAL and Average CRP level is significantly higher in groups IIIA compared to Group IIIB (Table 3).

Table 4 shows description of variables of Oral hygiene habits and periodontal disease. 35 patients reported brushing once a day and 25 patients reported brushing twice a day. 32 participants who brushed their teeth once a day showed the signs of periodontal disease while 25 subjects who brushed their teeth more than once a day had no signs of



periodontal disease. Similarly, of the 28 participants who visited their dentist at least once a year had no signs of periodontal disease, on the other hand, 32 subjects who visited their dentist only in response to some dental problem had Periodontitis. The possible impact of the oral hygiene habits of the patients on their periodontal status was analyzed using the chi square test. There was statistically significant difference in the periodontal status with regards to brushing frequency and visit to dentist.

TABLE NO. 1 Shows overall comparison of Gingival index, mean Clinical attachment loss (CAL) and CRP mean values and standard deviations. Group wise significance has been shown using One way Analysis of Variance (ANOVA).

S/no	Groups	GI	CAL (mm)	CRP (mg/dl)
1	Group-1 (n=20)	0.57 (0.22)	1.42 (0.23)	0.26 (0.07)
2	Group-2 (n=20)	1.93 (0.36)	5.79 (1.54)	0.85 (0.39)
3	Group-3 (n=20)	1.87 (0.29)	5.09 (2.36)	2.07 (0.50)

Overall comparison of GI, CAL and CRP showed significant variations among the three groups.

TABLE NO. 2 Shows Pair wise significance of various parameters of Age, Sex, Gingival index, Clinical attachment loss (CAL) and CRP of group I with other groups

s/no	Pairs	Age	Sex	GI	CAL	CRP(mm/dl)
1	Group-1 Vs Group-2	P=0.698	P=0.752	P=0.000	P=0.000	P=0.000
2	Group-1 Vs Group-3	P=0.989	P=0.525	P=0.000	P=0.000	P=0.000
3	Group-2 Vs Group-3	P=0.862	P=0.342	P=0.698	P=0.277	P=0.000



TABLE NO. 3: Shows the distribution of several parameters of group III (Patients with cardiovascular diseases and with/without periodontal diseases) which was further sub-divided into group IIIA and group IIIB based on patients with Periodontitis or without Periodontitis

Parameters	Group IIIA (n=12) with periodontitis	Group IIIB (n=8) without periodontitis	P-value
Age (years)	44.4 (4.9)	47.3 (5.9)	0.262
Sex			
Male	4 (33.3)	4 (50.0)	0.648
Female	8 (66.7)	4 (50.0)	
GI	2.00 (0.25)	1.67 (0.22)	0.007
CAL	6.72 (1.54)	2.66 (0.16)	0.000
CRP (mg/dL)	2.36 (0.35)	1.62 (0.34)	0.000

TABLE NO. 4: Shows description of variables of Oral hygiene habits and periodontal disease.

variables		Periodontal disease		Total	Significance
		Yes	No		
Brushing	Once a day	32	3	35	Significant (P=0.000)
	More than once	0	25	25	
Visit to dentist	Once a year	0	28	28	Significant (P=0.000)
	Infrequently	26	6	32	

DISCUSSION:

Several parameters of inflammation have been identified as markers for cardiovascular diseases. C-reactive protein (CRP) has recently gained special attention as risk factor for cardiac and cerebrovascular events. It has been proposed that elevated CRP in patients with cardiovascular disease may be a result of chronic infections and inflammatory



process. Chronic Periodontitis is a common chronic infection of supporting tissues of teeth. Periodontal tissue destruction is caused by complex interplay between host response and microorganisms and their products. Emerging evidence in the last decade has shed light on the potential effects of periodontal disease over wide range of organ systems. Periodontal infection may affect the onset or progression of atherosclerosis and cardiovascular diseases through various mechanisms. C-reactive protein assessment in earlier studies was done by slide agglutination method, ELISA method and recently with latex nephelometric method. In the present study immunoturbidimetry method (CRP-Turbilatax agglutination assay) was used. The assay consists of a Latex particles coated with specific human anti-CRP are agglutinated when mixed with samples containing CRP. The agglutination causes an absorbance change, dependent upon the CRP contents of the patient sample that can be quantified by comparison from a calibrator of known CRP concentration. This test offer sensitivity measurements of CRP (0.6 mg/L), low cost, easy to perform and easily available in market. The study aims at comparing levels of C-reactive protein in cardiovascular disease and periodontal disease and probable interrelationship. Comparison of various study parameters i.e. The GI Index, CAL and CRP level in patient with periodontal disease and without cardiovascular diseases (groups II) & patient with cardiovascular diseases and with/ or without periodontal disease (group III) compared to control (group I) were statistically significant ($P=0.000$). The GI ($P=0.698$) and CAL ($P=0.277$) in group II compare to group III were statistically non significant. Where as CRP levels are statistically significant ($P=0.000$) in group III when compared to group II.

