

Assessment of Serum Parameters in Stable Coronary Artery Disease Patients in Correlation with Healthy and Chronic Periodontitis Patients

Abstract

Background: Periodontitis is a chronic inflammatory disease and has been strongly associated with elevation of systemic markers such as C-reactive protein (CRP), fibrinogen (FIB), and lipid profile, which have also been significantly associated with coronary heart disease (CHD). Hence, there is a need to assess the possible association between chronic periodontitis and coronary artery disease. **Materials and Methods:** A study included 100 subjects divided into four groups. Group I: stable coronary artery disease with chronic periodontitis, Group II: stable coronary artery disease without chronic periodontitis, Group III: chronic periodontitis without coronary artery disease, and Group IV: healthy controls. Gingival index, Russell's periodontal index, pocket depth, and clinical attachment level were recorded. Venous blood was collected from the patients, and serum fibrinogen, CRP, and lipid profile levels were estimated. **Results:** The intragroup comparison of biochemical and periodontal parameters showed statistically significant results with $P < 0.05$. The intergroup comparison of serum FIB, total cholesterol, high density lipoprotein, low density lipoprotein, and clinical attachment level showed statistical significant results ($P = 0.000$, $P = 0.000$, $P = 0.001$, $P = 0.025$, and $P = 0.000$, respectively) between Groups I and III. **Conclusion:** The results of the study indicate that there might be a possible correlation between coronary artery disease and chronic periodontitis, but periodontitis-cardiovascular link is complex and difficult to define though there is sufficient evidence for their association. Leakage of pro-inflammatory cytokines from the ulcerated periodontium causes the production of acute-phase proteins by the liver. To prove the relationship, further studies should be considered making use of other markers of inflammation with prospective randomized controlled studies involving large population.

Keywords: Chronic periodontitis, coronary artery disease, high sensitivity C-reactive protein, lipid profile, serum fibrinogen

Introduction

The effect of oral health on the rest of the human body was proposed by the Assyrians in the seventh B.C.^[1] 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.^[2] To further explore periodontal disease and coronary heart disease (CHD)/atherosclerosis association, investigators have studied specific systemic disorders to determine their relationship to periodontal status. CHD-related events are a major cause of death. Environmental risk factors such as smoking, diabetes, and hypertension do not explain the association of coronary atherosclerosis in a large number of patients.

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Several cross-sectional studies of patients with acute myocardial infarction (MI) or -confirmed CHD had found significantly with increased periodontitis than controls.^[3-5] Similarly, there may be a greater risk for CHD-related events such as MI when periodontitis affects a greater number of teeth in mouth compared with subjects having periodontitis with fewer teeth.^[6] A prospective study of subjects with periodontitis had a 25% increase in the risk for CHD compared with those with no or minimal periodontal disease.^[7]

The risk factors associated with the formation of CHD are increased blood viscosity and thrombus formation by fibrinogen (FIB), increased thrombogenesis by aggregation of platelets induced by platelet aggregation associated protein by some strains of *Streptococcus sanguis*, *Porphyromonas gingivalis*

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closely associated with periodontitis, and formation of atherosclerosis by foam cells/monocytes ingesting low-density lipoprotein (LDL), leading to thickening the arterial wall and narrowing the lumen.

Acute-phase proteins such as C-reactive protein (CRP) induce monocytes/macrophages to produce tissue factor leads to stimulation of coagulation pathway and increased blood coagulability. Elevated serum CRP and FIB levels are well-accepted risk factors for cardiovascular disease.^[8]

Periodontitis is a chronic inflammatory disease of infectious nature and has been strongly associated with the elevation of inflammatory mediators such as cytokines, systemic markers such as CRP, FIB, lipid profile, and white blood cells. These biomarkers have been significantly associated with CHD.^[9,10]

Abundant evidence supports a strong association between periodontitis and CHD which is potentially explained by diverse biological mechanisms such as the inflammatory burden, the oral microbial burden, and hemostatic factors.^[9]

Despite the evidence linking periodontitis and coronary artery disease, there are limited data on the periodontal parameters with any individual systemic biomarker such as plasma FIB, CRP, and lipid profile levels. Therefore, a study was carried out to assess the possible association between chronic periodontitis and systemic biomarkers of coronary artery disease.

