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Periodontal Disease and Cardiovascular Risk Factors: A Cross-Sectional Analysis of Inflammatory Pathway Associations

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Annotation: Background: Periodontal disease represents a significant global health burden and has been implicated as a potential contributor to the risk of cardiovascular disease (CVD). This study aimed to investigate the relationship between periodontal disease severity and established cardiovascular risk factors while exploring potential inflammatory mediators.

Methods: A cross-sectional study was conducted with 387 participants (aged 35-65) without established cardiovascular disease. Comprehensive periodontal examinations were performed, including measurements of pocket depth (PD), clinical attachment loss (CAL), bleeding on probing (BOP), and alveolar bone loss. Cardiovascular risk assessments included blood pressure, lipid profiles, glucose metabolism markers, high-sensitivity C-reactive protein (hs-CRP), and carotid intima-media thickness (cIMT). Linear and logistic regression models were used to analyze associations between periodontal parameters and cardiovascular risk factors, adjusting for relevant confounders.

Results: The severity of periodontal disease (defined by CAL ≥3 mm at ≥30% of sites) was significantly associated with elevated systolic blood pressure ($\beta = 4.37$ mmHg, 95% CI: 2.18-6.56, $p < 0.001$), higher hs-CRP levels ($\beta = 0.76$ mg/L, 95% CI: 0.41-1.11, $p < 0.001$), and increased cIMT ($\beta = 0.038$ mm, 95% CI: 0.012-0.064, $p = 0.004$) after adjusting for age, sex, smoking, body mass index, and socioeconomic factors. Path analysis demonstrated that approximately 27% of the association between periodontal disease and increased cIMT was mediated by elevated hs-CRP levels, suggesting potential involvement of an inflammatory pathway.

Conclusions: Our findings provide evidence for an independent association between periodontal disease severity and key cardiovascular risk factors, particularly systemic inflammation and subclinical atherosclerosis. These results support the hypothesis that periodontal disease may contribute to cardiovascular risk through inflammatory pathways, highlighting the importance of oral health in cardiovascular risk assessment and management.

Keywords: Periodontal disease; Cardiovascular risk factors; Inflammation; Atherosclerosis; C-reactive protein.

Introduction

Periodontal disease refers to a group of inflammatory conditions that affect the supporting structures of teeth, and dysbiotic dental biofilms in susceptible individuals generally cause it. It is one of the most prevalent types of chronic inflammatory disease globally. Severe types of periodontal diseases affect approximately 10-15% of adults worldwide (1). The localized inflammatory response to periodontal pathogens leads to a series of possibilities labelled as gingival inflammation, destruction of connective tissue, and resorption of the alveolar bone, resulting in tooth loss if untreated(2). In addition to local consequences, periodontal disease continues to be increasingly associated with systemic consequences, especially concerning cardiovascular effects.

Cardiovascular disease (CVD) continues to be the number one killer in the world, accounting for an estimated 32% of all deaths globally(3). CVD has many contributing factors, with risk factors such as hypertension, dyslipidemia, diabetes mellitus, obesity, and smoking being very well characterized. However, traditional risk factors do not account for all instances of CVD, implying that additional, less

recognized roles may contribute to the overall cardiovascular risk profile(4). The role chronic infection and inflammatory conditions may play in atherogenesis and cardiovascular events has gained interest over the last three decades, and periodontal disease has emerged as a potential risk factor of note.

The biological plausibility of a relationship between periodontal disease and pathology associated with cardiovascular disease can be explained by multiple mechanisms. Periodontal infection and inflammation may be involved in atherogenesis and thrombotic events through direct and indirect pathways (5). Periodontal pathogenic bacteria and their products can enter the systemic circulation during everyday activities, such as chewing food or brushing teeth, especially for individuals with periodontal disease, where the ulcerated pocket epithelium provides a pathway into the circulatory system (6). Certain studies have shown that oral bacteria, including periodontal pathogens like Porphyromonas gingivalis, Tannerella forsythia, and Treponema denticola, are present in atherosclerotic plaques, indicating the potential for these pathogens to invade the vascular endothelium (7). Periodontal pathological bacteria contain virulence factors that can cause endothelial dysfunction, vascular smooth muscle cell proliferation, and platelet aggregation, all essential steps in the development of atherosclerosis.(8)

Perhaps more importantly, periodontal disease may affect cardiovascular health indirectly through systemic inflammation; systemic inflammation is considered a significant factor in the pathogenesis of atherosclerosis (9). The local inflammatory response to periodontal pathogens leads to the secretion of pro-inflammatory cytokines, including interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6), into systemic circulation, eventually leading to an acute phase response in the liver characterized by increased synthesis of C-reactive protein (CRP), fibrinogen, and serum amyloid A (10). The association of higher levels of inflammatory markers, including CRP, with higher cardiovascular risk is well established. In addition, CRP, as a putative mediator between periodontal disease and cardiovascular disease (CVD), has also been proposed.(11)

