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Association between periodontal disease and coronary artery disease

Research article

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Abstract: The etiology of coronary artery disease (CAD) is multifunctional. There is increasing evidence that dental infections could play a role in the initiation and development of CAD. In a case control double blind study, one hundred male and female (mean age 51 ± 9.4) angiographically documented CAD, compared with one hundred male and female patients (mean age 50.6 ± 9) with angiographically negative coronary artery. All the patients (cases and control) underwent dental examination for the presence and severity of periodontitis by a dentist who was oblivious the result of the angiography performed. The association between periodontal disease status and CAD was significant (P=0.011); periodontitis was apparently more frequent in CAD positive patients than in control (86% versus 61%}. Adjustment of coronary risk factors (smoking, DM, hypertension and hyperlipidemia) in both cases and control groups suggests that the association between periodontitis and CAD in our study was independent of coronary risk factors. There is increasing evidence that dental infection, especially aerobic organisms which have capability of aggregation of platelets, is the most important cause. Dental infection would be an independent risk factor for CAD.

Keywords: *Coronary artery disease • Periodontal disease • Risk factors*

1. Introduction

Despite substantial progress in the primary and secondary prevention of cardiovascular disease, coronary artery disease (CAD) is the major cause of morbidity and mortality worldwide [1]. It has been projected that by 2020, cardiovascular diseases will be the leading causes of death and disability worldwide. The etiology of CAD is multifactorial. A substantial proportion of patients with CAD do not present with traditional risk factors, however, recent evidence suggests a role for infectious agents in the pathogenesis of CAD [2,3]. Moreover, there is increasing evidence that dental infections, particularly chronic periodontal diseases, could play a role in the initiation and development of CAD [4,5]. The reason for this is unclear, but one explanation could be that the association between periodontitis and CAD may be due to chronicity of periodontitis and the presence of periodontal anaerobic microorganisms such as *Streptococcus sanguis* and *Porphyromonas gingivalis*. These microorganisms have been associated with dental calculi formation and also have been reported to have the capability to increase the aggregation of platelets, a factor which contributes to the development of atherosclerosis [6]. In addition, the process of calcification, which is a basic process in the formation of dental calculus, is also detected in the atheromatous plaque of coronary arteries of CAD patients [7,8].

Most of the published reports have evaluated CAD primarily based on the observations consistent with acute events. Methods for identifying CAD include hospital records of acute events, self-reported histories of CAD, and CAD-related deaths [9,10]. Consistent with this, several investigations utilized angiographic data to identify CAD-positive individuals, combining this data with the data from other individuals in which acute events defined their CAD status [11,12]. In addition, suspected MI often entered into patients' records or was cited by patients at the time of hospitalization and on being treated for chest pain.

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One case-control investigation compared the prevalence of periodontal disease between subjects with CAD having a history of an acute event and those subjects with CAD having no clinical history of acute events, that is, patients with chronic CAD. As a consequence, they found an association between acute myocardial infarction and probing depth ≥4 mm, but only 10 of the 60 AMI patients were women. Unfortunately, chronic CAD was not defined in this report [13-16].

Continuing with the series of studies, a Swedish study [17] indicated that women with CAD have worse oral health than those in a comparable group with no history of CAD. Concomitantly, several studies have found a significant relationship between tooth loss and even self-reported periodontal disease and CAD [8,18,19]. However, in our study, patients with dentures were excluded from the study, and both males and females were equally enrolled in the study.

Regarding the importance of this subject and lack of sufficient research on the aforementioned relation in Asia, our study aimed at investigating the association between angiographically defined CAD and periodontal disease for the first time in Iran. The potential for novel therapeutic management of cardiovascular disease and stroke would be even greater if periodontal diseases are proven to cause or accelerate atherosclerosis.

2. Material and Methods

2.1. Patients' characteristics

A case-control, double blind study was conducted on 200 subjects.

One hundred male and female patients, with a mean age of (51±9.4) and with angiographically documented coronary artery disease, participated in the study. Positive angiography was defined as the presence of greater than 50% coronary diameter reduction, as described by an experienced cardiologist. The indication for doing coronary angiography was according to the patients' physician's decision.

One hundred male and female patients, with a mean age of (50.6±9) and with normal coronary angiography, were entered in the study. The indication for doing coronary angiography was according to the patients' physician's decision. Negative angiography was defined as totally normal angiographically documented coronary arteries, as described by an experienced cardiologist.

The cases and controls underwent coronary angiography at the cardiac catheterization laboratory of Nemazee Hospital. Informed written consent was obtained from each patient.

Exclusion criteria were as follows: age less than 25 years, age more than 65 years, complete dentures, and the presence of factors requiring antibiotic prophylaxis prior to a dental examination.

