Original Article

High Sensitivity C-Reactive Protein and Cholesterol Level as Risk Markers for Both Periodontitis and Coronary Artery Disease

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Abstract

Objectives: The association between periodontal disease and cardiovascular disease (CVD) has received considerable attention, although it is unclear whether there is a causal component. Therefore, this study aimed to determine the Correlation between high sensitivity C reactive protein (hs-CRP) and total blood cholesterol levels in periodontitis (PD) and coronary artery disease (CAD).

Methods: Eighty subjects (40 males and 40 females) divided into four equal groups: Group 1: control group, healthy without CAD or PD, group 2: PD without CAD (n=20). group 3: PD with CAD, and group 4: CAD without PD. Periodontitis was defined according to the 2017 periodontal disease classification. Periodontal probing depth (PPD) and clinical attachment level (CAL) were recorded. All participants were assessed for CAD by angiography (coronary computed tomography angiography or coronary angiography). Finally, serum hs-CRP and total cholesterol levels were determined by using the particle enhanced immunoturbidimetric assay method.

Results: The median of serum cholesterol and hs-CRP levels was significantly lower in the control group than the patients' groups ($P<0.05$). There were no statistically significant differences in gender and age among the studied groups ($P>0.05$). Furthermore, significant, positive, and strong correlations of PPD and CAL with the hs-CRP and Cholesterol.

Conclusions: Serum levels of hs-CRP and Cholesterol were positively proportionate to the measurements of CAL and PPD by increasing the severity of PD parameters (PPD and CAL), serum level of CAD biomarkers (hs-CRP and Cholesterol) were increased.

Keywords: *Periodontitis, Coronary artery disease, Hs-CRP, Cholesterol.*

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Introduction

Coronary artery disease (CAD) is an abnormal narrowing of coronary arteries associated with the local accumulation of lipids in cholesterol-containing deposits (plaques), leading to the limited blood supply to the heart muscles. This condition is called ischemia[1]; it can cause death and disability in affected patients and impose a vast burden on the healthcare system[2]. Periodontitis (PD) is a local inflammatory process with the destruction of periodontal tissues, triggered by bacterial insult known as dental plaque[3]. Dental plaque is an essential cause of periodontal attachment loss and alveolar bone loss, which subsequently leads to pocket formation, teeth mobility, and finally, teeth loss[3]. Periodontitis is estimated to be detectable in 20-50% of the general population and is one of the major causes of teeth loss in adults[4].

In the last few decades, researchers have focused on the effects of local inflammation, whether intraoral or extraoral, on increased markers' levels of certain systemic diseases[5,6]. The relation of periodontal diseases has attracted the most interest and attention to diabetes mellitus, cardiovascular diseases, and osteoporosis[7]. During PD, the inflamed tissue and inflammatory cells release abundant amounts of cytokines, mainly interleukin 1-beta (IL-1β), IL-6, prostaglandin E2, and tumor necrosis factor-alpha (TNF-α), which may have systemic effects on the host[8]. These proinflammatory mediators are usually released at the site of inflammation as part of the natural host reaction and response to bacterial insult[8].

It is acknowledged that elevated serum levels of C reactive protein (CRP) and cytokines sustain the idea that PD may influence other systemic diseases and may have a negative effect on these conditions[9]. However, there is much dispute about the direction of cause and effect[9,10]. This is referred to as a bidirectional relationship between oral inflammation, namely PD, and the other systemic diseases mentioned in this section[11]. CRP is a liver-produced acute phase protein (reactant) that reflects a measure of the acute phase response and serves as a systemic marker of inflammation levels that can be used to monitor patients' consuming infections[12].

The term "acute phase" refers to local and systemic events that accompany inflammation. Local responses include vasodilatation, platelet aggregation, neutrophil chemotaxis, and the release of lysosomal enzymes. Systemic responses include fever, leukocytosis, and a change in the hepatic synthesis of acute-phase proteins[12]. Elevated high sensitivity C reactive protein (hs-CRP) levels have been demonstrated in ischemic heart diseases and myocardial infarction[13,14].

One interesting point is that many mutual risk factors, such as inflammation, gender, smoking, genetics, and lifestyles, have been correlated to periodontal disease and CVD[15]. Even more interesting is that cardiovascular diseases' markers reported being significantly associated with the severity of PD, including phospholipids, Cholesterol, and its sub-fractions low-density lipoprotein (LDL) and high-density lipoprotein (HDL), hence a close inter-relationship has been hypothesized between CVD and PD[16]. This is considered a potential risk and other existing risk factors such as smoking, diabetes, and low socioeconomic status[16].

