A multi-center study on the relationship of Periodontal Disease to the Presence and Severity of Coronary Artery Disease

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ABSTRACT

Statement of problem: Association between coronary artery disease (CAD) and periodontal disease (PD) is now of significant public health importance that reducing periodontal disease might have the potential benefit of reducing the risk of CAD.

Purpose of study: To examine the relationship between periodontal disease and the presence and severity of CAD based on angiographic findings.

Materials and Methods: Study subjects comprised 183 consecutive patients including dentate (122 patients) and edentulous (61 patients), admitted for elective coronary angiography at three angiography centers in Rasht, Iran. Periodontal and laboratory examinations were carried out before angiography. A coronary stenosis greater than 75% was used to define CAD. Periodontal parameters and coronary angiograms were blindly evaluated by a dentist and a cardiologist.

Results: Mean clinical attachment level (CAL) was significantly higher in the individuals with CAD compared to non-CAD group after adjustment for potential confounders (OR = 1.6, P = 0.029). Severe PD was found in 33.3% of non-CAD group compared to 38.1% and 49.6% of those having single-vessel and multi-vessel CAD respectively. Individuals with more extent periodontal disease exhibited significantly elevated odds of having CAD (OR = 2.7). Logistic Regression model showed that CAD severity could be predicted by male gender (OR = 3.1, P = 0.013) as well as history of diabetes mellitus (OR = 2.3, P = 0.030) in total study population, but not with edentulism. CAD severity was positively associated with the CAL measure in dentate patients (OR = 1.6, P = 0.038).

Conclusion: Based on our data, PD represents as a potential risk factor for CAD. To modify this potential risk factor, successful treatment and preventive care programs are suggested.

Key words: Angiography, periodontal disease, coronary artery, risk

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INTRODUCTION

Quantifying association between coronary artery disease (CAD) and periodontal disease is now of significant public health importance. A study primarily performed in the late 1980s by Simonka et al [1] revealed that patients with heart disease had a higher prevalence of periodontal disease. Since then, a variety of studies have focused on this hypothesis that reducing periodontal

disease might have the potential benefit of reducing the risk of CAD [2, 3]. Some probable mechanisms have been proposed whereby the burden of bacterial infections and inflammatory cytokines contribute to the coronary atherogenesis processing. In this regard, the susceptible individuals may exhibit greater expression of inflammatory mediators and might thereby be at increased risk for atherosclerosis [4-6]. In fact, periodontal disease is associated with elevating serum levels of several chronic inflammatory bio-markers which might raise the susceptibility to CAD and its severity [7-9]. Besides, it seems that successful periodontal treatment might have beneficial impacts on surrogate cardiovascular end points including moderation of serum inflammatory bio-markers and endothelial function [10, 11].

Although some studies could find an association between periodontal disease and CAD risk independent of a variety of potential confounders [12,13], some other studies did not observe this association even after adjustment for important confounding factors [14,15]. These inconsistencies have led to concerns and uncertainties about the validity of the association between CAD and periodontal disease and its strength. In the present study, we examined the relationship between periodontal disease parameters and the presence and severity of CAD based on angiographic findings after adjustment for potential cofounders.

METHODS

In a prospective, epidemiological study, 183 patients, including 122 patients with at least 15 teeth and 61 edentulous patients, who underwent elective coronary angiography at three angiography centers in Rasht, Iran, were consecutively evaluated. This study included patients who presented with typical angina pectoris or with ambiguous symptoms but had resting ECG

findings suggestive of myocardial ischemia or those having abnormal exercise tolerance test and/or abnormal perfusion imaging scan. Individuals with any factor influencing periodontal parameters such as current antibiotic use, oral cavity infections, or history of periodontal treatments or interventions were not included into the study. Informed consent was obtained from all participants before examination and the review committee of Guilan University of Medical Sciences approved the research project.

