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Evaluation of Serum C-reactive Protein, Plasma Fibrinogen, and Blood Leukocytes in Patients with Chronic Periodontitis

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ABSTRACT

Introduction: Periodontal health is crucial and indispensable element of general health. Epidemiologically, it has been linked with cardiovascular diseases with elevated acute phase reactant C-reactive protein, fibrinogen, and rheological variables such as total leukocyte count and differential leukocyte counts, which are potential predictors of cardiovascular diseases.

Objective: To evaluate and compare cardiovascular disease-related biochemical markers in periodontally healthy subjects, and patients with moderate and severe chronic periodontitis.

Methods: An analytical cross-sectional study was conducted in patients attending Department of Periodontology and Oral Implantology, Chitwan Medical College and Teaching hospital, Bharatpur, Chitwan, Nepal from September 2019 to January 2021. A total of 81 individuals of both gender of which 27 periodontally healthy individuals, 27 diagnosed with moderate and 27 diagnosed with severe periodontitis based on gingival index, probing pocket depth, and clinical attachment level were enrolled in a study. After which, peripheral blood samples were drawn and serum C-reactive protein, plasma fibrinogen, total leukocyte count, and differential leukocyte counts were quantified using the turbidimetric immunoassay. Convenience sampling technique was done. Data was analysed in SPSS v.26.0.

Results: The mean serum levels of C-reactive protein, plasma fibrinogen, total leukocyte and differential leukocytes were found to be statistically (P value <0.001) higher in severe and moderate periodontitis subjects compared to periodontally healthy subjects.

Conclusion: The increased levels of serum C-reactive protein, plasma fibrinogen, total leukocyte count, and differential leukocyte counts in chronic periodontitis contribute to the inflammatory burden of the individual potentially striking toward an increasing risk for cardiovascular events.

Keywords: Cardiovascular diseases; c-reactive protein; fibrinogen; leukocytes; periodontitis.

INTRODUCTION

Chronic periodontitis, a highly prevalent and recurrent form of periodontal disease, is an infectious disease resulting from inflammation within the supporting tissues of teeth characterised by progressive attachment and bone loss.[1] In present scenerio, it is of utmost importance to be aware about actual current scientific evidence regarding association of periodontal disease and systemic health. Various cross-sectional and prospective epidemiological studies have already established an association between chronic periodontitis with cardiovascular diseases (CVD) which have complex aetiologies, gender, and genetic predispositions and possibly might share common risk factors and pathogenic mechanisms.[2-5] The increased levels of serum C-reactive protein (CRP), plasma fibrinogen, total leukocyte count (TLC), and differential leukocyte count (DLC) in periodontitis contribute to inflammatory burden of individual potentially increasing risk for cardiovascular events. Further research is needed to find their role in inflammatory burden and ascertain the specificity of these markers.[6-8]

In context of Nepal, few researches[9] have been done related to CRP only although other systemic markers of inflammation like fibrinogen, TLC and DLC have also been identified as risk factors for CVD. Thus, this research aimed to present an integral overview and provide baseline information of

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cardiovascular biomarkers and its association with the severity of periodontitis.

METHODS

An analytical cross-sectional study was conducted in patients attending Department of Periodontology and Oral Implantology, Chitwan Medical College and Teaching hospital, Bharatpur, Chitwan, Nepal from September 2019 to January 2021 after obtaining the ethical approval (Ref. 076/077-021) from Institutional Review Committee of the same institute (CMC-IRC).

Convenience sampling was done. Sample size was calculated using the following formula by Cochran et al. (1997). Sample size (n) = $Z^2_{\alpha/2}\sigma^2/e^2$; Where, $Z_{\alpha/2}$ = value of the standard normal variate = 1.96; e = acceptable error or level of significance = 0.1 (10%); σ = standard deviation of the population with reference to an article by Gani et al. (2009)[10] = 0.264. Thus, n = $(1.96)^2$ X $(0.264)^2/(0.1)^2$; n = 26.67 ≈ 27.

