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Periodontal and coronary heart disease in patients undergoing coronary angiography

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Abstract

Periodontal inflammation has been implicated in atherosclerosis and coronary heart disease (CHD). Coronary angiography (CA) is used in the assessment of CHD; only a few studies have evaluated periodontal disease (PD) and angiographic measures of coronary atherosclerosis. The aim of this study was to investigate the association between CHD and PD. In this prospective epidemiologic study, 466 patients underwent CA and were assessed for PD. All patients underwent physical, laboratory, cardiac, and dental examination including dental x-rays. Periodontal disease and coronary angiograms were evaluated blindly by a dentist and 2 cardiologists, respectively. A coronary stenosis greater than 50% was ruled as CHD. Periodontal disease was defined and measured with the Community Periodontal Index of Treatment Needs (CPITN); and if at least 2 sextants (segments dividing mandible and maxilla into 6) were recorded as having CPITN of at least 3 (signifying that sextant had periodontal pocket depth ≥3.5 mm), the patient was coded as having PD. Three-hundred forty-nine patients (74.9%) had CHD assessed by CA The CHD patients had PD in 55.6% vs 41.9% in the non-CHD patients ($P < .01$). The CPITN scores were significantly higher in patients with vs without CHD, 2.43 vs 2.16, respectively ($P = .023$). After adjusting for age, sex, and risk factors for atherosclerosis with additional inclusion of C-reactive protein and erythrocyte sedimentation rate, PD remained significantly related to CHD (odds ratio = 1.9; 95% confidence interval, 1.2-3.1). Other predictors for CHD were male sex, age, high-density lipoprotein cholesterol, and diabetes. Our results demonstrate an increased odds ratio for angiographically determined CHD in patients with PD and that CHD and PD may cluster in particular groups of a population. Our data indicate that PD represents a potentially modifiable risk factor that is both preventable and treatable with predictable treatments that pose negligible risk.

1. Introduction

Recent investigations suggest an association between periodontal disease (PD) and coronary heart disease (CHD) and other manifestations of atherosclerosis. Atherosclerosis, the main cause of CHD, is an inflammatory disease resulting from interactions of immune mechanisms with metabolic risk factors that initiate, propagate, and activate lesions in the arterial tree. Coronary heart disease is the main cause of death globally owing to a rapidly increasing prevalence in developing countries and Eastern Europe, and the increased incidence of obesity and diabetes in the Western industrial countries [1].

Periodontitis is a common tissue destructive inflammatory disease that generally begins to show clinical signs in early middle age. The inflammation and tissue destruction result in degradation of the attachment apparatus of the teeth, causing tooth loss and, in its most severe form, edentulousness. The more severe form of the disease is present in approximately 10% to 15% of adult population, whereas 35% exhibit moderate or mild signs of the disease.

Epidemiologic studies suggest that periodontal infections may increase the risk for CHD. Several studies have found an

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association between severe PD and increased risk for acute cardiovascular events such as myocardial infarction, stroke, and revascularization procedures after adjusting for traditional cardiovascular risk factors such as age, sex, smoking, obesity, and blood lipids and lipoproteins [2]. Periodontal disease has also been associated with increased carotid intima-media wall thickness as a measure of subclinical atherosclerosis [3–5]. Both PD and atherosclerosis share several risk factors, that is, smoking and diabetes; and patient lack of health awareness poses a particular challenge [6,7]. Another possible mechanism connecting periodontitis and CHD may be related to release of bacteria, bacterial products, or blood appearance of proinflammatory cytokines from the chronic periodontal lesion. This could lead to a systemic inflammatory response that resembles a risk factor profile that may increase the risk for cardiovascular disease (CVD) [8].

In this regard, periodontitis is associated with increased systemic concentrations of C-reactive protein (CRP), fibrinogen, and cytokines, all of which have been causally linked to atherosclerosis-induced disease. Standard nonsurgical periodontal treatment to reduce periodontal inflammation has been shown to decrease serum inflammatory markers and CRP. Data from in vitro and animal studies suggest that periodontal bacteria can both promote platelet aggregation and induce the formation of foam cells from macrophages and initiate fatty streaks in arterial tree [9]. More than half of all cells at the immediate site of plaque rupture are macrophages, constituting the dominant type of atherosclerotic inflammatory cell infiltrates [10].