CRP has been shown to predict CVD mortality; on the other hand, elevated CRP levels have been observed in middle-aged patients with PD. Such evidence suggests that the combination of chronic infections like PD with elevated CRP might be associated with a higher rate of chronic heart diseases[17].

The relation between PD and atherosclerotic vascular disease (ASVD) is potential of great public health importance because of their high prevalence and the presence of several confounder risk factors such as age, smoking, and diabetes mellitus well as, confounder biomarkers[18]. Although most of the collected information was obtained from observational studies that are unlikely to confirm the cause-effect relation between PD and ASVD pathogenesis, extensive evidence confirms a strong correlation between PD and CAD[18]. The link between PD and CVD in humans is based on observational and cross-sectional studies; however, several longitudinal and cohort studies demonstrated that PD increases the risk of ASVD[19,20]. Therefore, this study aimed to determine the Correlation between hs- CRP and total blood cholesterol levels in PD and CAD.

Patients and methods

Sample selection

The study proposal was submitted to the Scientific Committee of Kurdistan Board for Medical Specialties, Erbil, for registration and ethical approval, which was granted by letter no. 418 on 23/09/2018. The study was conducted according to the Helsinki Declaration of 1975, as revised in 2000. Verbal and written informed consent was obtained from all subjects before their enrolment in the study. The study sample was selected among patients attending Shar Hospital in Sulaimani city, Kurdistan Region of Iraq, from April to September 2019. Participants were screened and selected according to their cardiovascular and periodontal condition. All

participants were assessed for CAD by angiography (coronary computed tomography angiography or coronary angiography), and their periodontal condition was examined according to the 2017 classification. Inclusion criteria were male and female, aged 40-70 years, having a minimum of twenty teeth, and exclusion criteria: patients suspected of having a disease or condition that might increase CRP level, for example, infection or inflammation. There is evidence of myocardial infarction within 6 months of the dental examination and a history of any periodontal surgery, dental trauma, or recent tooth extraction in the past six months. The samples were divided into four groups with 20 samples for each, as follows: group 1: control group, healthy without CAD and PD, group 2: PD without CAD, Group 3: PD with CAD, and group 4: CAD without PD.

Serum levels of hs-CRP were measured using the particle enhanced immunoturbidimetric assay method (Cobas C 311 automated chemistry analyzer), levels below two mg/L considered normal[21]. A total cholesterol level below 200 mg/dl was regarded as normal. According to the 2013 American College of Cardiology and American Heart Association guidelines[21], total Cholesterol was measured using the particle enhanced immunoturbidimetric assay method (Cobas C 111 automated chemistry analyzer).

Periodontal examination

Periodontal examination was conducted under clinical conditions and included probing pocket depth (PPD) and clinical attachment loss (CAL) on the remaining teeth. All fully erupted teeth were assessed. PPD and CAL were calculated using a color-coded periodontal WHO probe at six sites per tooth (mesiobuccal, mesiolingual, distobuccal, distolingual, midbuccal, and midlingual aspects). CAL was determined by estimating the distance from the cementoenamel junction to the bottom of the periodontal pocket and PPD by calculating the distance from the gingival margin to the periodontal pocket.

According to the 2017 periodontal disease classification[22], a patient has PD if the interdental CAL is detectable at ≥two non-adjacent teeth or buccal or lingual/palatal CAL ≥3 mm pocketing >3 mm is detectable at ≥two teeth.

Statistical analysis

Shapiro-Wilk test was applied to determine the normality of the data. Accordingly, nonparametric tests were applied for the analysis of the study's data. Kruskal-Wallis and Mann-Whitney U tests were used to compare the clinical periodontal parameters (PPD and CAL) and the serum biomarkers (hs-CRP and Cholesterol) among the four study groups. Additionally, Spearman's rank correlation coefficient (rho) was used to study the correlations between the study parameters. The statistical software SPSS, V23, was employed to identify the level of significance between the parameters among the study groups; differences were considered statistically significant at the level of ($p \leq 0.05$).