Over the past thirty years, a growing body of epidemiological evidence has demonstrated an association between periodontal disease and increased cardiovascular risk. Meta-analyses evaluating observational studies among periodontal disease have suggested individuals with periodontitis may have a 15- 40% higher risk of coronary heart disease than healthy controls, independent of traditional cardiovascular risk factors (12,13). Similarly, periodontal disease is linked to an increased risk of stroke, peripheral arterial disease, and cardiovascular mortality(14,15). Nevertheless, associations among these studies have varied widely, and methodological heterogeneity is to blame. Studies varied in terms of definitions of periodontal disease, adjustments for confounding factors, and populations studied.(16)

Some studies have examined the potential implications of periodontal disease on subclinical markers of atherosclerosis, such as carotid intima-media thickness (cIMT) and endothelial dysfunction. These subclinical markers reflect early and/or pre-symptomatic stages of atherosclerosis, which may one day predict future cardiovascular events (17). A few cross-sectional studies have presented evidence of associations between periodontal disease and cIMT, with more severe periodontal disease being associated with greater carotid wall thickness (18, 19). Additionally, when compared to periodontally healthy controls, some studies have demonstrated impaired flow-mediated dilation, leading researchers to conclude that individuals with periodontal disease have impaired endothelial function .(20)

While evidence of associations between periodontal disease and traditional cardiovascular risk factors such as hypertension, dyslipidemia, and disturbances in glucose metabolism is also inconclusive, some studies have shown associations between periodontal disease and increased blood pressure, unfavorable lipid profiles, and insulin resistance. In contrast, others had no significant associations after adjustments were made for common risks like age, smoking, and obesity(21,22). These conflicting findings imply a complex interaction between periodontal disease and cardiovascular risk factors and other common determinants of these risks. Multi-level assessments of periodontal disease, cardiovascular risk factors, and potential confounding and mediating factors are warranted. Moreover, studies of interventions investigating periodontal management and cardiovascular risk markers have

added to the body of evidence. Systematic review and meta-analysis of randomized controlled trials have shown that intensive periodontal treatment has been and can result in improved endothelial function, decreases in markers of inflammation, and beneficial changes in blood pressure and lipids over short to medium timeframes (23,24); however, limited research exists quantifying the impact of periodontal management on hard cardiovascular endpoints in the long term.

Despite the expanding evidence base showing the relationship between periodontal disease and cardiovascular health, there are still areas of knowledge and literature gaps. For example, it is unclear how much independent epidemiologic risk is conferred by a prior history of periodontal disease, controlling for shared risk factors and other confounders. It is also unclear what elements or periodontal parameters are most closely associated with cardiovascular risk factors, as well as what the mechanism (if any) is that mediates the association. Although the theoretical role of systemic inflammatory mediators as possible mediators of the relationship between periodontal health and cardiovascular disease is plausible, it may take more robust evidence from sufficiently powered, well-designed studies that measure inflammatory biomarkers and incorporate pathway analyses with epidemiologic methods.

Most studies to date have defined periodontal disease according to a variety of definitions, often limiting their analysis to a single parameter, such as pocket depth or attachment loss, which may not represent the complete range of periodontal disease status (25). Furthermore, many of the studies can either fail to control sufficiently for confounding variables that influence periodontal or cardiovascular health (e.g., socioeconomic status, addressing healthcare availability, psychosocial factors).(26)

The research agenda presented here represents an opportunity to advance further the investigation of the association between multiple forms of periodontal disease and established cardiovascular risk factors, particularly regarding potential mediating pathways associated with systemic inflammation and subclinical atherosclerosis. By taking into account numerous periodontal measures and adjusting for some of the possible confounding factors discussed, this agenda would enable the assessment of the independent association between periodontal disease and cardiovascular risk, as well as the possibility of an oral contribution to systemic health.

Specifically, this study hypothesizes that: 1) Severity of periodontal disease, characterized by clinical attachment loss, pocket depth, bleeding on probing, and alveolar bone loss, is independently associated with traditional cardiovascular risk factors (hypertension, dyslipidemia, glucose metabolism disorders) after adjusting for common risk determinants; 2) Periodontal disease severity is associated with elevated systemic inflammatory markers, particularly high-sensitivity C-reactive protein; 3) Periodontal disease is independently associated with subclinical atherosclerosis, as measured by carotid intima-media thickness; and 4) The association between periodontal disease and subclinical atherosclerosis is partially mediated by systemic inflammation.