Materials and Methods

Study design

A case-control study was designed and conducted in the Department of Periodontics and Oral Implantology, A.M.E's Dental College and Hospital and Shivam Hospital, Raichur, Karnataka. Study included 100 subjects with the age group of 35–55 years of both genders. The subjects were selected from the outpatient department of the same institution and hospital mentioned above. Study was reviewed by board of ethical committee, and after seeking approval, the study was envisaged.

Inclusion criteria

Patients between the age group of 35 years and 55 years with at least 14 natural teeth were include in the study. Individuals diagnosed with chronic periodontitis, having more than ten sites with probing depth (PD) ≥ 5 mm and clinical attachment loss (CAL) ≥ 4 mm. Cardiovascular disease individuals with stable coronary artery disease who were in outpatient care for at least 6 months. To be included in the study, stable coronary artery disease was defined as the occurrence of at least one of the following events 6 months before entering the study: (1) history of myocardial infarction; (2) stable angina or ischemia in noninvasive tests; and (3) surgical or percutaneous myocardial revascularization and a lesion $>50\%$ in at least

one coronary artery assessed by angiography. Healthy controls who are systemically healthy individuals, with clinically healthy gingiva with a gingival index (GI) score of ≤ 1 and no teeth with PD ≥ 5 mm.

Exclusion criteria

Individuals were excluded if they had a history of diabetes mellitus, hypertension, or smoking, who underwent any periodontal therapy in the past 6 months, and patients using or who have received medicines such as antibiotics, anti-inflammatory drugs, steroids, immunosuppressants, anticoagulants, and regulators of cholesterol.

Methodology

A medical and dental history was taken for each patient in the prepared pro forma for this study. The periodontal parameters such as GI,^[11] Russell's periodontal index (RPI),^[12] pocket depth, and clinical attachment level were measured with mouth mirror and with a William's graduated periodontal probe.

Subjects included in the study were divided into four groups with 25 subjects in each group. Group I: stable coronary artery disease with chronic periodontitis, [Figure 1], Group II: stable coronary artery disease without chronic periodontitis [Figure 2], Group III: chronic periodontitis without coronary artery disease, [Figure 3] and Group IV: healthy controls [Figure 4].

Biochemical parameters

Blood samples were taken from all subjects from antecubital vein. Plasma FIB level, high sensitivity CRP, total cholesterol, high-density lipoproteins (HDLs), LDLs, very low-density lipoproteins (VLDLs), and triglycerides are determined by autoanalyzer in the clinical biochemistry laboratory. Plasma FIB level was determined using FIBROQUANT System pack kit,^[13] high sensitivity CRP was determined by measurement of antigen-antibody reaction by the end-point method,^[14] Total Cholesterol, HDLs, VLDLs, triglycerides were determined using Erba Mannheim's semi-autoanalyzer,^[15] and LDL cholesterol was assessed according to the formula by Friedewald *et al.* in 1972, in which $LDL = TC - (HDL + TG/5)$.

Results

This study included 100 subjects with age group ranging from 35 to 55 years who satisfied the selection criteria. The selected subjects were explained about the study, and an informed consent was obtained. The periodontal and biochemical parameters were obtained. The obtained data were statistically analyzed using Microsoft Excel and Statistical software (IBM SPSS version 20, Chicago, Illinois, USA). For all these tests, a $P = 0.05$ or less was set for statistical significance (S). Kruskal-Wallis ANOVA test was done for multiple group comparisons. The Mann-Whitney U-test was done to compare between two groups.

