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Association between Periodontal Disease and Atherosclerotic Cardiovascular Diseases: A Prospective Study

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Abstract

Background: It has been suggested that periodontal disease (PD) was associated with an increased risk for cardiovascular diseases (CVD), although evidence is inconclusive. ***Purpose****:* We first sought to prospectively evaluate the relationship of PD to CVD and all-cause mortality using a national representative sample in the United States. ***Methods:*** A prospective study was carried out of 147 patients with a periodontal disease who referred for periodontal consultation.. The severity of PD was categorized as non-PD, modest and severe PD based on clinical attachment loss and pocket depth. ***Results****:* The levels of inflammation markers (high sensitivity C-reactive protein, white cell count and fibrinogen) were significantly higher in men with severe PD compared to men without PD ($p < 0.05$). The prospective associations were evaluated using multivariable Cox proportional-hazards models. After adjusting for age, gender, household income and traditional risk factors of CVD, severe PD was associated with an increase risk of CVD mortality and all-cause mortality in men aged 30–64 years (HR = 2.13 with 95% confidence interval of 1.37–3.31 for CVD mortality; HR = 1.64 with 95% confidence interval of 1.25–2.15 for all-cause mortality). In addition, significant linear trends were found in CVD and all-cause mortality across the severity of PD ($p < 0.001$). However, no significant associations were found in men aged ≥65 and in women. ***Conclusions:*** There appears to be prospective associations between PD and CVD and all-cause mortality in men aged 30–64 years. Inflammation may be one possible pathway to link PD with CVD.

Keywords- Periodontal Disease, Cardiovascular Diseases, Atherosclerosis

Introduction

From a global perspective, cardiovascular diseases still account for the majority of deaths, although significant improvement in survival after being affected by cardiovascular disease has been achievedin the last decades. Periodontal diseases are also a common global burden. It is estimated that periodontitis, in severe forms, affects around 9% of the global population and is considered to be the 10thmost common noncommunicable disease of all.[1] Several studieshave shown a link between cardiovascular disease and periodontitis,although evidence is still lacking regarding the direct cause-effect relation.

Cardiovascular disease (CVD) is the leading cause of death in the United States [1]. Traditional risk factors such as cigarette smok- ing, hyperlipidemia, hypertension, and diabetes only explain partof the variation in the risk of CVD [2]. In the last decade, low-grade systemic inflammation has been advocated as one of the impor- tant novel risk factors for CVD [3]. Periodontal disease (PD), which is a chronic infection in

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the supportive tissue of teeth and caused by complex dental biofilms composed of microorganisms found in the oral microbiota, is common among U.S. adults [4]. The association between PD and CVD has been reviewed extensively in the literature [5–7]. The majority of epidemiological studies have shown the presence of a significant positive association between PD and CVD [8–10], although reports from the Health Professionals Study [11] and the Physicians' Health Study [12] observed no association between PD and either coronary heart disease or stroke among more than 66,000 male health professionals. The large sample sizes of these two studies provide a good reason for caution with regard to the overall hypothesis. To date, few studies have investigated the prospective associations between PD and CVD and all-cause mortality, especially in a national representative sample.

Methodology

A prospective study was carried out of 147 patients with a periodontal disease who referred for periodontal consultation to the Department of Periodontology and Implantology, at Institute of Dental Sciences and Rohilkhand Medical College and Hospital, Bareilly from 2020-2022. The parameters evaluated included patient age, sex, periodontal disease and cardiovascular diseases.

The periodontal examination was conducted in the mobile examination centers. Briefly, the periodontal examination was conducted at 2 sites, mid-buccal and mesiobuccal for each tooth, in 2 randomly chosen quadrants, 1 maxillary and 1 mandibular, on the assumption that conditions in these 2 quadrants would represent the mouth. Third molars were excluded because of their frequent extraction in young adulthood, so a maximum 14 teeth and 28 sites per individual were examined. Detailed examination procedures can be obtained from the CDC website [13]. Currently uniform criteria for an accurate definition of PD have not been established in epidemiological studies [15]. For this study, we defined modest PD as at least one site with >4 mm clinical attachment loss or at least one site with probing depths >5 mm; severe PD as at least one site with CAL ≥6 mm and one or more sites with PD ≥5 mm in 2 quadrants (half mouth).

We evaluated several variables for potential confounding. Demographic variables included age (in years), education (high school education or less versus more than high school) and household income level. Household income level was measured based on poverty income ratio (PIR) which is the ratio of family income to the appropriate poverty threshold: low (PIR < 1.35), medium (1.35 PIR < 3.0) and high (PIR 3.0). The potential risk factors for CVD included smoking status, alcohol use, total to HDL cholesterol ratio (TC/HDL ratio), hypertension, diabetes, and a history of coronary heart disease (CHD) or stroke. Smoking was categorized as never, current and former smoking. Alcohol use was dichotomized as at least 12 drinks in the last 12 months or not. TC/HDL ratio was calculated as total cholesterol divided by HDL cholesterol (<5 and 5) [17]. Obesity was defined as body mass index 30 kg/m^2. Hypertension was defined as mean SBP 140 mm Hg, mean DBP 90 mm Hg, or current treatment for hypertension with medication. Diabetes was defined from self-report of diagnosis or taking diabetes medications. A history of coronary heart disease (CHD) or stroke was determined by self-reported.