Thus, inflammation has been implicated in the cause and pathogenesis of atherosclerosis; and periodontal inflammation may play a role in the initiation and progression of CHD. The inflammatory component of atherothrombosis is a topic of intense research. A recent medical trial reported by the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) study group documents that inflammatory biomarkers measured in peripheral blood serve as indicators for risk assessment in a healthy general population without hyperlipidemia. The administration of rosuvastatin reduced the risk of major cardiovascular events in patients with elevated high-sensitivity CRP levels [11].

Coronary angiography (CA) is widely used for assessment of CHD; however, only a few studies have evaluated PD and angiographic measures of coronary atherosclerosis [8,12]. Therefore, the purpose of this study was to investigate the association between positive findings of angiography and signs of PD in a group of 466 patients.

2. Methods

2.1. Patients

Four-hundred sixty-six patients (332 men, 134 women) were admitted for CA to our institution or the General Hospital in Wels on recommendation of their physicians.

Table 1
Characteristics of study population

Variables	CHD (n = 349/75%)	no CHD (n = 117/25%)	*P* value CHD/non-CHD
Men (n/%)	272/78	60/51	
Women (n/%)	77/22	57/49	
Current smokers	73/21	20/17	
Age (y)	65 ± 11	63 ± 11	NS
BMI (kg m^{-2})	28 ± 4	28 ± 5	NS
Hypertension (n/%)	276/79	77/66	.007
Type 2 diabetes mellitus (%)	94/27	15/13	.003
CPITN	2.43 ± 1.12	2.15 ± 1.05	.023
No. of teeth	15 ± 10	15 ± 10	NS
Cholesterol (mg dL^{-1})	183 ± 43	196 ± 42	.027
HDL-C (mg dL^{-1})	49 ± 12	56 ± 16	<.001
LDL-C (mg dL^{-1})	111 ± 35	115 ± 38	.32
Non–HDL-C (mg dL^{-1})	134 ± 40	140 ± 38	.01
TRIG (mg dL^{-1})	159 ± 86	142 ± 87	NS
HbA_{1c} (%)	6.86 ± 0.87	7.2 ± 1.44	NS
eGFR (mL min^{-1} 1.73 m^{-2})	76 ± 22	74 ± 18	NS
Leukocytes ($G{\cdot}L^{-1}$)($10^9{\cdot}L^{-1}$)	7.8 ± 4.7	7.2 ± 2.3	NS
Monocytes ($G{\cdot}L^{-1}$)($10^9{\cdot}L^{-1}$)	0.45 ± 0.43	0.42 ± 0.17	NS
ESR 1 h (mm)	18 ± 19	12 ± 12	<.001
CRP (mg dL^{-1})	0.80 ± 1.23	0.81 ± 0.91	NS

Values are means ± SD. BMI indicates body mass index; eGFR, estimated glomerular filtration rate (Modification of Diet in Renal Disease equation); HbA_{1c}, glycosylated hemoglobin.

The average age of our patients was 66 ± 11 years, with an average body mass index of 27.6 ± 4.5. Hypertension in patients was classified according to the Joint National Committee VII criteria or if patients were already on antihypertensive medications [13]. Diabetic patients were classified and treated according to the guidelines of the American Diabetes Association [14]. Disease diagnoses of patients are depicted in Table 1, and a list of prescribed medications is shown in Table 2.

2.2. Coronary angiography

All patients underwent CA using the Judkins technique on digitized CA equipment (Cathcor, Siemens, Germany)

Table 2
Prescribed medications in patients with and without CHD (N = 466)

	CHD (n = 349/75%)	no CHD (n = 117/25%)
β-Blocker	289/83	88/75
ACE Inhibitor	207/59	59/50
AT II RA	67/19	19/16
Statins	280/80	60/51
Diuretics	164/47	60/51
Amiodarone	17/5	6/5
Aspirin	331/95	112/96

ACE indicates angiotensin-converting enzyme; AT II RA, angiotensin II receptor antagonist.