Demographic characteristics and clinical criteria of assigned patients were extracted from hospital recorded files as well as face to face interviewing if required and entered into a computerized database form. The patients were given self-administered questionnaires about their medical history including: general characteristics (gender, age, educational level, and occupational status), coronary artery disease risk factors comprising: current smoking history (patients regularly smoke a tobacco product/products one or more times per day or have smoked in the 30 days prior to admission) [16], hypercholesterolemia (total cholesterol ≥5.0 mmol/l, HDL-cholesterol ≥1.0 mmol/l in men, or ≥1.1 mmol/l in women, and triglycerides ≥2.0 mmol/l) [17], family history of CAD (first-degree relatives before the age of 55 in men and 65 years in women) [18], hypertension (systolic blood pressure ≥140 mmHg and/or diastolic ≥90 mmHg and/or on antihypertensive treatment) [19], and diabetes mellitus (symptoms of diabetes plus at least one of the following: plasma glucose concentration ≥11.1 mmol/l, fasting plasma glucose ≥7.0mmol/l, and 2-hpp ≥11.1 mmol/l) [20].

Body mass index was calculated from measured weight and height. Blood pressure was measured by standard mercury sphygmomanometer in each arm in seated subjects. Mean readings from both arms were used for systolic and diastolic blood pressure. Venous blood samples of 5.0 ^{cc} were collected from each patient in the fasting state in the morning from an

antecubital vein. Standard measurements of lipid profile and fasting glucose were performed and standard blood analysis was determined via Hitachi system (Roche Diagnostics, Mannheim, Germany).

All patients underwent coronary angiography using the Judkins technique on digital coronary angiography equipment. In this study, we defined a significant CAD as at least one 70% or greater diameter narrowing observed in multiple right anterior oblique and left anterior oblique views in at least one coronary vessel [21]. The extent of CAD was defined as 1-, 2-, or 3-vessel disease.

Periodontal examination was conducted before angiography by a trained and calibrated periodontist using a mouth mirror and a William's periodontal probe with 1 mm graduation and a diameter of 0.4 mm. Number of lost teeth was determined. The periodontal examinations included measurement of probing pocket depth (PPD), and clinical attachment level (CAL), at six sites around all standing teeth as well as plaque index (PI) of the Ramford teeth. PI was graded as scores from 0 to 3 based on the Silness-Löe plaque index scoring system. Bleeding index was also determined at the facial and mesiofacial sites of the teeth in two randomly selected quadrants, one maxillary and one mandibular, using NIDCR (National Institute of Dental and Craniofacial Research) criteria. Classification of periodontitis was made according to a consensus report in 1999 by Lindhe et al.

Results were reported as mean ± standard deviation (SD) for the quantitative variables and percentages for the categorical variables. The groups were compared using the Student's *t*-test or one-way ANOVA test for the continuous variables and the chi-square test (or Fisher's exact test if required) for the categorical variables. Predictors exhibiting a statistically significant relation

to CAD extension in either CAD or non-CAD groups in univariate analyses (with a p-value > 0.1) were taken for a backward Stepwise Wald logistic regression analysis to investigate their independence as predictors. P values of 0.05 or less were considered statistically significant. All the statistical analyses were performed using SPSS version 19.0 (SPSS Inc., Chicago, IL, USA) and SAS version 9.1 for Windows (SAS Institute Inc., Cary, NC, USA).

RESULTS

The patients with multi-vessel disease were more likely to have diabetes mellitus; however, subjects with normal coronary and those with different severity of CAD were similar with respect to demographics, socioeconomic level, and most cardiovascular risk factors (Table 1). Also, no statistically significant difference in complete edentulous status was observed between the participants with and without CAD.

Periodontal disease severity was significantly associated with demo-topographic factors. In comparison to individuals with a mild periodontal disease, individuals with more severe disease were significantly more likely to be female and had lower body mass index (Table 2). The former group was also more likely to use daily tooth brushing. But, the groups with the different severity of periodontal disease were similar in terms of socioeconomic level as well as CAD risk factors.