All the patients underwent dental examination for the presence and severity of periodontitis by a dentist, who was oblivious of the results of the angiography performed. Additionally, knowledge regarding the medical history and cardiovascular risk factors for each patientwas gained through a questionnaire. Fortunately, all the patients agreed and signed the form to take part in this study. Most of the subjects presented the results of BS, TG and HDL.

The cardiovascular risk factors are defined as:

- Diabetes mellitus: History of Diabetes mellitus, or FBS≥126 mg/dl
- Hypertension: History of hypertension, BP≥140/90 mmHg or subjects taking antihypertensive drugs
- Smoking habits: Both current and former smokers were considered to be smokers
- The family history of CAD: Positive history of CHD in male first degree relative <55 years, and female first-degree relative <65 years. The first degree relatives considered were father, mother, brother, and sister
- Hyperlipidemia: A history of hyperlipidemia or: 1) TG≥150 mg/dl 2) Total cholesterol≥ 220 mg/dl 3) LDL≥100 mg/dl.

Furthermore, the patients and the control group underwent another dental examination, for the presence and severity of periodontitis. The examining dentist was kept ignorant about the CAD classification and the medical history of the subjects. Periodontal disease severity was measured through bleeding on probing, probing depth, clinical attachment level (CAL), gingival recession, number of missing teeth, and radiographic bone loss. Pocket depth was measured from gingival margin to base of pocket, with the gingival pockets ≥3 mm being considered pathogenic. Loss of attachment was measured from cement enamel junction to the base of pocket. A total probing depth score (*i.e.*, the sum of the depth of pockets for each participant) was calculated to obtain a respective value of the overall inflammation. The severity of periodontitis was measured by Russell's index as follows:

1)0-0.2 – normal tissue
2)0.3-0.9 - simple gingivitis
3)0.7-1.9 -initiation of periodontitis
4)1.6-5- established destructive periodontitis
5)3.8-8- terminal stage of disease

The clinical measurements described above were also combined with the marginal and vertical bone height evaluated from the panoramic radiograph to assess the

Table 1. Demographic characteristics and conventional risk factors in cases and controls

Characteristic		CAD positive	CAD negative	P-value
Age (Mean±SD)		51.0±9.4	50.6±9	0.719
HDL cholesterol concentration (mg/dl)		39.9±9.4	43.4±8.4	0.235
LDL cholesterol concentration (mg/dl)		120.7±18.695	104.0±23.6	0.155
Triglyceride concentration (mg/dl)		147.9±19.7	127.9±22.8	0.003*
Systolic BP		139.8±10.5	136.7±11.4	0.005*
Diastolic BP		79.9±7.9	77.2±6.8	0.010*
Fasting Blood Sugar		119.1±18.2	93.2±16.4	0.045*
	smoker		17	12
	Non-smoker		83	88
	Positive		21	18
	Negative		79	82
	Male		58	50
	Female		42	50

P>0.05 or statistically non-significant

Table 2. Association between periodontal disease status and coronary artery disease status in case and control groups.

Periodontal disease status	CAD positive	CAD negative
Mild	11	15
Moderate	35	28
Severe	40	18
X^2=21.53	DF=3	P-value=0.000

extent of the periodontal disease. Gingival inflammation was noted as bleeding on probing and expressed as the proportion of bleeding sites against the total number of sites in the dentition. The periodontal disease status (severity) was graded as mild, moderate and severe periodontitis.

The severity of periodontitis was graded as:

- No periodontitis: Gingival pocket ≤3 mm deep or none
- Mild periodontitis: Gingival pocket 4-5 mm deep
- Moderate periodontitis: Gingival pocket ≥6 mm deep
- Severe periodontitis: Macroscopically puss in gingival pocket.

2.2. Statistical Analysis

Statistical analysis was done by Chi-square test, T-Test, Exact Fisher Test, and descriptive statistics. The level of significance was set at <0.05 and the confidence interval at 95%.

3. Results

A total of 200 subjects (100 CAD positive and 100 CAD negative) were included in this study.

Table 1 shows the demographic characteristics and values of conventional risk factors of the study groups.

The mean age in both case and control groups was not statistically significant (51±9.4 years versus 50.6±9 years: p=0.719). 57% of CAD positive subjects were male and 43% were female. In the CAD negative group, 50% were male and 50% were female (p=0.395). Moreover, the mean value of HDL cholesterol and LDL cholesterol in both groups was the same (p=0.235 and p=0.155), but the mean value of triglyceride concentration was statistically significant (p=0.003). In addition, the mean value of systolic blood pressure (SBP) in case and control groups was 139.8 versus 136.7 (p=0.005), whereas the mean value for diastolic blood pressure (DBP) in case and control groups was 79.9 versus 77.2 (p=0.010). Concomitantly, the mean value of blood sugar in case and control groups was 119.1 versus 93.2 (p=0.045). Smoking habits in case and control group were not significantly different (17% versus 12% respectively, p=0.089). The frequency of family history of CAD between patients and controls was not significant (p=0.721).