[15]. All coronary angiograms were visually assessed by at least 2 experienced angiographers (caseload >5000 angiograms each). In this study, we defined *significant CHD* as at least one 50% or greater diameter stenosis in at least one coronary vessel or prior percutaneous or surgical coronary revascularization. The extent of CHD was defined as (1) 1-, 2-, or 3-vessel disease and (2) addition of a modified stenosis score system (minimum score was 0; maximum score was 27) with 0, 1, 2, and 3 points, respectively, for less than 50%, 50% to 70%, 71% to 89%, at least 90% diameter stenosis in 1 to 3 segments of the 3 main coronary arteries (a total of 9 segments) [16].

2.3. Oral examination and interview

The study was approved by the local ethics committee, and signed written consent was obtained from all patients before data collection. Clinical dental examinations were performed by a dentist after panoramic radiography using the World Health Organization format [17]. Periapical lesions, which signify advanced dental caries or periodontal abscess, were categorized into 3 levels: 0, 1, and 2 or more.

Pericoronitis was assessed by clinical examination and radiographic evaluation according to Armitage [18]. Remaining root remnants were categorized in 3 levels: 0, 1, and 2 or more. Periodontal disease was categorized and measured by using the Community Periodontal Index of Treatment Needs (CPITN) [19]. The oral cavity was divided into sextants; for each sextant, the highest index found was recorded. If at least 2 sextants (segments dividing mandible and maxilla into 6) were recorded as having CPITN of at least 3 (sextant had depth ≥3.5 mm), the patient was coded as having PD. In addition, the number of missing teeth and the number of toothless sextants were recorded.

After oral examination, a short interview was conducted with the patients to ascertain information about their daily toothbrushing habits, their use of dental floss, and the rate of consulting a dentist per year.

2.4. Biochemical analysis

Venous blood samples of 5.0 mL were collected from each patient in the fasting state in the morning from a nonoccluded antecubital vein. Standard measurements of cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglyceride (TRIG), fasting glucose, glycosylated hemoglobin, creatinine, and standard blood analysis were determined via Hitachi 717 system (Roche Diagnostics, Mannheim, Germany). The erythrocyte sedimentation rate (ESR) was measured by the Westergren method in glass capillary tubes, and leukocyte count was measured by an automated hematology analyzer (Sysmex SF-3000; SYSMEX Austria, Vienna, Austria). A high-sensitivity immunoturbidometry assay was used to measure CRP with a Hitachi 717 analyzer.

2.5. Statistical analysis

Data are presented as mean and standard deviation. Dichotomous variables are described as counts and percentages. Student t test (for parametric variables) or Mann-Whitney U test (for nonparametric variables) was conducted. Multivariable logistic regression was used to adjust for age, sex, and traditional risk factors for CHD including LDL-C, HDL-C, diabetes, hypertension, and TRIG with addition of CRP and ESR. A P value < .05 was considered statistically significant. All analyses were performed using Statistica version 6.0 (StatSoft,Tulsa, OK).

A limitation of this study was a partial assessment of smoking habits only at the time of admission. Descriptive data for smokers for each group are depicted in Table 1.

3. Results

3.1. Coronary heart disease

Three-hundred forty-nine patients (74.9%) had CHD confirmed by CA. The CHD patients had PD in 56% compared with 42% in the non-CHD patients ($P < .01$) (Fig. 1). After adjusting for age, sex, and traditional risk factors for coronary atherosclerosis, CRP, and ESR, PD remained statistically significantly associated with CHD (odds ratio = 1.9; 95% confidence interval [CI], 1.2-3.1). Other well-documented independent risk factors for CHD, HDL-C and diabetes, were significantly different in our group of patients (Table 1).