In order to have an equal distribution of study subjects, a total sample size of 81 with 27 in each group was recruited for the study. Study participants were divided into three groups based on severity of periodontitis as follows depending upon the measurement of probing pocket depth (PPD) and clinical attachment level (CAL).

Group A (n = 27): Periodontally healthy control group; PPD <3 mm, CAL <3 mm

Group B (n = 27): Moderate chronic periodontitis; PPD = 4-6 mm, CAL = 3-4 mm

Group C (n = 27): Severe chronic periodontitis; PPD >6 mm, CAL ≥5 mm.

Individuals of both gender with no history of CVD or other acute/chronic systemic disorders who satisfied the inclusion criteria were enrolled. Patients with known history of smoking, systemic diseases like cardiovascular and respiratory diseases, inflammatory conditions like rheumatoid arthritis, acute infections, pregnant women, and lactating mothers were excluded. Similarly, individuals with trauma or who underwent recent tooth extractions, patients undergoing orthodontic therapy, individuals who had undergone any antibiotic, anti-inflammatory or immunosuppressive therapy before the commencement of study for at least the past three months and who had undergone any periodontal therapy six months prior to and during the period of study were also excluded from a study. Written informed consent was taken from each participant of the study. Participation was voluntary and utmost confidentiality and personal identity of all the participants were assured.

The periodontal examination was performed by a single examiner (SK) for all the recruited subjects for gingival index (GI) by Loe and Silness (1963),[11] PPD, and CAL. Probing pocket depth (PPD) was measured from gingival margin to base of periodontal pocket at mesiobuccal, midbuccal, distobuccal, mesiolingual, midlingual, and distolingual surfaces of all teeth and CAL was measured from the cementoenamel junction to base of pocket of all teeth on same surfaces using William's graduated periodontal probe. PPD depth and CAL nearest to the lower values were considered.

After fully explaining all the procedures to the patients, about 4-5 mL peripheral blood samples were collected

Figure 1: a. Blood withdrawal.
b. Centrifuge machine for CRP.
c. Blood sample after centrifugation.
d. C-reactive protein analyser.
e. Inside CRP analyser.
f. Blood sample with anticoagulant-sodium citrate.
g. Fibrinogen reagent kit (Wondfo Optical Coagulation Analyser (OCG-102), Wondfo Biotech Co., Ltd, Guangzhou, China).

from each subject from the antecubital fossa, by aseptic technique using a five 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 analysis at a later date and laboratory estimation of serum CRP, plasma fibrinogen, TLC and DLC were done. The serum CRP method was based on a particle enhanced turbidimetric immunoassay technique. The reference range of serum CRP is 0-5 mg/l. Similarly, for estimation of plasma fibrinogen, the fibrinogen kit based on Clauss method was utilised which is an in vitro diagnostic assay intended for quantitative determination of fibrinogen in plasma.[12]

The Clauss method measures the rate of fibrinogen to fibrin conversion in the presence of excess thrombin and has been shown to be rapid, sensitive and precise. The normal range for fibrinogen levels in human plasma is considered to be 1.8-4.0 g/l. The method for estimation of TLC is based on flow cytometry, the normal range for which is 4000-11000/mm.[3] Similarly, DLC is also estimated by flow cytometry. The reference range of neutrophil is 40-70%, lymphocyte is 20-40%, monocyte is 2-10%, eosinophil is 2-6% and basophil is 0-1%.

Collected data were coded, entered into Microsoft Excel and transformed to IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, N.Y., USA) for statistical analysis. Continuous data were expressed as mean and standard deviation. Mean values of each parameter were compared between the groups using one-way analysis of variance (ANOVA). The pairwise differences among the three groups were carried by Newman-Keuls post hoc procedure. Independent sample t-test was applied to compare the mean values of periodontal and biochemical markers between two groups. The P value < 0.001 was considered statistically highly significant; P value <0.01 as very significant; P value <0.05 as significant and P value >0.05 as not significant.