In this study, the association between periodontal disease status and CAD status was statistically significant (p=0.001, Table 2). Periodontitis was apparently more frequent in CAD positive patients than in control (86% versus 61%). In case and control groups, the frequencies of both moderate periodontitis (35% versus 28% respectively) and severe periodontitis (40%

Table 3. Comparsion of the effect of smoking habit and diabetes mellitus on periodontal disease status in CAD positives.

Characteristic		Non	Periodontitis	P-value
Smoking	Positive	0	7	0.006
	Negative	14	79	
Diabetes Mellitus	Positive	0	32	0.268
	Negative	14	54	

Table 4. The odds ratio and 95% confidence interval for relationship between periodontitis status and CAD.

Periodontitis	Odds Ratio	P-value	95% interval	confidence
			Lower	Upper
Mild	2.04	0.157	0.76	5.49
Moderate	3.61	0.001	1.64	7.96
Severe	6.19	0.000	2.7	14.14

versus 18% respectively) were statistically significantly different. In CAD and control groups, the frequencies of the patients with no periodontitis were 14% and 39%, respectively.

As shown in Table 3, a correlation was found between smoking habits and periodontitis in the CAD positive group (p=0.006), but there was no significant relationship between diabetes mellitus and the CAD positive group (p=0.268).

Table 4 shows the odds ratio for the association between periodontal disease status and CAD. Periodontitis is a significant risk factor for CAD, and the more severe the periodontitis, the greater the risk for developing CAD. As shown in Table 4, mild periodontitis is 2.04 times more frequent in CAD group than control group (odds ratio= 2.04, p=0.157). The association of CAD and moderate periodontitis was statistically significant (odds ratio= 3.61, p=0.001). However, this correlation is more pronounced in the case of severe periodontitis (odds ratio=6.19, p=0.000).

Tables 5 and 6 depict the influence of adjustment of smoking habits with respect to the association of periodontitis and CAD in case and control groups. The sole intention of carrying out this adjustment was to minimize any confounding effect that smoking might have on the association of periodontitis and CAD (p<0.05), suggesting that the association between periodontitis and CAD in our study was independent of smoking status.

Likewise, a similar adjustment was performed to monitor the contribution of diabetes mellitus on the correlation of CAD and periodontitis, however, no statistically remarkable association between periodontitis and CAD was found (p=0.000).

Table 5. Adjustment of diabetes mellitus for association of CAD with periodontitis.

		Severity of periodontitis			P value
		Mild	Moderate	Severe	
Negative	CAD-	10	12	19	0.036
Diabetes	CAD+	8	24	22	
Positive	CAD-	5	6	8	0.048
Diabetes	CAD+	3	16	13	

Table 6. Adjustment of smoking status for association of CAD with periodontitis.

		Severity of periodontitis			P value
		Mild	Moderate	Severe	
Non-smoker	CAD-	13	18	22	0.01
	CAD+	9	35	29	
Smoker	CAD-	2	0	5	0.021
	CAD+	2	5	6	

4. Discussion

This is the first study highlighting the association between periodontal disease and CAD in Iran, and also the most significant among the few studies conducted throughout the world that has used angiographic finding to define both CAD positive and CAD negative groups. The current study found a relationship, when adjusted for common confounders such as smoking and diabetes mellitus, between periodontitis and CAD. In CAD patients and the control group, the frequency of moderate periodontitis (35% versus 28%), and the frequency of severe periodontitis (40% versus 18%) were significantly different. Our finding demonstrates that the relationship between angiographically significant CAD and periodontal disease is strong even after adjustment for risk factors common to both diseases, such as smoking and DM. The reason for this relationship is still unclear, but several possible explanations should be considered. Firstly, subjects with periodontal infections are reported to have an aberrant inflammatory response with increased levels of IL-1β, TNF-α and other proinflammatory cytokines. Proinflammatory cytokines could accelerate the development of the atherosclerotic process in the vessel walls, and this may be a possible reason for an association [20,21]. Secondly, the chronicity of periodontitis and the presence of periodontal anaerobic microorganism such as Streptococcus sanguis and Porphyromonas gingivalis might be responsible in this case. These microorganisms have been associated with dental calculi formation and also have been reported to have the capability to increase the aggregation of

platelets, a factor which contributes to the development of atherosclerosis [6]. Another explanation is that subjects who take care of their dentition may also be concerned about other aspects of their health, including a lifestyle conducive to coronary heart disease.