3.2. Stenosis score

The extent of CHD expressed as the degree of stenosis score system showed no relationship with the CPITN score ($P > .78$). However, in patients with normal coronary arteries and a stenosis score of 0, CPITN scores (CPITN 2.15 ± 1.05) were significantly lower compared with those in CHD patients who had a mean stenosis score of 6.52 ± 3.71 (CPITN 2.43 ± 1.12), $P < .02$ (Fig. 2).

There was a weak ($r = 0.13$) but significant ($P < .01$) association between the stenosis score and the ESR, but no

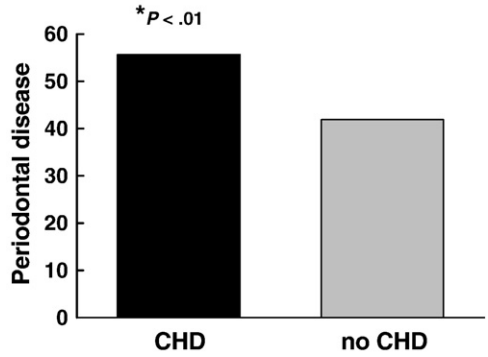

Fig. 1. Association between PD and CHD, depicting increased presence of CHD in patients with PD.

association with renal function assessed by the Modification of Diet in Renal Disease equation($P > .45$). Furthermore, differences in CRP between patients with and without CHD were not significant ($P > .86$).

Patients with CHD who had diabetes (27%) demonstrated a stenosis score of 6.80 ± 3.87 compared with a score of 6.42 ± 3.65 in patients with CHD and no diabetes. This difference was not statistically significant ($P = .39$). The patients with diabetes and periodontitis had a stenosis score of 7.10 ± 4.03 and patients without diabetes had a score of 6.24 ± 3.47, again not a statistically significant difference ($P = .15$).

3.3. Community Periodontal Index of Treatment Needs

Community Periodontal Index of Treatment Needs scores of at least 3 were observed in 38% of patients with CHD and in 27% of patients without CHD ($P = .041$). It is notable that CPITN scores of 4 were more frequently found in patients with CHD (17%) compared with those without CHD (9%) ($P < .001$). In diabetic patients, CPITN scores were significantly higher (2.58 ± 1.18) than in those without diabetes (2.31 ± 1.08) ($P = .041$)

3.4. Tooth loss and edentulousness

Tooth loss and, in its most severe form, edentulousness were not different in patients with and without CHD, 15.1% vs 14.8% ($P > .8$). Seventy-seven percent of edentulousness patients had angiographically determined CHD. There was no difference in CHD in patients with 1 to 10 teeth in comparison with those with greater than 10 teeth (77% and 76% with CHD). However, edentulousness was more often found in diabetics than in nondiabetics, 23% and 12% ($P = .015$).

3.5. History of dental care

Interviewing the patients after their dental examination revealed no difference in rate of daily toothbrushing (1.7 times a day in CHD and non-CHD patients), use of dental floss (10% of patients in each group), and annual rate of consulting a dentist (0.8 times a year in CHD and 0.9 times a year in non-CHD patients).

The number of patients with periodontitis and CHD was similar in each group when comparing the rates of toothbrushing regardless of how often they brushed their teeth. The stenosis score was higher in patients with reduced rates of toothbrushing (≤1 time a day, 6.73 ± 3.75; 2 times a day, 6.53 ± 3.54; >2 times a day, 5.91 ± 4.34).

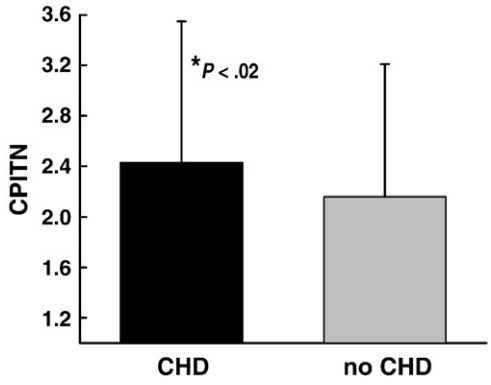

Fig. 2. Association between CPITN score and CHD. After adjusting for age, sex, and traditional risk factors for coronary atherosclerosis with additional inclusion of CRP and ESR, patients with PD remained at higher risk for CHD ($P < .02$) compared with patients without CHD.