RESULTS

A total of 81 subjects equally divided into three groups were enrolled for the study. Mean age of the study participants was 42.73±18.38 years with minimum age of 30 years and maximum age of 56 years respectively (Figure 2). The mean age of the study participants in three different groups I, II, and III were 45.38±14.14 years, 39.69±15.55 years, and 39±15 years respectively as depicted in Figure 2.

The gender-wise distribution of the study participants in each group is as presented in Figure 3. Out of 81 participants, male and female were 39 (48.15%) and 42 (51.85%) respectively.

The intergroup comparison of periodontal parameters was carried out by ANOVA test. The results of which showed the highly significant differences between the three groups in terms of all parameters studied (P <0.001, Table 1).

The pairwise comparisons of all parameters among the three groups were as demonstrated in Table 2. Highly significant difference in mean serum CRP level and plasma fibrinogen level were observed in intergroup comparison (P <0.001). Similarly, intergroup comparison showed significant difference in TLC (P <0.001) and DLC (P <0.001) in all three groups except eosinophils.

Intergroup comparison using independent sample t-test, for various parameters among the three groups are shown in Table 3, 4, and 5. The severe periodontitis group had higher mean level of CRP compared with moderate periodontitis patients versus periodontally healthy group as tabulated in Table 4 and Table 5, 7.26 ±0.89/mm^3 vs 2.61 ±1.03/mm^3 and 0.70±0.31/mm^3 respectively. Likewise, the mean level

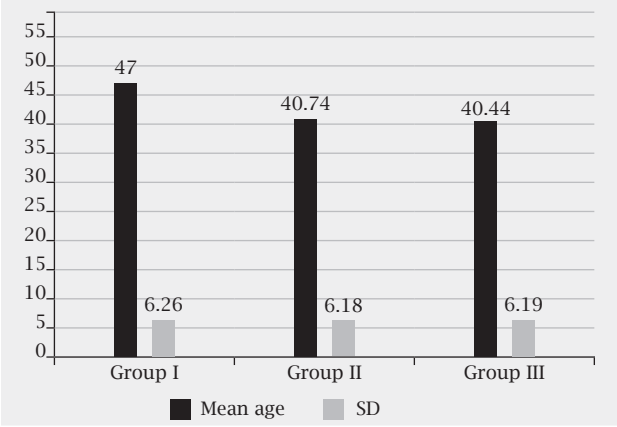

Figure 2: Agewise distribution of the study participants.

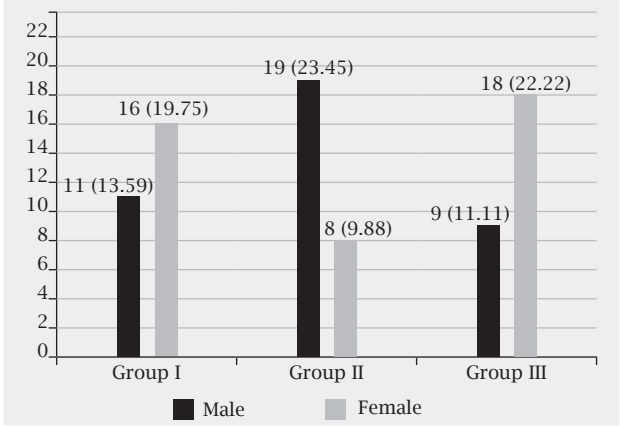

Figure 3: Genderwise distribution of the study participants, n (%).

Table 1: One-way analysis of variance test showing mean and standard deviation of various parameters among three groups.