Analyses were performed using SPSS to account for the complex sampling scheme. Descriptive statistics were used to summarize variables as well as to detect outliers and missing values. We compared characteristics of the sample according to periodontal status. All the analyses were stratified by gender and two age groups (30 age < 65 and age 65). We evaluated the associations between PD and inflammation markers by fitting 3 multiple linear regression models with hsCRP, white blood cell count and fibrinogen

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as continuous out- comes respectively. hsCRP and white blood cell count were natural logarithm transformed in the analyses due to the skewed distributions. The effects of PD and other covariates were evaluated using adjusted hazard ratios with 95% confidence intervals [18].

Results

Demographic characteristics and potential risk factors of CVD in the study population with and without PD are presented in Table 1. Individuals with modest or severe PD were more likely to be younger, non-Hispanic black, current smoker and have lower levels of education and family income, and higher levels of TC/HDL ratio, and more likely to have hypertension, diabetes and a history of CHD or stroke compared with non-PD participants. We explored the associations between PD and systemic inflammation markers including hsCRP, white cell count and fibrinogen. The separate multiple linear regression models illustrated that there were consistent relationships between PD and systemic inflammation markers after adjusting for other covariates (Table 2). The levels of hsCRP, white cell count and fibrinogen were significantly higher in men with severe PD compared to men without PD ($p < 0.05$). In women severe PD cases have higher levels of fibrinogen than non-PD participants ($p = 0.001$).

Table 1-Baseline characteristics of study participants by periodontal disease (PD), NHANES III mortality follow-up study, 2020–2022.[a]

	Men				Women				Total			
	Non	Modest	Severe	*P*	Non	Modest	Severe	*P*	Non	Modest	Severe	*P*
	(*n* = 3046)	(*n* = 1729)	(*n* = 381)		(*n* = 4137)	(*n* = 1376)	(*n* = 180)		(*n* = 7183)	(*n* = 3105)	(*n* = 561)	
Age year% 30–39	41.58	21.18	25.88		36.92	19.25	19.06		38.98	20.32	23.73	
40–49	27.12	25.57	26.10		26.54	19.88	22.89		26.80	23.07	25.09	
50–59	12.88	23.02	17.84		14.07	19.65	16.59		13.54	21.54	17.45	
60–69	10.58	16.76	18.64		11.52	20.30	21.94		11.11	18.32	19.68	
70–79	5.95	10.04	10.10		7.64	13.61	15.72		6.89	11.61	11.87	
80+	1.89	3.44	1.44	<0.001	3.31	7.30	3.80	<0.001	2.68	5.14	2.18	<0.001
Poverty ratio %												
Low (<1.35)	16.00	21.63	32.20		22.82	28.60	43.67		19.79	24.70	35.81	
Medium (1.35–2.99)	30.52	30.75	36.30		30.92	36.09	41.70		30.74	33.10	38.00	
High (≥3.00)	53.48	47.62	31.50	<0.001	46.26	35.31	14.63	<0.001	49.47	42.21	26.19	<0.001
Education (<12 yrs) %	21.17	27.79	44.89	<0.001	21.25	32.11	36.59	<0.001	21.21	29.69	42.28	<0.001
Smoking %												
Never	38.23	23.70	20.10		58.27	45.82	40.59		49.36	33.43	26.56	
Current	25.32	37.53	48.01		20.24	30.44	34.04		22.50	34.41	43.61	
Former	36.45	38.77	31.89	<0.001	21.49	23.74	25.36	<0.001	28.14	32.16	29.83	<0.001
Alcohol use %	66.75	59.89	67.43	0.012	43.15	35.30	29.61	<0.001	53.63	49.07	55.52	0.016
TC/HDL ≥ 5.0[b]	41.42	44.92	39.29	0.188	19.29	23.31	33.57	0.002	29.12	35.42	37.49	0.001
Hypertension %	24.36	27.13	30.63	0.001	24.83	31.97	40.34	<0.001	24.62	29.26	33.69	0.001
Obesity %	21.81	21.09	26.73	0.391	26.36	28.04	42.21	0.024	24.34	24.15	31.61	0.078
Diabetes %	4.27	7.54	12.76	<0.001	5.70	7.70	13.82	0.002	5.06	7.61	13.09	<0.001
CHD/stroke history %	3.62	6.48	6.09	0.005	1.77	2.75	0.61	0.036	2.60	4.84	4.36	0.001

a All proportions are weighted to account for the sample design.

b TC/HDL, total cholesterol/HDL cholesterol ratio.