3.6. Diabetes and inflammatory markers

Twenty-seven percent of the patients with CHD were diabetics vs 13% of those without CHD ($P = .003$). After adjusting for traditional coronary risk factors, age, sex, ESR, and CRP, multivariate logistic regression revealed a statistically significant association between CHD and PD. There was no statistically significant association between these 2 inflammatory markers and the CPITN score.

4. Discussion

In our prospective epidemiologic study, 466 patients who had undergone CA were assessed for PD. After adjustment for age, sex, and traditional risk factors for CHD, PD remained a statistically significant factor associated with CHD. We found a statistically significant relationship between the mean CPITN score and CHD. No obvious dose-response relationships were observed between the severity of CHD and periodontitis. In a recently published meta-analysis, the prevalence and incidence of CHD are significantly increased in periodontitis, indicating that periodontitis may be a risk factor for CHD [12].

The contribution of PD to the pathogenesis of CHD is not well understood. However, systemic inflammation and its effect on endothelial function may be implicated [20]. Evidence of this biological mechanism is derived from a study showing that people with higher levels of bacteria in their mouths also tended to have thicker carotid arteries, an indicator of CVD [4]. Others have shown that the systemic antibody response to periodontal bacteria was associated with CHD [21]. It is of interest to note that, in our study, the clinical signs of PD were not associated with severity of CHD. It may be that the quantity and quality of the immune response against oral bacteria provide a better measure of the association between PD and CHD. Other scientific evidence suggests that periodontal microorganisms are found in the plaque buildup in the arteries [22,23]. Janket et al [24] have shown that the more accurate the dental health score is, the stronger is its associations with CHD and stroke. They used a recently developed Asymptotic Dental Score that uses dental factors expected to generate inflammatory mediators, that is, dental caries,

dentate status, and root remnants. Spahr et al support the proposition of biological markers in contrast to clinical signs [8]. Their study showed that microbiological parameters, such as total periodontal pathogen burden, are of greater importance as a potential risk factor for CHD than the clinical parameter of the CPITN. However, because several types of pathogens may contribute to CHD, it is unlikely that a single microbe causes atherosclerosis. Instead, the total burden of infection at various sites may affect the progression of atherosclerosis and elicit clinical manifestations [25].

Patients with PD share many of the same risk factors as patients with CVD [6]. In severe periodontitis, gingival infection and inflammation destroy the attachment apparatus, leading to alveolar bone and tooth loss. Epidemiologic research provides evidence that severe periodontitis is a risk factor for CVD. In 2003, Scannapieco et al [26] conducted a systematic review of the evidence and found that PD may be modestly associated with atherosclerosis, myocardial infarction, and CVD. Meurman et al [27] reported a 20% increase in CVD risk among patients with PD (95% CI, 1.08-1.32) and an even higher risk ratio for stroke, varying from 2.85 (95% CI, 1.78-4.56) to 1.74 (95% CI, 1.08-2.81). Similarly, Khader et al [28] reported relative risk estimates of 1.19 (95% CI, 1.08-1.32) and 1.15 (95% CI, .06-1.25), respectively. These meta-analyses of human data suggest a modest but statistically significant increase in the risk for CVD with PD. Furthermore, a positive dose-dependent association between chronic periodontitis and the incidence of CHD among men younger than 60 years was recently found to be independent of established cardiovascular risk factors in a longitudinal cohort study with a median follow-up of 24 years [29].