Biochemical parameters

The mean comparison showed statistically significant results among all four groups with respect to all the biochemical parameters [Table 1]. Serum levels of FIB were higher in chronic periodontitis patients (mean: 442.92) followed by other groups and showed statistically significant results between all the four groups ($P < 0.05$). High-sensitivity CRP was found to be more in stable coronary artery disease patients (mean: 6.30) when compared with other groups and showed significant results between all the groups except when compared the stable coronary artery disease and chronic periodontitis group with stable coronary artery disease group.

Lipid profile

The serum levels of total cholesterol were higher in the stable coronary artery disease group (mean: 262.00), followed by other groups with statistically significant results between all the groups except between the stable coronary artery disease and chronic periodontitis group and healthy group. Similar results were observed for LDL levels with statistically significant results between all the groups but showed not significant results between stable coronary artery disease and chronic periodontitis group with healthy group and VLDL levels were found to be more in periodontitis and stable coronary artery disease group (mean: 43.72), followed by other groups with statistically significant results between few groups only. Conversely, the levels of triglycerides were higher in periodontitis and stable coronary artery disease group compared to healthy (mean: 218.76 vs. 149.28) and HDL

were lower in stable coronary artery disease group (mean: 37.80), followed by other groups and showed significant results between all groups except between periodontitis and stable coronary artery disease group and only periodontitis group and healthy group.

Periodontal parameters

Mean comparison among groups of GI score, RPI, probing pocket depth (PPD,) and CAL showed statistically significant results among all the four groups [Table 2]. GI score (mean: 2.00) and clinical attachment level (mean: 2.53) were found to be higher in periodontitis and stable coronary artery disease group with no statistically significant difference when compared with only periodontitis group. RPI (mean: 3.62) and PPD (mean: 5.85) showed a higher score in periodontitis group with statistically significant results when compared with stable coronary artery disease group and periodontitis group.

Discussion

The possibility of a connection between oral infection and systemic health was suggested already during the 19th century,^[16] and a discussion on the oral focal infection theory continued a debate that is still going on. In the late 1980s, after suggestions by Mattila and Beck *et al.*, an increased interest on the association between oral health and cardiovascular disease emerged.^[4,17] Since then, the interest for this link has persevered.

Periodontitis is a chronic inflammatory condition following bacterial colonization of the gingiva that successively degrades the tissues attaching the teeth to the alveolar

Table 1: Mean comparison of biochemical parameters among groups

Variables	Group I		Group II		Group III		Group IV		P
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
FIB	313.34	85.20	367.12	44.98	442.92	132.22	224.64	53.96	0.000*
HSCRP	6.30	6.43	1.32	2.13	0.77	0.61	0.29	0.11	0.000*
TC	154.44	30.12	262.00	38.16	206.56	46.25	163.40	32.51	0.000*
HDL	37.80	8.04	49.48	8.35	45.96	8.15	44.12	5.95	0.000*
LDL	91.08	34.52	168.64	35.78	119.16	42.66	89.40	32.78	0.000*
VLDL	34.91	15.18	43.72	16.27	37.58	13.61	29.88	10.82	0.011*
TG	180.60	79.53	218.76	81.92	186.16	69.79	149.28	54.25	0.017*

Statistical analysis: Kruskal–Wallis test. Statistically significant if $P < 0.05$. *Significant. SD: Standard deviation; FIB: Fibrinogen; HDL: High-density lipoproteins; LDL: Low-density lipoproteins; VLDL: Very low-density lipoproteins; TG: Triglyceride; TC: Total cholesterol

Table 2: Mean comparison of periodontal parameters among groups

Variables	Group I		Group II		Group III		Group IV		P
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
GI score	2.00	0.02	0.81	0.26	1.99	0.03	0.81	0.19	0.000*
RPI	3.16	0.43	0.86	0.11	3.62	0.45	0.82	0.10	0.000*
PPD	5.59	0.26	0.00	0.00	5.85	0.68	0.00	0.00	0.000*
CAL	2.53	0.29	0.00	0.00	0.61	1.01	0.00	0.00	0.000*