Methodology

Study Design and Population

This cross-sectional study was conducted at the a private hospital in Baghdad between January 2023 and December 2023. The study protocol was approved, and written informed consent was obtained from all participants before enrollment. A total of 387 participants aged 35-65 years without known cardiovascular disease were recruited through community advertisements and from dental and primary care clinics.

Exclusion criteria included a history of myocardial infarction, stroke, or revascularization procedures; antibiotic use within three months before enrollment; periodontal treatment within six months before enrollment; fewer than 12 natural teeth; pregnancy or lactation; chronic inflammatory conditions (e.g., rheumatoid arthritis, inflammatory bowel disease); immunosuppressive therapy; and an inability to provide informed consent.

Sample Size Calculation

The sample size calculation was based on detecting a moderate correlation (r = 0.20) between periodontal disease parameters and cardiovascular risk factors, with 90% power and a 5% significance level, yielding a minimum required sample size of 259 participants. Allowing for a 20% dropout rate and incomplete data, we aimed to recruit 325 participants.

Data Collection

Trained research personnel collected demographic data, medical history, and lifestyle information using standardized questionnaires. Demographic variables included age, sex, ethnicity, educational level, and household income. Medical history focused on cardiovascular risk factors, family history of cardiovascular disease, and current medications. Lifestyle factors included smoking status (never, former, current), alcohol consumption, physical activity, and dietary habits.

Periodontal Examination

Comprehensive periodontal examinations were performed by three calibrated periodontists, with an inter-examiner kappa value of greater than 0.80 for pocket depth (PD) and clinical attachment loss (CAL) measurements. Periodontal parameters were assessed at six sites per tooth (mesiobuccal, buccal, distobuccal, mesiolingual, lingual, and distolingual) for all teeth, excluding third molars.

The following periodontal parameters were recorded:

1. Probing pocket depth (PD): Distance from the gingival margin to the base of the periodontal pocket, measured to the nearest millimeter using a UNC-15 periodontal probe.
2. Clinical attachment loss (CAL): Distance from the cemento-enamel junction to the base of the periodontal pocket.
3. Bleeding on probing (BOP): Present or absent within 30 seconds after probing.
4. Plaque index: Present or absent at four sites per tooth.
5. Alveolar bone loss: Assessed using digital panoramic radiographs and periapical radiographs. The distance from the cemento-enamel junction to the alveolar bone crest was measured at mesial and distal sites of each tooth.

Periodontal disease severity was categorized according to the 2018 classification system by Papapanou et al.(27) as:

- ✓ Stage I (mild): CAL 1-2 mm, PD ≤4 mm, bone loss <15%
- ✓ Stage II (moderate): CAL 3-4 mm, PD ≤5 mm, bone loss 15-33%
- ✓ Stage III (severe): CAL ≥5 mm, PD ≥6 mm, bone loss extending to mid-third of root
- ✓ Stage IV (advanced): CAL ≥5 mm, PD ≥6 mm, bone loss extending beyond mid-third of root, with tooth loss due to periodontitis

Cardiovascular Risk Assessment

Blood pressure was measured using an automated device after a five-minute rest, with the average of three readings recorded. Anthropometric measurements included height, weight, waist circumference, and hip circumference. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2).

Fasting blood samples were collected for laboratory analyses, including:

1. Lipid profile: Total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides.
2. Glucose metabolism: Fasting plasma glucose and hemoglobin A1c (HbA1c).

3. Inflammatory markers: High-sensitivity C-reactive protein (hs-CRP), fibrinogen, and interleukin-6 (IL-6).

Carotid intima-media thickness (cIMT) was measured using high-resolution B-mode ultrasonography with a 7.5 MHz linear array transducer. Three measurements were taken at the far wall of the common carotid artery, 1 cm proximal to the carotid bulb, and the mean value was recorded. The presence of carotid plaques, defined as focal thickening exceeding 1.5 mm, was also documented.

Statistical Analysis

Statistical analyses were performed using SPSS version 27.0 (IBM Corp., Armonk, NY, USA) and R version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were presented as mean ± standard deviation or median (interquartile range) as appropriate, and categorical variables as frequencies and percentages.

Periodontal disease severity stages stratified participants for descriptive analyses. Differences between groups were assessed using one-way ANOVA or Kruskal-Wallis test for continuous variables and chi-square test for categorical variables.

Multiple linear regression models were constructed to examine the association between periodontal parameters (as continuous variables) and cardiovascular risk factors, adjusting for potential confounders. Model 1 adjusted for age and sex; Model 2 additionally adjusted for smoking status, body mass index (BMI), and socioeconomic indicators; and Model 3 further adjusted for physical activity, alcohol consumption, and medication use.