Comparison of various study parameters of group III which was further subdivided into group IIIA (patients with cardiovascular and periodontal diseases) and group IIIB (patients with cardiovascular diseases and without periodontal diseases) based on patients with or without periodontitis. The Average GI Index ($P=0.007$), CAL ($P=0.000$) and CRP level ($P=0.000$) were significantly higher in groups IIIA compared to group IIIB. Possible impact of variables such as age and sex on CRP levels was also statistically analyzed. Age is a known risk factor for both cardiovascular diseases as well as periodontal diseases.⁶ The mean age of the sample in the present study was between 35-55 years which is slightly less than that of other comparable study done by **Rahmati et al (2002)**⁷ with a mean age of 53 ± 16.1 years. No significant difference was found in CRP levels among the subjects > 40 years of age compared to those < 40 years of age. These results do not support the observations in other studies of the possible association with elevated CRP levels with increased age.^{8,9} Serum CRP values in the range of 0.8-2.0 mg/dl in 55-74 year-old subjects are at risk for cardiovascular disease as proposed by **Ridker (1998)**,¹⁰ **Napoli et al (2005)**.¹¹ The gingival index, Clinical attachment loss (CAL) and periodontal indices noted in this study increased in patients above 40 years. The extent of periodontal changes like gingival index, attachment loss and gingival recession is associated with history of heart attack among persons aged 40 years and above has been reported by **Beck et al(1999)**.¹² The mean CRP levels in the present study essentially did not differ between males and females in the three study groups. A significant association between periodontal infection and elevated CRP serum values has been observed in the present study. The mean value of CRP in Chronic Periodontitis group is 0.85mg/L. The mean value of CRP in healthy control group is 0.26 mg/dl. Which was in agreement to studies done by **Loos et al (2000)**.¹³ **Yamazaki et al (2005)**.¹⁴ **Frederiksson et al,**⁹



Ebersole et al,¹⁵ and Noack et al (2001).¹⁶ Data from the present study indicate that patients with periodontitis showed significantly elevated CRP levels ($P=0.000$) compared to those with healthy periodontium. It was also seen that CRP levels increased significantly with increase in mean Clinical attachment loss (CAL). And vice versa but the difference was not statistically significant. However, normal CRP levels were also observed in subjects with periodontitis. The possible explanation for this observation is that in most cases the parameters that are measured for the estimation of periodontal disease, such as gingival index, attachment loss, are the measurement of past disease and do not give an indication as to whether the disease is active or progressing. Moreover, there are important differences in the host response to the bacterial challenges.^{17, 18} In the present study, subjects with cardiovascular disease had elevated CRP values (mean 2.07mg/dl). When compared to periodontitis group (mean 0.85mg/dl) and healthy control group (mean 0.26mg/dl). This finding is in correlation with studies conducted by **Ridker et al (1998)**,¹⁰ **Beck et al (1989)**,¹⁹ and **Persson et al (2005)**²⁰ who described that CRP concentration can increase rapidly in response to acute coronary heart disease. **Mattila (1993)**²¹ described that a serum CRP >1.4 mg/dl may be an independent predictor of a first ever transient ischaemic stroke event. Similarly, patients with cardiovascular and periodontal diseases (group IIIA) demonstrated CRP mean value of 2.36 mg/dl as compared to patients with cardiovascular diseases and without periodontal diseases (group IIIB) who demonstrated CRP mean value of 1.62 mg/dl. So upon comparison between both the groups the raise of CRP of 2.36 mg/dl in group IIIA can be attributed to Chronic Periodontitis which is statistically significant ($P=0.000$). American Heart Association and Centre for Disease Control and Prevention (AHA/CDC) proposed risk groups with values of CRP as follows.²² Low risk: less than 1.0 mg/dl. Average risk: 1.0 to 3.0 mg/dl. High risk: above 3.0 mg/dl. Accordingly this study group comes in average risk (2.07). This suggests that the assessment of CRP serum levels in subjects with Chronic Periodontitis could provide important guidance in order to identify subjects who are at risk for cardiovascular diseases. Periodontal disease and cardiovascular disease have many common risk factors. Besides sharing common risk factors, it is becoming more evident that these diseases have common pathogenic pathways. In spite of several scientific studies the mechanism of the formation of atherosclerotic plaque is unanswered and the intricate relationship between Periodontitis and atherosclerotic formation is a mystery. Several hypotheses, based on inflammatory models of disease, have been proposed for the role of Chronic Periodontitis in cardiovascular disease. Hypothesis that a monocyte phenotype that secretes higher than normal levels of pro-inflammatory mediators (IL6, IL-8, TNF- and C-reactive protein) in response to bacterial infections was proposed by **Beck et al (1996)**²³ and **Kinane (1998)**²⁴ Periodontal disease is an infectious disease, and in response to periodontal pathogens and their endotoxins including its smallest fraction Muramyl dipeptide, the release of pro-inflammatory mediators (IL-6, IL-8, TNF- and C-reactive protein) by monocytes leads to periodontal connective tissue and crestal alveolar bone destruction due to transformation of monocytes to osteoclasts. There is growing evidence for a role of inflammation in atherosclerosis. **Beck et al. (1996)**²³ suggested that people with hyperresponsive monocytes may be at risk for both periodontal and cardiovascular disease. Also, periodontal infections play a direct role in atherosclerosis by providing a systemic source for bacterial endotoxins and pro- inflammatory mediators (**Beck et al., 1996**)²³. Another