Statistical analysis: Kruskal–Wallis test. Statistically significant if $P < 0.05$. *Significant. SD: Standard deviation GI: Gingival index; RPI: Russell's periodontal index; PPD: Probing pocket depth; CAL: Clinical attachment level



Figure 1: Group I: Stable coronary artery disease with chronic periodontitis



Figure 2: Group II: Stable coronary artery disease without chronic periodontitis



Figure 3: Group III: Chronic periodontitis without coronary artery disease



Figure 4: Group IV: Healthy controls

bone. Its mildest form, gingivitis or a bleeding gum, does not affect the underlying supporting structures of the teeth and is reversible with treatment. Periodontitis is common, and it has been estimated that 46% of US adults have periodontitis^[18] and its severe form, which often result in tooth loss, affect 5%–15% worldwide.^[19] Furthermore, in the presence of an oral infection or inflammation, the inner wall of the gingival pocket will become ulcerated, and its role as a barrier to the systemic circulation is disrupted. Under these conditions, bacteria as well as bacterial products and inflammatory mediators can move from the gingival pocket to the well-vascularized periodontal tissues and into the circulation.

Atherosclerosis is a multifactorial disease promoted by chronic inflammatory conditions. An activation of systemic inflammation increases the risk for rupture of the atherosclerotic plaques and is considered of importance for the onset of acute coronary syndromes.^[20,21] Cardiovascular disease, an expression of atherosclerosis, is the major cause of mortality in the Western world, contributing to almost half of all deaths in Europe.^[22] Although a multitude of risk factors including smoking, hypertension, dyslipidemia, and diabetes are known to be behind a large proportion of myocardial infarctions,^[23] there are still gaps in the knowledge regarding causes that contribute to the progress of atherosclerosis and cardiovascular events.

It has been postulated that an association between periodontal and cardiovascular diseases may be one of these gaps.^[24] Both conditions are promoted by similar risk factors, which may be a likely, but perhaps not the only, reason for the connection. An alternate explanation is that systemic inflammation promoted by periodontitis accelerates the atherosclerotic vascular injury and plaque rupture. Then, periodontitis becomes a cause of, rather than just a condition that coexists with cardiovascular disease.^[21,25] The DNA from *P. gingivalis* and *Aggregatibacter actinomycetemcomitans* has been identified in arterial plaques further support that there is a link between the oral microflora and cardiovascular disease.^[26] Together with studies in which periodontal intervention influenced inflammatory markers of cardiovascular risk for up to 6 months after the intervention,^[27,28] these findings were taken as evidence of a causal relationship.

Systemic inflammation from moderate-to-severe periodontitis has been forwarded as a third biologic mechanism linking atherosclerotic vascular disease (ASVD) and periodontal disease. This mechanism is particularly attractive since the pathogenesis of both atherosclerosis

and periodontitis has strong inflammatory components. The local periodontal generation of the pro-inflammatory cytokines tumor necrosis factor-alpha, interleukin 1 (IL-1), and IL-6 in moderate-to-severe periodontitis has been shown to elevate systemic levels of these cytokines which in turn induce an acute phase response. Elevated CRP, FIB, blood glucose, white blood cell counts, total cholesterol, triglycerides, and LDL and depressed HDL are all components of the acute phase response, are recognized ASVD risk factors, and all have been reported in patients with moderate-to-severe periodontitis. As discussed earlier, elevated CRP in particular has been shown to be a risk factor for ASVD. However, since many sources of systemic inflammation exist, and none of the inflammatory markers characterized to date are specific to periodontitis, attempts to link ASVD and periodontitis through increased systemic inflammation have been complicated by the need to control for an array of confounding variables. In addition, periodontal intervention studies have also been complicated by the modest degree of association between the two diseases. As a consequence, it has been difficult to definitively demonstrate that increased systemic inflammation from moderate-to-severe periodontitis directly contributes to ASVD or ASVD events.^[29] Data from several epidemiologic studies have supported the concept that periodontitis or periodontal conditions are linked to atherosclerosis and subsequent diseases such as CVD.^[30]