Logistic regression models were used to analyze the association between periodontal disease severity stages and categorical cardiovascular outcomes (e.g., hypertension, defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or use of antihypertensive medication). The results are presented as odds ratios (OR) with 95% confidence intervals (CI).

Mediation analyses using structural equation modeling were performed to assess whether systemic inflammation (hs-CRP) mediated the relationship between periodontal disease and subclinical atherosclerosis (cIMT). The proportion of the total effect mediated through the inflammatory pathway was calculated.

All statistical tests were two-sided, with a significance level set at $p<0.05$. The Benjamini-Hochberg procedure was applied to control for multiple comparisons when appropriate.

Results

Demographic and Clinical Characteristics

Table 1: Demographic and Clinical Characteristics of Study Participants Stratified by Periodontal Disease Severity

Characteristic	Total (n=387)	No/Mild Periodontitis (n=112)	Moderate Periodontitis (n=147)	Severe/Advanced Periodontitis (n=128)	p-value
Demographics					
Age, years	51.3 ± 8.7	46.2 ± 7.8	51.6 ± 8.4	55.7 ± 7.6	<0.001
Female sex, n (%)	204 (52.7)	68 (60.7)	79 (53.7)	57 (44.5)	0.029
Education, n (%)					<0.001
- High school or less	92 (23.8)	15 (13.4)	35 (23.8)	42 (32.8)	
- Some college	142 (36.7)	38 (33.9)	56 (38.1)	48 (37.5)	

- College graduate	153 (39.5)	59 (52.7)	56 (38.1)	38 (29.7)	
Health Behaviors					
Smoking status, n (%)					<0.001
- Never	189 (48.8)	71 (63.4)	74 (50.3)	44 (34.4)	
- Former	121 (31.3)	33 (29.5)	46 (31.3)	42 (32.8)	
- Current	77 (19.9)	8 (7.1)	27 (18.4)	42 (32.8)	
Alcohol consumption, n (%)					0.248
- None	119 (30.7)	32 (28.6)	43 (29.3)	44 (34.4)	
- Moderate	218 (56.3)	69 (61.6)	84 (57.1)	65 (50.8)	
- Heavy	50 (12.9)	11 (9.8)	20 (13.6)	19 (14.8)	
Regular physical activity, n (%)	157 (40.6)	58 (51.8)	61 (41.5)	38 (29.7)	0.002
Clinical Measurements					
BMI, kg/m²	27.6 ± 4.9	26.3 ± 4.1	27.7 ± 4.8	28.6 ± 5.3	0.001
Waist circumference, cm	93.8 ± 13.2	90.2 ± 11.8	93.6 ± 12.9	97.3 ± 13.8	<0.001
Systolic BP, mmHg	128.4 ± 16.5	123.1 ± 14.2	127.9 ± 15.9	133.7 ± 17.3	<0.001
Diastolic BP, mmHg	79.8 ± 9.7	77.3 ± 8.9	79.5 ± 9.4	82.4 ± 10.1	<0.001
Hypertension, n (%)	138 (35.7)	25 (22.3)	51 (34.7)	62 (48.4)	<0.001
Diabetes mellitus, n (%)	58 (15.0)	9 (8.0)	21 (14.3)	28 (21.9)	0.007

Data are presented as mean ± standard deviation or number (percentage)—BP: blood pressure; BMI: body mass index. P-values were calculated using one-way ANOVA for continuous variables and chi-square test for categorical variables.

Periodontal Parameters and Laboratory Findings

Table 2: Periodontal Parameters and Laboratory Findings by Periodontal Disease Severity

Parameter	Total (n=387)	No/Mild Periodontitis (n=112)	Moderate Periodontitis (n=147)	Severe/Advanced Periodontitis (n=128)	p-value
Periodontal Parameters					
Pocket depth, mm	2.8 ± 0.9	2.1 ± 0.3	2.7 ± 0.4	3.6 ± 1.0	<0.001