The findings from the present study are consistent with several investigations that showed a significant association between periodontal disease and coronary heart disease, even after adjustment for common risk factors [7,9,12,22]. While several of these previous investigations utilized angiographic data as part of assessment of CAD, these studies also relied upon data such as patient histories and hospital records to establish CAD status. In addition, suspected myocardial infarction area often entered into patient records or was cited by patients, at the time of hospitalization and on being treated for chest pain, especially when many heart-attack like symptoms may be related to various non-cardiac related conditions. This methodology may result in a heterogeneous mixture of CAD patients at different stages in the pathogenesis of CAD. In our study, CAD positive patients represented a population of patients with angiographically significant, but stable CAD. In the present study, patients with >50% stenosis in one or more major epicardial arteries were considered positive for CAD. This definition defines the patient with hemodynamically significant stenosis [23].

The selection criteria in this study excluded patients with complete dentures, age <25 and age >65, and the presence of factors requiring antibiotic prophylaxis prior to a dental examination. Several studies found a significant relationship between tooth loss and CAD [8,18,19]. The relationship could be attributable to bacterial products and proinflammatory cytokines from the periodontal disease sites, which may have caused the loss of teeth. Another possible explanation could be the prevalence of these two diseases among similar behavioral and risk pattern such as level of education, smoking and socioeconomic status, which could further contribute to the explanation that why some studies revealed a significant relationship whereas others did not.

Presumably, the presence of teeth was essential to assess periodontal disease in the current study. It has been speculated that the relationship between CAD and periodontitis is age dependent. Consistent with this speculation, previous studies suggested that the relationship is more important in a younger rather than an older population [15,16,22]. Since the subjects in the present study had a mean age of approximately 51 years, it is possible that in younger individuals, periodontal disease has a more pronounced association with CAD. However, the present investigation did not examine the relationship between CAD status and need for antibiotic prophylaxis prior to dental care. In fact 15% of potential subjects were excluded from both CAD positive and CAD negative groups, due to this criterion. Our findings are consistent with previous reports on the lack of a relationship between CAD and mitral valve prolapse, which may be considered an indication for antibiotic prophylaxis [22,23]. It is unlikely that the exclusion of subjects based on the need for antibiotic prophylaxis would affect the outcome of this investigation.

Smoking is a risk factor for both periodontitis and CAD and since there have been some debates as to whether the association between oral disease, especially periodontitis, and CAD is due to smoking, this study minimized the effect of smoking as a joint risk factor. The prevalence of smoking among patients and controls in our study revealed to be 17% versus 12%, respectively, p=0.170, which was not statistically significant.

Since smoking is associated with both CHD and periodontitis and influences both, it is interesting to investigate the relationship between the two groups of non-smokers, since smoking does not play a role in these groups. Case–control designs in general have their shortcomings. One of them is that the results are applicable only to the specific case-controls and not to other populations. Another problem is the possibility of unknown differences between the groups which could influence the results. Therefore, it could be difficult to draw conclusions out of invariant comparisons. However, it should be noted that our study shows a relationship between CAD and periodontitis, even when adjusted for smoking, diabetes, and other risk factors. Moreover, the relationship between periodontal disease and CAD was prevalent even among non-smokers.

The possible mechanisms which relate periodontitis to CAD will be discussed below briefly.

Periodontal disease is a candidate infectious disease that can predispose to vascular disease given the abundance of gram-negative species involved, the local production of lipopolysaccharide with detectable levels of proinflammatory cytokines, the involvement of inflammatory cells, the association of periodontal disease with increased peripheral fibrinogen and leukocyte count, and the chronicity of disease. Streptococcus sanguis, a supragingival plaque organism, can increase platelet aggregation [6], and *P. gingivalis*, expressing the platelet-aggregation-associated protein (PAAP), may increase the risk of acute thrombosis. In a rabbit model, infusion of PAAP positive *S. sanguis* resulted in acute electrocardiographic changes indicative of ischemia that are not possibly apparent with the PAAP-negative strain [6]. Another probable explanation could be that

subjects who take care of their dentition may also be concerned about other aspects of their health, including a lifestyle conducive to coronary heart disease.

In conclusion, our study indicates that periodontitis is more common among patients with CAD positive than among controls, and after accounting for factors common to both periodontitis and CAD, such as smoking and DM, there was significant association between periodontitis and CAD as assessed angiographically. Moreover, the pathogenesis between periodontal disease and CAD is still unclear. Further investigations into the relationship between periodontal disease and CAD will be needed to clarify the pathogenesis between periodontitis and CAD.

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