In the present study, parameters plasma FIB level, high-sensitivity CRP, total cholesterol, HDLs, LDLs, VLDLs, and triglycerides showed a statistically significant difference among all the four groups.

The FIB level was highest in Group III when compared to other three groups which is similar to results as observed in a study by Amabile *et al.* in 2008.^[31] high-sensitivity C-reactive protein (HSCR) levels showed highest in Group I which reflects the potential significance of the local periodontal inflammatory burden for systemic inflammation as observed in previous studies by Bokhari *et al.* in 2014.^[9] The total cholesterol levels was highest in Group II patients followed by Group III, Group IV, and Group I reflecting that total cholesterol levels are increased in periodontitis with coronary artery disease patients as observed in a previous study by Emingil *et al.* in 2000.^[32] Similarly, high density lipoprotein, which is known to be a favorable lipoprotein^[33] for health appeared to be decreased in Group I than the other groups which highlighted the association of high-density lipoprotein to coronary artery disease which is supported by the hypothesis of association between periodontitis and CHD.^[34] This coincided with the previous research reports of Beck *et al.* in 1996^[17] and Mattila *et al.* in 1989.^[4] LDL in Group II was maximal with decrease in order of Group III, Group I, and Group IV, respectively, as observed in previous study by Emingil *et al.* in 2000.^[32] VLDL showed highest levels in Group II followed by other groups reflecting no significant effect

of inflammatory condition on VLDL levels. Furthermore, triglyceride levels were higher in Group II, which again showed the etiology for cardiovascular events. Acute infections are known to interfere with lipid metabolism, and elevation of triglyceride had been observed, especially in infection with Gram-negative bacteria.

Periodontal parameters GI, Russell's periodontal index, pocket depth, and clinical attachment level showed statistically significant difference among all four groups.

The GI score and PPD showed highest value in Group I followed by other groups with no statistical significance between Groups I and III and the RPI and clinical attachment level score showed highest value in Group III followed other groups with statistical significance between Group I and III. As periodontitis predisposes to cardiovascular disease by increasing levels of acute phase proteins and pro-inflammatory mediators, it leads to increased inflammatory activity aggravating the formation of atherosclerotic lesions and an accelerated development of cardiovascular diseases, if left untreated. The current observations may explain the epidemiological links between periodontitis and cardiovascular diseases as determined by Beck *et al.*^[17] and Joshipura *et al.*^[35] which fits the general hypothesis that various infectious processes contribute to the pathogenesis of cardiovascular diseases.

Conclusion

In the present study with stable coronary artery disease, current periodontal inflammation and tissue breakdown are associated with high levels of cardiovascular markers such as serum FIB, CRP, and lipids. With recent epidemiological, clinical, and experimental evidence, the proposed mechanism of bacteremia inducing pro-atherogenic lesions is further supported. To determine the exact biological mechanism and confirm a direct or causal relationship, more interventional and longitudinal studies are needed.

Limitations of the study

1. Sample size would have been increased
2. Microbial analysis would have been included in the study
3. Interventional studies would have been included.

Clinical relevance of the study

Chronic periodontitis has been implicated in the pathogenesis of stable coronary artery disease. The current study has been carried out to evaluate the relationship or possible role of periodontitis for causing CHD. In this sample of patients with stable coronary artery disease, current periodontal inflammation, and tissue breakdown are associated with high levels of cardiovascular markers compared with healthy individuals.

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Conflicts of interest

There are no conflicts of interest.

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