Clinical attachment loss, mm	2.7 ± 1.4	1.3 ± 0.5	2.4 ± 0.7	4.2 ± 1.4	<0.001
Bleeding on probing, %	32.4 ± 19.8	18.7 ± 10.9	31.3 ± 16.7	45.8 ± 20.3	<0.001
Plaque index, %	39.2 ± 21.4	24.6 ± 15.3	39.1 ± 18.9	52.3 ± 21.1	<0.001
Alveolar bone loss, %	21.8 ± 14.6	9.2 ± 5.7	19.7 ± 8.2	35.1 ± 13.8	<0.001
Laboratory Parameters					
Total cholesterol, mg/dL	196.4 ± 37.9	189.3 ± 35.2	197.2 ± 37.4	202.1 ± 39.8	0.039
LDL cholesterol, mg/dL	121.6 ± 34.2	115.8 ± 32.7	122.3 ± 33.9	126.1 ± 35.3	0.071
HDL cholesterol, mg/dL	53.7 ± 14.6	57.2 ± 15.4	53.9 ± 14.3	50.3 ± 13.5	0.001
Triglycerides, mg/dL	127.8 (89.5-183.2)	108.5 (76.4-156.3)	124.7 (90.2-176.8)	148.6 (102.3-209.4)	<0.001
Fasting glucose, mg/dL	98.7 ± 19.6	94.3 ± 13.8	98.1 ± 18.7	103.2 ± 23.9	0.002
HbA1c, %	5.7 ± 0.8	5.5 ± 0.6	5.7 ± 0.7	6.0 ± 0.9	<0.001
hs-CRP, mg/L	1.8 (0.9-3.7)	1.1 (0.6-2.2)	1.7 (0.9-3.5)	2.8 (1.4-5.2)	<0.001
IL-6, pg/mL	2.4 (1.5-3.8)	1.7 (1.1-2.6)	2.3 (1.4-3.7)	3.3 (2.1-5.0)	<0.001
Fibrinogen, mg/dL	348.6 ± 82.4	320.3 ± 69.7	345.9 ± 79.8	376.8 ± 87.9	<0.001
cIMT, mm	0.72 ± 0.16	0.66 ± 0.13	0.71 ± 0.15	0.78 ± 0.17	<0.001
Carotid plaque, n (%)	92 (23.8)	14 (12.5)	32 (21.8)	46 (35.9)	<0.001

Data are presented as mean ± standard deviation, median (interquartile range), or number (percentage). LDL: low-density lipoprotein; HDL: high-density lipoprotein; HbA1c: hemoglobin A1c; hs-CRP: high-sensitivity C-reactive protein; IL-6: interleukin-6; cIMT: carotid intima-media thickness. P-values were calculated using one-way ANOVA or Kruskal-Wallis test for continuous variables and chi-square test for categorical variables.

Association Between Periodontal Parameters and Cardiovascular Risk Factors

Table 3: Multiple Linear Regression Analysis of Association Between Clinical Attachment Loss and Cardiovascular Risk Factors

Dependent Variable	Model 1	Model 2	Model 3
Systolic BP (mmHg)	β=5.86 (3.42, 8.30) p<0.001	β=4.78 (2.52, 7.04) p<0.001	β=4.37 (2.18, 6.56) p<0.001
Diastolic BP (mmHg)	β=3.15 (1.76, 4.54) p<0.001	β=2.59 (1.28, 3.90) p<0.001	β=2.36 (1.08, 3.64) p<0.001
Total cholesterol (mg/dL)	β=6.74 (0.95, 12.53) p=0.023	β=5.28 (-0.56, 11.12) p=0.076	β=4.92 (-0.97, 10.81) p=0.101
LDL cholesterol (mg/dL)	β=6.18 (1.07, 11.29) p=0.018	β=4.85 (-0.31, 10.01) p=0.065	β=4.63 (-0.57, 9.83) p=0.081
HDL cholesterol (mg/dL)	β=-4.25 (-6.68, -1.82) p<0.001	β=-2.87 (-5.19, -0.55) p=0.016	β=-2.69 (-5.04, -0.34) p=0.025
Log-transformed triglycerides	β=0.13 (0.07, 0.19) p<0.001	β=0.09 (0.04, 0.14) p<0.001	β=0.08 (0.03, 0.13) p=0.002
Fasting glucose (mg/dL)	β=5.29 (2.17, 8.41) p=0.001	β=3.67 (0.71, 6.63) p=0.015	β=3.41 (0.47, 6.35) p=0.023
HbA1c (%)	β=0.28 (0.13, 0.43) p<0.001	β=0.21 (0.07, 0.35) p=0.003	β=0.19 (0.05, 0.33) p=0.008
Log-transformed hs-CRP (mg/L)	β=0.32 (0.21, 0.43) p<0.001	β=0.27 (0.17, 0.37) p<0.001	β=0.25 (0.15, 0.35) p<0.001
cIMT (mm)	β=0.058 (0.029, 0.087) p<0.001	β=0.042 (0.016, 0.068) p=0.002	β=0.038 (0.012, 0.064) p=0.004

Data are presented as β coefficient (95% confidence interval) and p-value. β represents the change in the dependent variable associated with a 1 mm increase in mean clinical attachment loss. Model 1: Adjusted for age and sex Model 2: Additionally adjusted for smoking status, BMI, education level, and household income Model 3: Additionally adjusted for physical activity, alcohol consumption, and medication use BP: blood pressure; LDL: low-density lipoprotein; HDL: high-density lipoprotein; HbA1c: hemoglobin A1c; hs-CRP: high-sensitivity C-reactive protein; cIMT: carotid intima-media thickness.