Parameters	Groups	N	Mean± SD	F value	P value
GI score	I	27	0.49±0.12	1379.190	<0.001
	II	27	1.55±0.83		
	III	27	2.15±0.13		
PPD (mm)	I	27	1.88±0.32	582.39	
	II	27	4.81±0.83		
	III	7.85	7.85±0.66		
CAL (mm)	I	27	0.55±0.69	292.0	
	II	27	3.70±0.54		
	III	27	6.55±1.31		
CRP (mg/l)	I	27	0.70±0.31	465.71	
	II	27	2.61±1.03		
	III	27	7.26±0.89		
Fibrinogen (g/l)	I	27	1.99±0.12	100.47	
	II	27	2.53±0.53		
	III	27	3.59±0.48		
TLC (/mm3)	I	27	5676.67±939.54	83.882	
	II	27	7216.29±1078.78		
	III	27	9194.8±978.26		
Neutrophil count (%)	I	27	45.07±2.93	233.89	
	II	27	57.52±4.80		
	III	27	70.43±4.89		
Leukocyte count (%)	I	27	24.40±3.05	100.30	
	II	27	32.80±3.72		
	III	27	40.50±5.40		
Monocyte count (%)	I	27	2.72±0.66	55.75	
	II	27	4.13±0.92		
	III	27	5.80±1.46		
Eosinophil (%)	I	27	1.60±0.97	16.61	
	II	27	2.61±1.33		
	III	27	3.58±1.43		
Basophil (%)	I	27	0.05±0.17	41.54	
	II	27	0.50±0.22		
	III	27	0.94±0.55		

Table 2: Pairwise comparison of mean periodontal and cardiovascular parameters using Newman Keuls post hoc procedure.

Parameters	Group I versus Group II	Group III versus Group II	Group I versus Group III
GI score	P <0.001	P <0.001	P <0.001
PD (mm)			
CAL (mm)			
CRP (mg/l)			
Fibrinogen (g/l)			
TLC (/mm^3)			
Neutrophil count (%)			
Leukocyte count (%)			
Monocyte count (%)			
Eosinophil count (%)	P = 0.012	P = 0.017	
Basophil count (%)	P <0.001	P <0.001	

Table 3: Independent sample t-test comparing periodontal and cardiovascular parameters between group I and group II.

Parameters	Groups	N	Mean± SD	F value	P value
GI	I	27	0.49±0.12	3.89	<0.001
	II	27	1.55±0.83		
PPD (mm)	I	27	1.88±0.32	35.26	
	II	27	4.81±0.83		
CAL (mm)	I	27	0.55±0.69	3.78	
	II	27	3.70±0.54		
CRP (mg/l)	I	27	0.70±0.31	45.96	
	II	27	2.61±1.03		
Fibrinogen (g/l)	I	27	1.99±0.12	59.56	
	II	27	2.53±0.53		
TLC (/mm^3)	I	27	5676.66±939.54	0.065	
	II	27	7216.29±1078.78		
Neutrophil (%)	I	27	45.07±2.93	4.63	
	II	27	57.52		
Lymphocytes (%)	I	27	32.80	1.83	
	II	27	24.40		
Monocytes (%)	I	27	2.72	2.26	
	II	27	4.13		
Eosinophils (%)	I	27	1.60	1.08	
	II	27	2.61		0.002
Basophils (%)	I	27	0.05±0.17	10.54	<0.001
	II	27	0.50±0.22		

Table 4: Independent sample t-test comparing periodontal and cardiovascular parameters between group II and group III.