Individuals with CAD showed significantly higher mean CAL compared to non-CAD group (Table 3). This association also remained significant after adjustment for potential cofounders including gender, smoking, diabetes, physical inactivity, and diastolic hypertension (OR = 1.6,

95% CI = 1.1 – 2.9, P = 0.029). However other parameters including PPD, BOP, and PI were similar between CAD and non-CAD groups.

TABLE 1: Socio-demographic characteristics and coronary disease risk factors of the study population (n = 183)

Characteristics	Without CAD	With CAD			P value
		One-vessel	Two-vessel	Three-vessel	
	(n=45)	(n=21)	(n=48)	(n=69)	
Male gender	21 (46.7)	10 (47.6)	33 (68.8)	45 (65.2)	0.070
Age (yr)	54.5 ± 1.0	57.0 ± 9.0	57.0 ± 8.1	56.9 ± 7.3	0.425
Body mass index (kg/m^2)	32.4 ± 1.1	33.1 ± 8.1	30.6 ± 9.1	30.0 ± 8.8	0.395
Socio-economic level:					0.320
UPLE*	26 (57.8)	16 (76.2)	24 (50.0)	39 (56.5)	
EPLE†	9 (20.0)	3 (14.3)	12 (25.0)	22 (31.9)	
UHLE‡	5 (11.1)	0 (0.0)	7 (14.6)	4 (5.8)	
EULE§	5 (11.1)	2 (9.5)	5 (10.4)	4 (5.8)	
Physical activity	8 (17.8)	3 (14.3)	15 (31.3)	9 (13.0)	0.086
Current cigarette smoking	13 (28.9)	5 (23.8)	18 (37.5)	17 (24.6)	0.458
Family history of CAD	23 (51.1)	6 (28.6)	20 (41.7)	35 (50.7)	0.259
Hyperlipidemia	24 (53.3)	14 (66.7)	22 (45.8)	36 (52.2)	0.464
Hypertension	20 (44.4)	9 (42.9)	20 (41.7)	28 (40.6)	0.981
Diabetes mellitus	12 (26.7)	8 (38.1)	16 (33.3)	35 (50.7)	0.050
Mean systolic BP‖ (mmHg)	12.6 ± 1.4	12.9 ± 9.0	12.7 ± 1.7	12.6 ± 1.5	0.756
Mean diastolic BP (mmHg)	7.9 ± 7.8	8.0 ± 6.7	8.2 ± 1.0	7.7 ± 8.4	0.079
Mean FBS¶ (mg/l)	78.8 ± 7.8	116.6 ± 28.2	122.2 ± 55.1	137.2 ± 53.2	0.287
Complete edentulous	12 (26.7)	7 (33.3)	19 (39.6)	23 (33.3)	0.627

TABLE 2: Socio-demographic characteristics and coronary disease risk factors regarding periodontal disease severity (n = 122)

Variable	Severity of periodontal disease			P value
	Mild (n=22)	Moderate (n=80)	Severe (n=20)	
Male gender	10 (45.5)	37 (46.3)	1 (5.5)	0.003
Age (yr)	50.9 ± 8.4	54.0 ± 8.4	56.0 ± 8.50	0.122
Body mass index (kg/m^2)	30.2 ± 8.2	33.7 ± 9.5	28.8 ± 7.4	0.050
Socio-economic level:				0.260
UPLE*	8 (36.4)	46 (57.5)	7 (35.0)	
EPLE†	6 (27.3)	19 (23.8)	9 (45.0)	
UHLE‡	4 (18.2)	8 (10.0)	2 (10.0)	
EHLE§	4 (18.2)	7 (8.8)	2 (10.0)	
Physical activity	7 (31.8)	15 (18.8)	5 (25.0)	0.423
Current cigarette smoking	4 (18.2)	23 (28.8)	10 (50.0)	0.079
Family history of CAD	11 (50.0)	46 (57.5)	10 (50.0)	0.730
Hyperlipidemia	8 (36.4)	46 (57.5)	9 (45.0)	0.171
Hypertension	5 (22.7)	44 (55.0)	14 (70.0)	0.114
Diabetes mellitus	8 (36.4)	32 (40.0)	10 (50.0)	0.638
Mean systolic BP‖ (mmHg)	12.0 ± 1.3	12.7 ± 1.6	12.9 ± 1.4	0.154
Mean diastolic BP (mmHg)	7.8 ± 5.9	7.8 ± 5.9	7.8 ± 8.5	0.950
Mean FBS¶ (mg/l)	120.3 ± 28.1	128.2 ± 60.5	138.2 ± 50.0	0.715
Number of daily tooth brushing				0.011
None	0 (0.0)	7 (8.8)	7 (35.0)	
Rarely	6 (27.3)	20 (25.0)	5 (25.0)	
Once a day	8 (36.4)	35 (43.8)	6 (30.0)	
Twice a day	8 (36.4)	18 (22.5)	2 (10.0)	
Use of dental floss	5 (22.7)	7 (8.8)	0 (0.0)	0.041