Risk of Cardiovascular Outcomes by Periodontal Disease Severity

Table 4: Logistic Regression Analysis for Cardiovascular Outcomes by Periodontal Disease Severity

Outcome	Periodontal Disease Category	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
Hypertension	No/Mild	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
	Moderate	1.64 (0.93, 2.89) p=0.087	1.48 (0.82, 2.67) p=0.192	1.43 (0.79, 2.59) p=0.238
	Severe/Advanced	2.78 (1.55, 4.97) p<0.001	2.31 (1.25, 4.27) p=0.007	2.18 (1.16, 4.08) p=0.015

Dyslipidemia	No/Mild	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
	Moderate	1.59 (0.95, 2.66) p=0.076	1.41 (0.83, 2.40) p=0.204	1.38 (0.81, 2.36) p=0.237
	Severe/Advanced	2.12 (1.24, 3.62) p=0.006	1.75 (1.00, 3.07) p=0.049	1.70 (0.96, 3.00) p=0.068
Elevated hs-CRP (>3 mg/L)	No/Mild	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
	Moderate	2.05 (1.16, 3.63) p=0.014	1.83 (1.01, 3.31) p=0.046	1.79 (0.98, 3.26) p=0.058
	Severe/Advanced	3.72 (2.12, 6.54) p<0.001	2.87 (1.58, 5.21) p<0.001	2.75 (1.50, 5.03) p=0.001
Carotid Plaque	No/Mild	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
	Moderate	1.65 (0.83, 3.29) p=0.154	1.41 (0.70, 2.85) p=0.339	1.36 (0.67, 2.77) p=0.398
	Severe/Advanced	2.88 (1.47, 5.65) p=0.002	2.24 (1.12, 4.51) p=0.023	2.15 (1.06, 4.36) p=0.034
Elevated cIMT (>75th percentile)	No/Mild	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
	Moderate	1.79 (0.96, 3.35) p=0.067	1.58 (0.83, 3.00) p=0.164	1.52 (0.79, 2.91) p=0.208
	Severe/Advanced	2.97 (1.60, 5.52) p<0.001	2.38 (1.25, 4.54) p=0.008	2.29 (1.19, 4.41) p=0.013

Data are presented as odds ratios (95% confidence intervals) and p-values. Model 1: Adjusted for age and sex Model 2: Additionally adjusted for smoking status, BMI, education level, and household income Model 3: Additionally adjusted for physical activity, alcohol consumption, and medication use Hypertension: systolic BP ≥140 mmHg, diastolic BP ≥90 mmHg, or antihypertensive medication use Dyslipidemia: LDL-C ≥130 mg/dL, HDL-C <40 mg/dL for men or <50 mg/dL for women, triglycerides ≥150 mg/dL, or lipid-lowering medication use hs-CRP: high-sensitivity C-reactive protein; cIMT: carotid intima-media thickness

Mediation Analysis of Inflammatory Pathways

Table 5: Mediation Analysis of the Effect of Periodontal Disease on Carotid Intima-Media Thickness Through Inflammatory Pathways

Pathway	Direct Effect β (95% CI)	Indirect Effect β (95% CI)	Total Effect β (95% CI)	Proportion Mediated (%)
CAL → hs-CRP → cIMT	0.028 (0.005, 0.051) p=0.016	0.010 (0.004, 0.016) p=0.001	0.038 (0.012, 0.064) p=0.004	26.8%
CAL → IL-6 → cIMT	0.030 (0.007, 0.053) p=0.010	0.008 (0.003, 0.013) p=0.002	0.038 (0.012, 0.064) p=0.004	21.3%
PD → hs-CRP → cIMT	0.024 (0.002, 0.046) p=0.035	0.009 (0.003, 0.015) p=0.002	0.033 (0.008, 0.058) p=0.010	27.5%
BOP → hs-CRP → cIMT	0.0012 (0.0003, 0.0021) p=0.012	0.0005 (0.0002, 0.0008) p=0.001	0.0017 (0.0006, 0.0028) p=0.003	29.6%

Data are presented as β coefficient (95% confidence interval) and p-value. All models are adjusted for age, sex, smoking status, BMI, education level, household income, physical activity, alcohol consumption, and medication use. CAL: clinical attachment loss; PD: pocket depth; BOP: bleeding on probing; hs-CRP: high-sensitivity C-reactive protein; IL-6: interleukin-6; cIMT: carotid intima-media thickness. β for CAL and PD represents the change in cIMT (mm) associated with a 1 mm increase in the periodontal parameter. β for BOP represents the change in cIMT (mm) associated with a 1% increase in bleeding on probing.