Results

The descriptive statistics of the study data revealed that the mean age of all participants in this study was 52.95±8.44) years old, as shown in Table 1. Furthermore, the median values of PD parameters (PPD, CAL) and CAD biomarkers (hs-CRP, Cholesterol) in different studied groups s shown in Table 2. The median values of both hs-CRP and Cholesterol in the control group were significantly lower as compared to the three study groups (PD without CAD, PD with CAD, and CAD without PD) (Mann-Whitney U test, $p<0.05$), as shown in Tables 2 and 3. Additionally, the study found no statistically significant difference in the levels of hs-CRP or Cholesterol among the three study groups (PD without CAD, PD with CAD, and CAD without PD) (Mann-Whitney U test, $p>0.05$) (Table 3).

The severity of PD and CAD among males and females was assessed across the whole study sample by comparing the medians of PD parameters (PPD and CAL) and CAD biomarkers (hs-CRP and Cholesterol). Although the medians of all variables were found to be greater in males as compared to females, the differences were not statistically significant (Mann-Whitney test, $p>0.05$) (Table 4).

For further assessment, the study population was divided into two age groups. Participants aged over 55 years in one group and those aged younger than 55 years in the other. The severity of PD and CAD among these two age groups was then checked by comparing PPD, CAL, CRP, and Cholesterol. No statistically significant differences in the medians of these variables

Table 1: Demographics of the study sample.

Total	Male	Female	Age	
			Range (40-70) – Mean 52.95 (±8.44)	
			G1 <55	G2 >55
80	40 (50%)	40 (50%)	N. 50 - (60 %)	N. 30 - (40%)

Table 2: The median values of PD parameters (PPD, CAL) and CAD biomarkers (hs-CRP, Cholesterol) in different studied groups.

Variables	Groups			
	Control (n=20)	Periodontitis without CAD (n=20)	Periodontitis with CAD (n=20)	CAD without Periodontitis (n=20)
hs-CRP (mg/L)	1.475	10.05	13.8	7.025
CAL (mm)	0	3.1	2.6	0
PPD (mm)	0	4.3	4.65	0
Cholesterol (mg/dl)	171.5	213	243	203

Table 3: The differences of the PD measures (PPD, CAL) and CAD biomarkers (hs-CRP, Cholesterol) among the study groups.

Groups	hs-CRP	Cholesterol	CAL	PPD
PD without CAD vs control	0.000*	0.009*	0.000*	0.000*
PD with CAD vs control	0.000*	0.001*	0.000*	0.000*
CAD without PD vs control	0.001*	0.033*	1	1
PD without CAD vs PD with CAD	0.465	0.344	0.616	0.138
PD without CAD vs CAD without PD	0.317	0.808	0.000*	0.000*
PD with CAD vs CAD without PD	0.168	0.223	0.000*	0.000*

Mann-Whitney U test. *= Statistically significant ($p<0.05$).

Were detected between the two age groups (Mann-Whitney test, p>0.05) (Table 5).

Spearman's rank correlation coefficient analysis indicated significant, positive, and strong correlations of PPD with each of CAL, hs-CRP, and Cholesterol. Similarly, significant, positive, and strong correlations of the parameters mentioned above with the CAL were also found (Table 6).

Table 4: The differences among the study variables between males and females across the whole study sample.

Variables	Groups		p-value
	Female n=40	Male n=40	
hs-CRP	6.6	7.495	0.322
CAL	0	1.35	0.603
PPD	0	4	0.603
Cholesterol	189	214.5	0.052

Mann-Whitney U test

Table 5: The differences among the study variables between the elder and younger age groups.

Variables	**Age group**		**p-value**
	<55 (n=50)	**>55 (n=30)**	
hs-CRP	7.225	6.87	0.311
CAL	1.2	0	0.366
PPD	4	0	0.907
Cholesterol	203	201.540.07	0.897

Mann-Whitney U test

Table 6: Correlations of periodontitis measures and CAD biomarkers.

Parameters	rho correlation and p-value	PPD (n=80)	CAL (n=80)	hs-CRP (n=80)	Cholesterol (n=80)
hs-CRP	r	.495**	.514**	1.000	.653**
	p-value	<0.001	<0.001	-	<0.001
CAL	r	.901**	1.000	.514**	.376**
	p-value	<0.001	-	<0.001	0.001
PPD	r	1.000	.901**	.495**	.405**
	p-value	-	<0.001	<0.001	<0.001
Cholesterol	r	.405**	.376**	.653**	1.000
	p-value	<0.001	0.001	<0.001	-

Spearman's rho correlation. ** Correlation is significant at the 0.01 level (2-tailed).