Parameters	Groups	N	Mean± SD	F value	P value
GI	II	27	1.55±0.83	8.15	<0.001
	III	27	2.15±0.13		
PPD (mm)	II	27	1.88±0.32	4.008	
	III	27	4.81±0.83		
CAL (mm)	II	27	3.70±0.54	20.86	
	III	27	6.55±1.31		
CRP (mg/l)	II	27	2.61±1.03	1.50	
	III	27	7.26±0.89		
Fibrinogen (g/l)	II	27	2.53±0.53	2.63	
	III	27	3.59±0.48		
TLC (/mm^3)	II	27	7216.29±978.26	0.047	
	III	27	9194.81±1078.98		
Neutrophil (%)	II	27	57.52±4.89	0.12	
	III	27	70.43±4.80		
Lymphocytes (%)	II	27	32.80±3.72	4.03	
	III	27	40.50±5.40		
Monocytes (%)	II	27	4.13±0.92	4.28	
	III	27	5.80±1.46		
Eosinophils (%)	II	27	2.61±1.33	0.41	0.013
	III	27	3.58±1.43		
Basophils (%)	II	27	0.50±0.22	7.84	<0.001
	III	27	0.94±0.55		

Table 5: Independent sample T-test comparing periodontal and CVD parameters between group I and group III.

Parameters	Groups	N	Mean± SD	F value	P value
GI	III	27	2.15±0.13	0.63	0.001
	I	27	0.49±0.12		
PPD (mm)	III	27	7.85±0.66	10.79	
	I	27	1.88±0.32		
CAL (mm)	III	27	6.55±1.31	11.65	
	I	27	0.55±0.69		
CRP (mg/l)	III	27	7.26±0.89	29.86	
	I	27	0.70±0.31		
Fibrinogen (g/l)	III	27	3.59±0.48	13.73	
	I	27	1.99±0.12		
TLC (/mm^3)	III	27	9194.81±978.26	0.001	<0.001
	I	27	5676.66±939.54		
Neutrophil (%)	III	27	70.43±4.89	2.22	
	I	27	45.07±2.93		
Lymphocytes (%)	III	27	40.50±5.40	9.62	
	I	27	24.40±3.05		
Monocytes (%)	III	27	5.80±1.46	10.64	
	I	27	2.75±0.66		
Eosinophils (%)	III	27	3.58±1.43	3.41	
	I	27	1.60±0.97		
Basophils (%)	III	27	0.94±0.55	17.33	
	I	27	0.05±0.17		

of plasma fibrinogen was higher in severe periodontitis group compared to group with moderate periodontitis and periodontally healthy group. (3.59±0.48 vs 2.53±0.53 vs 1.99±0.12 respectively as depicted in Table 3, 4, and 5. The severe periodontitis group had higher mean number of total leukocytes compared to group with moderate and periodontally healthy group (9194.81/mm^3 vs 7216.29/mm^3 and 5676.67/mm^3 respectively). While the other types of differential leukocytes also vary significantly except eosinophils which did not show the statistically significant differences.

DISCUSSION

Periodontitis occurs in response to a predominantly gram-negative bacterial infection originating from dental plaque. It was speculated that periodontitis, a common condition, may predispose affected patients to CVD.[13] DeStefano et al. showed that subjects with periodontitis had a 25% increased risk of developing heart disease compared to those with little or no periodontal disease.[14]

The translocation of increased levels of pro-inflammatory cytokines as well as pathogenic bacteria occurs through systemic circulation resulting in direct exacerbation of CVD or influencing other systemic risk factors associated with CVD. Hepatocytes may also be activated in the liver to produce acute phase proteins including CRP which may lead to increased inflammatory activity in atherosclerotic lesions and accelerated development of CVD.[15,16] The findings of the present study support the fact that levels of serum CRP were found to be higher in patients with severe periodontitis when compared with moderate periodontitis patients and periodontally healthy subjects in accordance with other previous studies.[16,17] The elevated levels of such inflammatory markers can increase the severity of periodontal destruction as observed with raised periodontal parameters.[10] A systematic review and meta-analysis by Paraskevas et al.[18] concluded that there is convincing evidence which showed plasma CRP was elevated in periodontitis affected patients compared with controls. It has also been hypothesised that any association between periodontitis and CVD could be attributed to the moderate increase in CRP reported in subjects with poor periodontal health.[16]

The CRP levels were found to be ≤0.3 mg/l in healthy individuals. Following acute tissue damage, high CRP levels (42.1 mg/l) were found to be linked with higher incidence of stroke and myocardial infarction in a study conducted by