Discussion

This cross-sectional study investigated the relationship between periodontal disease and cardiovascular risk factors in a cohort of 387 adults without established cardiovascular disease. Our findings demonstrate significant associations between periodontal disease severity and multiple cardiovascular risk factors, including blood pressure, lipid profiles, glucose metabolism markers, systemic inflammation, and subclinical atherosclerosis, after adjusting for traditional risk factors and potential confounders. Notably, the relationship between periodontal disease and carotid intima-media thickness was partially mediated by systemic inflammatory markers, particularly high-sensitivity C-reactive protein, supporting the hypothesis that inflammatory pathways may play a crucial role in linking oral and cardiovascular health.

The observed association between periodontal disease severity and elevated blood pressure aligns with previous epidemiological studies. A systematic review and meta-analysis by Martin-Cabezas et al.(28) reported a significant association between periodontitis and hypertension, with a pooled odds ratio of 1.50 (95% CI: 1.27-1.78). Our findings extend this evidence by demonstrating a dose-response relationship, with more severe periodontal disease corresponding to higher blood pressure values and increased odds of hypertension. Furthermore, our results persisted after comprehensive adjustment for potential confounding factors, suggesting an independent relationship between periodontal health and blood pressure regulation.

Several biological mechanisms may underlie this association. Periodontal disease-associated systemic inflammation could impair endothelial function and increase arterial stiffness, both key determinants of blood pressure(29). Periodontopathic bacteria and their products, such as lipopolysaccharides, may induce vascular inflammation and oxidative stress, leading to endothelial dysfunction and reduced nitric oxide bioavailability(30). Additionally, periodontal inflammation may activate the renin-angiotensin-aldosterone system and the sympathetic nervous system, contributing to blood pressure elevation (31).

The relationships between periodontal disease and lipid profiles in our study were more nuanced. While we observed significant associations between clinical attachment loss and lower HDL cholesterol and higher triglyceride levels in fully adjusted models, the associations with total cholesterol and LDL cholesterol attenuated after adjustment for confounding factors. These findings are consistent with a systematic review by Nepomuceno et al.(32), which reported inconsistent associations between periodontal disease and lipid parameters across studies, with the most robust evidence for decreased HDL cholesterol and increased triglycerides. The differential effects on lipid fractions suggest that periodontal disease may influence specific aspects of lipid metabolism, potentially through inflammatory pathways that affect HDL functionality and triglyceride clearance(33).

Our results demonstrated significant associations between periodontal disease severity and markers of glucose metabolism, including fasting plasma glucose and HbA1c. These findings align with the bidirectional relationship between periodontal disease and diabetes mellitus established in the literature(34). Chronic periodontal inflammation may contribute to insulin resistance and impaired glucose regulation through various mechanisms, including the elevation of systemic inflammatory mediators such as TNF-α and IL-6, which can interfere with insulin receptor signaling pathways (35). The observed associations, although attenuated, remained significant after adjusting for confounding factors, supporting an independent relationship between periodontal health and glucose homeostasis.

A central finding of our study was the strong association between periodontal disease severity and elevated inflammatory markers, particularly high-sensitivity C-reactive protein. Participants with severe or advanced periodontal disease exhibited markedly higher levels of hs-CRP, interleukin-6 (IL-6), and fibrinogen compared to those with no or mild periodontitis, and these differences persisted after comprehensive adjustment for confounding factors. These results corroborate findings from previous studies and meta-analyses that have consistently demonstrated elevated systemic inflammatory markers in individuals with periodontal disease (36, 37). The chronic, low-grade inflammation associated with periodontal disease may contribute to a systemic inflammatory burden, with implications for cardiovascular risk, as inflammatory processes play a critical role in the initiation, progression, and destabilization of atherosclerotic lesions (38).

Perhaps the most clinically relevant finding of our study was the significant association between periodontal disease severity and subclinical atherosclerosis, as assessed by carotid intima-media thickness and the presence of carotid plaques. Participants with severe or advanced periodontitis demonstrated significantly higher cIMT values and approximately twice the odds of having carotid plaques compared to those with no or mild periodontitis, after adjusting for traditional cardiovascular risk factors. These results align with previous cross-sectional and longitudinal studies that have reported associations between periodontal disease and subclinical measures of atherosclerosis (39, 40). Notably, a longitudinal survey by Desvarieux et al. (41) demonstrated that improvements in periodontal status over three years were associated with a slower rate of cIMT progression, suggesting a potential causal relationship.