In our data, the extent of CHD expressed by the use of stenosis score showed no relationship with the CPITN score. Therefore, our findings do not provide consistent evidence required to support the hypothesis of a causal relationship between the severity of PD and CHD that is consistent with other studies [12]. Coronary heart disease and plaque burden seemed to be triggered by periodontitis per se, but this was independent and not influenced by the degree of PD. Regardless of the mechanisms, Tonetti et al [20], Seinost et al [30], and Janket et al [31] have shown that severe periodontitis is associated with significant endothelial dysfunction that is reversible after successful periodontal treatment. There is also increasing evidence from numerous clinical trials that improvement of endothelial function translates into lower rates for cardiovascular events [32]. Increased CRP is also associated with endothelial dysfunction and reduces endothelial nitric oxide synthase expression [33,34]. However, recent studies suggest that CRP does not promote atherosclerosis, which is in accordance with epidemiologic studies [35]. Thus, the increased cardiovascular risk implied by high CRP levels probably occurs via modulation of events that begin with plaque rupture and end with thrombotic arterial occlusion; so CRP serves as a potential mediator as well as a predictor of syndromes of vascular occlusion. C-reactive protein modulates prostanoid metabolism by decreasing cyclooxygenase (COX)-2 derived prostacyclin release, a potent platelet inhibitor and vasodilator, in endothelial cells. In contrast, COX-1–derived thromboxane A_2, mostly produced by platelets, is a potent vasoconstrictor and proaggregatory agent; and the contrasting effects of these lipids are important for vascular homeostasis. C-reactive protein modulating prostaglandin metabolism favors vascular occlusion by unbalancing prostaglandin metabolism, which may induce a predisposition to cardiovascular events. The study by Grad and coworkers [36] indicate that CRP modulates the COX-prostaglandin pathway in a way that disrupts thromboregulation and may favor predisposition to thrombosis. C-reactive protein is influenced by treatment with statins as shown in the JUPITER trial [11]. Patients taking rosuvastatin had significant reductions in both their cholesterol levels and their CRP. Most of our patients with CHD were on statins, which may have been responsible for the only slight increase in CRP. Periodontal treatment also results in a decrease of CRP and interleukin-6. Slade et al [37] found that people with extensive PD had nearly a 33% increase in mean CRP values and had twice the prevalence of elevated CRP compared with periodontally healthy individuals.

The American Diabetes Association acknowledges the link between PD and diabetes in their 2003 Report on the Diagnosis and Classification of Diabetes Mellitus: “periodontitis is often found in people with diabetes” [38]. Diabetes is also an established cardiovascular risk factor that may increase the susceptibility to both periodontitis and CVD through the increased formation of advanced glycosylation end products, which are proinflammatory [29,39]. As a consequence, the risk of developing periodontitis may be greater in patients with diabetes who have poor glycemic control than in patients with well-controlled diabetes. In the Third National Health and Nutrition Examination Survey, adults with poorly controlled diabetes had an almost 3-fold increased risk of having periodontitis compared with adults without diabetes, whereas patients with diabetes and good glycemic control had no significant increase in risk [40]. In our population, about one fourth of patients were diabetics. Although periodontitis is an independent risk factor for CHD in our population group, diabetes seemed not to be responsible for an increased risk of developing periodontitis. It is likely that there is individual patient variability in the degree to which the glycemic control influences periodontal status. This is not surprising, given the multifactorial nature of PD, in which systemic conditions play a modifying role rather than a primary causative role. Although most research on the relationship between diabetes and PD has focused on how

diabetes may affect periodontal status, a growing body of evidence also has examined the converse relationship, namely, how PD affects the metabolic state [41].

In conclusion, the results of our study demonstrate an association between CHD and PD, more specifically an increased odds ratio that those with PD also have angiographically defined CHD. However, it is essential to emphasize that large, randomized, multicenter trials have not yet been conducted to definitively ascertain the potential benefits of periodontal therapy to reduce the levels of CRP or, more importantly, whether periodontal treatments reduce overall cardiovascular risk. What is encouraging from a health care perspective is that PD represents a potentially modifiable risk factor that is both preventable and treatable with predictable treatments that pose negligible risk. Considering that periodontal therapy would improve oral health, we suggest that periodontal therapy as an integral component of preventive cardiology treatment is worthy of further studies in both longitudinal clinical studies designed to test causality as well as multicenter trials designed to evaluate the potential cardioprotective effects of periodontal treatment.

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