hypothesis by **Herzberg and Meyer in (1998)**²⁵ postulates that the periodontal pathogens may disseminate systemically through the blood stream and infect the vascular endothelium directly, leading to atherosclerosis and myocardial ischemia and infarction. Participants of the present study were also asked about their oral hygiene habits. The data showed highly significant difference in the periodontal status of the subjects in terms of brushing frequency. These results support the findings of the other studies which suggest that high prevalence of the periodontal diseases in cardiovascular patients compared to healthy individuals is due to negligence of the oral hygiene.^{26,27} It is seen that the patients who brushed their teeth more than once a day had a significantly less prevalence of periodontal disease as compared to those who brush their teeth only once a day. Therefore, it can be recommended that the patients with periodontal and cardiovascular diseases must be educated on regular basis about the importance of maintaining the oral health because it could directly effect the long term survival of the patients. Several studies have shown that periodontal therapy resulted in a decrease in serum CRP and other inflammatory markers in healthy individuals with periodontal disease.^{29, 30} Therefore; dentist could play a key role in maintaining the CRP levels of cardiovascular patients within acceptable limits by providing them with periodontal therapy, thus improving their quality of life. There were few limitations associated with this study. Present study has not taken Obesity, Body Mass Index into account. **Clearfield in (2005)**³¹ found that elevated CRP has been correlated with abdominal obesity in men with atherogenic dyslipidemia, an important clinical characteristic of the metabolic syndrome. It might have influenced the values in the present study. The exact relationship of CRP with cardiovascular disorders is still not certain. Hence, it is proposed that newer techniques are advocated to assess CRP levels in periodontal tissues either through gingival crevicular fluid (GCF) or through tissue homogenate could be able to provide a better answer. The results obtained from the study shows that C- reactive protein is elevated in Chronic Periodontitis. Similarly C-reactive protein levels are increased in cardiovascular patients. On comparison the values in both groups are significant. Hence the present study proves a possible relationship between Chronic Periodontitis and cardiovascular diseases. Further studies should be considered making use of other markers of inflammation to prove a definitive relationship. Prospective randomised controlled studies involving large population should be carried out to establish that Chronic Periodontitis is a risk factor for cardiovascular diseases.

CONCLUSION

The results of the study showed significantly elevated levels of CRP in cardiovascular patients with periodontal disease as compared to those with healthy periodontium. Hence the present study proves a possible relationship between Chronic Periodontitis and cardiovascular disease. Further studies should be considered making use of other markers of inflammation to prove the possible relationship. Prospective randomized controlled studies involving large population should be carried out to establish that Chronic Periodontitis is a definitive risk factor for cardiovascular diseases. It may be recommended that patients above 40-45 years of age with Chronic Periodontitis must



religiously undertake oral prophylaxis. By doing so, the out put of microbial contamination and release of proinflammatory mediators could be minimized. And thus chances of further cardiovascular events may be reduced.

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