TABLE 3: Clinical periodontal parameters in the patients with and without CAD

Variable	With CAD (n=138)	Without CAD (n=45)	P-value
CAL	4.1 ± 1.2	3.5 ± 1.1	0.018
PPD	2.8 ± 0.7	2.5 ± 0.6	0.094
BOP	57.6 ± 27.5	58.0 ± 28.0	0.280
PI	2.2 ± 0.6	2.1 ± 0.7	0.379
Lost teeth	10.9 ± 5.9	8.8 ± 6.0	0.660

Generalized periodontal disease was more frequent in those with more severe CAD status (Table 4). Also a positive relation was revealed between the severity of periodontal disease and CAD severity (Table 5) so that the severe periodontal disease was found in 33.3% of non-CAD group, in 38.1% of the group with single-vessel disease, and in 49.6% of those with multi-vessel CAD. As a result, individuals with more extent periodontal disease exhibited significantly elevated odds of having CAD (OR = 2.7, 95% CI= 1.4 – 5.1).

Backward Stepwise Wald Logistic Regression (Table 5) showed that the CAD severity could be predicted by male gender status (OR = 3.1, P = 0.013) as well as history of diabetes mellitus (OR = 2.3, P = 0.030) in total study population but not with edentulous status. With repeating this analytic modeling in study population excluding edentulous cases (Table 6), CAD severity was positively associated with the CAL measure (OR = 1.6, P = 0.038).

TABLE 4: Relationship between severity of CAD and severity of periodontal disease

Variable	Without CAD	With CAD			P value
		One-vessel	Two-vessel	Three-vessel	
	(n=45)	(n=21)	(n=48)	(n=69)	
Extension of PD:					
Localized	24 (53.3)	10 (47.6)	14 (29.2)	19 (27.5)	0.002
Generalized	21 (46.7)	11 (52.4)	34 (70.8)	50 (72.5)	
Severity of POD					0.030
Mild	9 (20.0)	3 (14.3)	4 (8.3)	6 (8.7)	
Moderate	21 (46.7)	10 (47.6)	19 (39.6)	30 (43.5)	
Severe	15 (33.3)	8 (38.1)	25 (52.1)	33 (47.8)	

TABLE 5: Backward Stepwise Wald Logistic Regression model for determining predictors of CAD in total study population

Variable	Beta	SE	Wald index	P-value	Odds Ratio
Male gender	1.155	0.465	6.182	0.013	3.1
Diabetes	0.852	0.393	4.714	0.030	2.3
Edentulous status	0.486	0.393	1.530	0.210	1.6

TABLE 6: Backward Stepwise Wald Logistic Regression model for determining predictors of CAD in study population excluding edentulous cases

Variable	Beta	SE	Wald index	P-value	Odds Ratio
CAL	0.503	0.242	4.324	0.038	1.6
Male gender	1.172	0.624	3.530	0.060	3.2
Diabetes	0.796	0.409	3.791	0.052	2.2