Discussion

Evidence exists to support the Correlation between periodontal disease and serious systemic conditions such as diabetes and ACVD[5,11]. In particular, a significantly higher prevalence of coronary heart disease has been reported among patients suffering from long-term PD after adjusting for risk factors such as smoking, diabetes, and high blood pressure[11]. Periodontitis is a chronic infection characterized by an exaggerated gingival inflammatory response to pathogen microbiota, which results in the loss of dental support tissue and eventually loss of teeth[3]. Periodontitis is associated with other systemic chronic conditions like ACVD through common pathophysiological pathways. Hence it may be considered that by reducing local and systemic inflammation and improving periodontal health, the cardiovascular risk may consequently be reduced[23].

The current study showed a significant relation of CAD biomarkers (hs-CRP and Cholesterol level) with clinical periodontal parameters used in this study (CAL and PPD), which marks the strength of Correlation between CAD and PD. This finding is consistent with the results of other studies that found a positive association between CRP and destructive periodontal disease, which provides a potential mechanism to link the destructive periodontal disease with an increased risk of atherosclerotic complications in ACVD[24,25].

The results of this study supported by the findings of other researchers who also demonstrated increased levels of Cholesterol and LDL and a decreased level of HDL in a group of patients with periodontal disease compared to a group of subjects with healthy periodontium[26-28]. Furthermore, periodontal pockets were positively associated with total cholesterol and LDL cholesterol[26-28]. This is perhaps due to the presence of a certain degree of inflammation that accompanies periodontal pockets, which consistently increases local and systemic inflammation markers.

The interventional study examined the effects of periodontal treatment on systemic markers such as Cholesterol and CRP, which has provided evidence of a causal direction between oral inflammation and systemic effect[29]. Periodontitis and cardiovascular diseases share common risk factors such as smoking, diabetes, and stress. Several reports have demonstrated that periodontitis is accompanied by systemic inflammation, which increases concentrations of circulating phospholipids and other lipids[16,30,31].

In the past, various studies reported an association between periodontal disease and serum lipid levels, but the results were controversial[23,26,27]. Some reports suggested a relationship between cholesterol levels and PD[26], while others indicated a relationship between total serum triglyceride levels and PD[32]. Moreover, recent solid evidence supports the association between PD and CADs, confirming that severe and advanced PD is associated with an increased risk of stroke[33].

The data from our study sample suggested that the relation between PD and CAD is independent of age and sex. This result is consistent with a cross-sectional study

conducted in Sao Paulo, Brazil, between February and November 2012[34]. The study used multinomial logistic regression for consecutive evaluation for the association between PD and cardiovascular risk factors of 539 subjects without prior cardiovascular disease seen within a health promotion program that included cardiovascular and dental evaluation. The study recorded no significant association between cardiovascular risk factors and periodontal disease[34]. Another study, carried out in the Netherlands by Beukers et al. in 2017, aimed to investigate the adjusted association between PD and ACVD among all individuals registered in a dental center in the Netherlands[35]. The study concluded that among the 60174 participants, PD was an independent risk indicator for atherosclerotic cardiovascular diseases[35]. Additionally, chronic PD was associated with CAD incidence among younger men, independent of established cardiovascular risk factors[36].

Furthermore, although our data reported no significant gender differences, it has been reported that long term PD was related to subclinical atherosclerosis in men rather than women and that sex variation in mortality and morbidity of CAD may be due to the specific role of novel risk factors across sex[37]. Moreover, it has been suggested that variations in the distribution and severity of periodontal diseases could be attributed to gender variation[37,38].

Therefore, dentists should be aware of the correlation between PD and CADs. Direct collaboration between dentist and cardiologist is required to manage patients with CVDs and avoid serious complications during periodontal intervention. Prior to any intervention, the cardiologist must check for signs of CADs and the patients should be informed about the possible relationship between PD and CVDs and their potential risk of further CVD complications if their periodontal health is compromised. Patients may require urgent treatment for PD and awareness raising about the importance of meticulous oral hygiene and regular dental visits[39,40].

Conclusions

Serum levels of hs-CRP and Cholesterol were positively proportionate to the parameters of PD (CAL and PPD). That's to say, increased severity of PD parameters (PPD and CAL), is associated with concomitant increase in the serum levels of CAD biomarkers (hs-CRP and Cholesterol).

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