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Table 2-Periodontal disease (PD) and levels of high-sensitivity C-reactive protein (hsCRP), white blood cell count and fibrinogen (regression parameter estimates ˇ and standard errors, SE).[a]

	hsCRP[b]		White cell count[b] Fibrinogen, mg/dL		
	ˇ (SE)	*P*	ˇ (SE)	*P*	ˇ (S
Men					
Non-PD	Referent	Referent	Referent		
Modest (5.98)	−0.01 (0.03) 0.471	0.774	0.02 (0.01)	0.270	4.34
Severe (8.63)	0.15 (0.06) 0.022	0.010	0.07 (0.02)	0.001	20.34
Women					
Non-PD	Referent	Referent	Referent		
Modest (3.38)	−0.02 (0.03) 0.073	0.553	0.01 (0.02)	0.417	−6.01
Severe (10.00)	0.14 (0.09) 0.001	0.096	0.04 (0.03)	0.239	34.21

In unadjusted analysis, subjects with PD were at higher risk for CVD mortality and all-cause mortality com- pared to subjects without PD in both men and women aged 30–64 years, but not in older age group (age ≥ 65 years). The relationships also demonstrated a significant linear trend across the severity of PD ($p < 0.01$). After controlling for age, race, education, household income, smoking status, alcohol use, TC/HDL ratio, hypertension, obesity, diabetes and a history of CHD or stroke in Cox proportional hazard models, the risk was reduced significantly for both CVD and all-cause mortality. Men with severe PD still have an increased risk for CVD and all-cause mortality compared to men without PD in the younger group (30–64 years) (HR = 2.13 for CVD mortality with 95% confidence interval of 1.37–3.31, $p < 0.001$; HR = 1.64 for all-cause mortality with 95% confidence interval of 1.25–2.15, $p < 0.001$). In addition, significant linear trends were found in CVD and all-cause mortality across the severity of PD ($p < 0.001$). However, no significant associations were found between PD and risk of CVD and all-cause mortality in men aged ≥ 65 and in women.

Discussion

Although a number of epidemiological studies have demon- strated that periodontal disease may significantly predict cardiovascular diseases, causality still needs to be confirmed. In this prospective analysis using national representative data, we observed significant associations between periodontal disease and CVD mortality and all-cause mortality among U.S. men aged 30–64 years after adjusting for demographic factors, traditional risk factors of CVD and other potential confounders. However, no sig-

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nificant associations were found in women and in men aged 65 years and over. Our findings are consistent with previous studies showing positive associations of poor oral health and CVD mortal- ity and all-cause mortality in young men [19–21]. More recently, a large prospective study with 7674 subjects and a median follow-up period of 12 years presented a dose-dependent relationship among number of teeth and CVD and all-cause mortality [22]. On the contrary, a large 6-year follow-up study of 44,119 male health professionals suggested that periodontal disease was not an independent predictor of subsequent cardiovascular disease in middle-aged to elderly men [12]. Similarly in the Physicians' Health Study of 22,071 U.S. male physicians, no association was observed between periodontal disease and subsequent CHD [11]. However, these two large cohort studies had no oral examination data, but instead relied on participant reports of periodontal disease (no medical records to confirm the reports).

The gender differences in CVD and metabolic syndrome risk factors have received a lot of attention [23,24]. Gender has a significant influence on the cause, clinical manifestation and prognosis of CVD. Modifiable risk factors, such as smoking, physical activity, show differences between the sexes. Sex hormones and sex-specific genetic factors are also likely to be involved in the pathogenesis of CVD [24]. Several possible pathways relating periodontal disease and CVD including bacteremia, inflammation and vascular injury have been discussed in previous studies [7,10,25]. The bacteria maycontribute to the vascular pathology either directly through their cytotoxicity or indirectly by inducing or exacerbating inflammation. They are present in atherosclerotic plaques and may play an important role in the development and progression of atherosclerosis leading to CVD [26]. Inflammation is a normal response to many physical states including fever, injury and infection. Laboratory evidence and findings from clinical and population studies suggest that a chronic low-grade inflammation, such as periodontal disease, may be involved in the process of development of atherosclerosis for CVD [27,28]. Inflammation (triggered by environmental factors or genetic influences) causes a sequence of actions in the artery such as, plaque rupture, thrombus formation and immobilization into the blood vessels, therefore increasing plaque build up and contributing to diminished flow in arteries [29]. The inflammatory biomarkers teleologically plays an important role in the body's immune response and has been associated with increased risk of CVD [30]. Additionally, previous studies have been shown that the systemic inflammation markers: C-reactive protein, IL-6, TNF- _ and fibrinogen were elevated in patients with PD [31,32]. Our multivariable analyses verified that PD cases had higher levels of hsCRP, white cell count and fibrinogen than non-cases. Therefore, our results also support that inflammation may be an important pathway linking PD with CVD.

Conclusion,

In conclusion, this study provides support for the hypothesis of the association of periodontal disease with CVD and all-cause mortality in men younger than 65, and for a potential oral-infection-inflammation pathway for CVD using national representative data. Our results will furnish novel information about oral health and CVD and general health, thus have large potential public health implications.

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