Chandy et al.[19] The CRP levels in serum or plasma could exceed 100 mg/l within 24 to 48 hours which could be useful for diagnosis, monitoring and therapy of inflammatory process and associated disease. A possible reason for the elevation of serum CRP may be its role in initial host response to injuries, infections, ischemic necrosis or malignancy where it plays a role in destroying infections or noxious agents, repairing affected tissue or organ and removing damaged tissue. It may be theorised, that patients affected with periodontitis may be predisposed to CVD by increasing the levels of acute phase proteins which in lead to increased inflammatory activity in atherosclerotic lesions.[19]

The synthesis of fibrinogen occurs in liver. Fibrinogen is a soluble plasma acute phase glycoprotein which is converted into fibrin during coagulation of blood and its level may be elevated in any form of inflammation.[20]

Fibrinogen is an important determinant of blood viscosity, platelet adhesion and aggregation, also the facilitator of wound healing. Fibrinogen has a role in promoting early plaque formation via different ways like damaging the endothelial cells of artery linings, stimulating the proliferation of vascular muscle cells and activating inflammatory cells.[21]

The normal fibrinogen level is about 1.5-3 g/l while increased levels that is ≥3.43 g/l have been found to be associated with CVD.[17] In the present study, mean fibrinogen level was found to be higher in patients with chronic periodontitis when compared to periodontally healthy subjects. This is in accordance with studies done by Sahingur et al.[22] who also found elevated levels of mean fibrinogen in periodontitis patients when compared with the control group. A probable reason for the increase may be correlated as higher percentage of patients with chronic periodontitis exhibit H1H2 or H2H2 genotypes which were found to be associated with higher fibrinogen levels when compared with healthy individuals.[22]

A number of epidemiological studies consistently also have shown a significant relationship between white blood cell count and the occurrence of CVD and stroke.[23,24] The findings of a study by Kweider et al.[25] showed a direct association between chronic periodontal infections and leukocytes.

Beck et al.[26] reported modification of blood rheology thereby promoting hypercoagulation with increase in leukocyte count. He also reported that subjects with the most severe probing pocket depth and bone loss at baseline had higher risk for developing coronary heart disease than those with minimal periodontal disease indicating that periodontal disease may be a risk factor for coronary heart disease.[25] Other rheological variables such as DLC which are potential predictors of CVD are increased in this study in accordance to a study by Kalburgi et al.[27]

There are few limitations in the current study. The sample size was small due to strict guidelines for recruiting patients; thus further studies can be conducted with larger sample size. The assessment of biochemical markers before and after treatment can be considered to highlight the interrelationship between periodontal disease, biochemical markers and CVD which act as a motivating tool for patients with chronic periodontitis for maintenance of their periodontal health which eventually assists in the prevention of cardiovascular events. Systemic conditions such as diabetes and infectious conditions were excluded purely on the basis of self-reported histories and there might be a possibility that this might have led to undiagnosed medical conditions. The estimation of other sensitive markers like serum amyloid A and α-2 macroglobulin from serum and plasma as well as quantitative evaluation of CRP in saliva and gingival crevicular fluid would provide greater clarity and comprehensive overview between between these biomarkers, periodontal and CVD.

CONCLUSION

The findings of the present study support the fact that levels of serum C-reactive protein, plasma fibrinogen, total leukocyte count, and differential leukocyte counts were increased in individuals with severe periodontitis when compared with moderate periodontitis and periodontally healthy individuals. Elevated levels of these inflammatory markers may increase the severity of periodontal destruction as observed with raised periodontal parameters.

Further research is needed to determine the specificity of these markers and their role in the inflammatory burden of one's systemic health. Also as the ability to predict cardiovascular risk markers in periodontal disease could have tremendous value in the prevention and treatment of such disease.

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Conflict of Interest: None.

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