DISCUSSION

In this prospective study, 183 patients who received coronary angiography were assessed for periodontal disease and its extension and severity. After adjustment for potential confounders, CAL remained a statistically significant factor associated with CAD severity. This study is consistent with some previous studies [7-9, 12, 13], but is contrary to some others [14, 15, 22-24]. One of the possible explanations for the contradiction is that some of the studies were not adequately adjusted for potential confounding factors such as smoking, which is considered one of the major contributing factors for developing CAD. In our study, individuals with more extent periodontal disease exhibited significantly elevated odds of having CAD to the ratio of 2.7. In a Meta-analysis, Humphery LL et al., found that periodontal disease measured through probing depth, gingivitis, bone and tooth loss, is a risk factors for CAD that is independent from traditional well known CAD risk factors. They reported that periodontal disease deliberates approximately a 24–35% increase in risk of CAD [7]. Some other reports suggested this summary relative risks in the range of 1.15 to 1.19 [25, 26].

Another Meta-analysis of five prospective cohort studies indicated a 1.14 times higher risk of developing CAD among individuals with periodontal disease compared to the controls [27]. Therefore, similar to the previous studies, our findings provide consistent evidence required to support the hypothesis of the relationship between periodontal disease and CAD. Many causal pathways might involve direct and indirect effects of the periodontal disease on CAD and its severity, while genetic and other host factors that increase the susceptibility to both atherosclerosis/thrombosis and chronic periodontitis would be considered as underlying partially shared pathogenic pathways [28].

Some evidences indicated that the chronic inflammatory burden of periodontal infection and the host response might provide the basis for the observed associations between periodontal disease and coronary atherosclerosis [29]. This assumption is supported by many studies which show elevated levels of fibrinogen, C-reactive protein (CRP), serum amyloid A, Leukotriene B_4, Interleukin $1_ß$, Interleukin 6, and some other factors in gingival crevicular fluid and /or plasma in association with periodontal disease [30-34]. In addition, periodontal treatment studies have shown improvements in measures of systemic inflammation such as CRP and serum IL-6 and TNF-alpha with treatment [35-37]. Piconi et al., performed a longitudinal interventional study on individuals with mild to moderate periodontitis and showed that periodontal treatment has beneficial effects upon intima-media thickness and also reduces oral bacterial load predominantly *porphiromonas gitngivalis*, serum levels of Hs-CRP, fibrinogen, WBCs, and neutrophils as well as CD_4^+ (activated) T lymphocytes[38]. Also, it has been shown that outer membrane vesicles of *p. gingivalis* that are shed into the periodontal pocket area cause cell impairment in vitro and are potent inducers of platelet activation in vivo. This extra-cellular secretion system may contribute to plaque instability and thromboembolic events [39]. Moreover, studies conducted on animal models have indicated an association between atheroma formation and exposure to periodontal pathogens [40]. Furthermore, presence of DNA from periodontitis-associated bacteria in the human atheromatous plaques obtained either by carotid endarterectomy or from coronary arteries has been confirmed. [41,42]. These findings provide some evidences for a causal role of periodontal disease in the pathogenesis of CAD via both direct and indirect pathways.

In the present study, number of teeth and edentulous status could not predict CAD existence or its severity. In a study by Bahekar et al, an inverse relationship between the number of teeth and

the risk of CAD existed. Some cohort studies also showed 1.24 times increased risk of developing CAD in patients with less than 10 remaining teeth [22, 43- 45]. In a recent study by Ashraf et al, an association was reported between poor oral health, including number of missing teeth, and CVD [46]. It seems that the discrepancy between our study and others might be related to the definition of edentulous status. Studies reporting significant relation between edentulism and CAD defined this status as number of teeth less than 10. However, this discrepancy might be also due to the small sample size which results in the lack of statistical power.

Although we showed an association between periodontal disease and CAD severity, no reference can be made about the cause and effect nature of our results. Since the co-existence of these two chronic diseases may be the simplest explanation although many common risk factors have been identified for PD and CAD.

In conclusion, this study strengthens the suggested relationship between CAD and periodontal disease, more specifically an increased odds ratio in those with periodontal disease for having angiographically defined CAD.

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