The mediation analyses conducted in our study provide novel insights into the potential mechanisms linking periodontal disease and subclinical atherosclerosis. Our results indicate that approximately 27% of the association between clinical attachment loss and carotid intima-media thickness was mediated by elevated high-sensitivity C-reactive protein (hs-CRP) levels, with similar proportions observed for other periodontal parameters. These findings support the hypothesis that systemic inflammation represents a key pathway through which periodontal disease may contribute to atherogenesis. The inflammatory response to periodontal pathogens may induce systemic inflammation, which, in turn, promotes endothelial activation, leukocyte recruitment, and lipid deposition in arterial walls, facilitating atherosclerotic plaque formation(42). While our mediation analyses provide valuable insights, it is essential to acknowledge that multiple pathways likely contribute to the relationship between periodontal disease and cardiovascular health, including direct effects of periodontal pathogens, immune cross-reactivity, and shared genetic determinants(43).

The strengths of our study include the comprehensive assessment of periodontal status using multiple clinical parameters, the evaluation of a wide range of cardiovascular risk factors, and the rigorous adjustment for potential confounding factors. Additionally, the use of mediation analyses to explore potential mechanistic pathways represents a methodological advancement compared to many previous studies in this field. However, several limitations should be acknowledged. First, the cross-sectional design precludes the establishment of temporal relationships and causal inferences. While our findings support associations between periodontal disease and cardiovascular risk factors, longitudinal studies are needed to determine whether periodontal disease precedes the development of these risk factors or whether the relationships are bidirectional. Second, despite comprehensive adjustment for known confounding factors, residual confounding by unmeasured variables, such as dietary patterns, psychosocial factors, and genetic predispositions, cannot be excluded. Third, the study population was recruited from a single metropolitan area, potentially limiting the generalizability of our findings to other populations with different demographic and socioeconomic characteristics.

The clinical implications of our findings are substantial. The observed associations between periodontal disease and cardiovascular risk factors, particularly systemic inflammation and subclinical atherosclerosis, suggest that periodontal health may represent an additional consideration in cardiovascular risk assessment and management. Healthcare providers should be aware of the potential systemic implications of periodontal disease and consider comprehensive oral examinations as part of cardiovascular risk assessment, especially in individuals with multiple risk factors or unexplained

elevations in inflammatory markers. Conversely, dental professionals should recognize the potential cardiovascular implications of periodontal disease and consider appropriate referrals for cardiovascular risk assessment in patients with severe periodontal disease, particularly those with additional risk factors.

Furthermore, our findings highlight the potential importance of periodontal treatment in cardiovascular risk management. Although our cross-sectional study cannot address the effects of periodontal interventions, previous randomized controlled trials have demonstrated that intensive periodontal therapy can lead to improvements in endothelial function, reductions in systemic inflammatory markers, and favorable changes in blood pressure and lipid profiles (44, 45). A recent systematic review and meta-analysis of intervention studies by D'Aiuto et al.(46) reported that periodontal treatment resulted in a mean reduction in hs-CRP levels of 0.50 mg/L (95% CI: 0.15-0.85) and a mean decrease in systolic blood pressure of 3.36 mmHg (95% CI: 0.93-5.77) after 2-6 months. These findings suggest that periodontal treatment may represent a non-pharmacological approach to modifying cardiovascular risk factors. However, long-term studies with hard cardiovascular endpoints are needed to establish definitive clinical recommendations.

Future research directions should include large-scale longitudinal studies to establish temporal relationships between periodontal disease, inflammatory markers, and the development of cardiovascular risk factors and clinical events. Additionally, randomized controlled trials with extended follow-up periods are needed to evaluate the effects of periodontal interventions on cardiovascular outcomes. Such studies should incorporate a comprehensive assessment of potential mediating pathways, including inflammatory markers, endothelial function, and subclinical atherosclerosis, to elucidate the mechanisms through which periodontal health may influence cardiovascular risk. Furthermore, investigations into the potential synergistic effects of periodontal therapy and traditional cardiovascular risk factor management could provide insights into optimal integrated approaches to cardiovascular disease prevention.

Conclusion

In this cross-sectional study of adults without established cardiovascular disease, the severity of periodontal disease was independently associated with multiple cardiovascular risk factors, including elevated blood pressure, adverse lipid profiles, impaired glucose metabolism, systemic inflammation, and subclinical atherosclerosis, after adjusting for traditional risk factors and potential confounders. The relationship between periodontal disease and carotid intima-media thickness was partially mediated by systemic inflammatory markers, particularly high-sensitivity C-reactive protein, supporting the hypothesis that inflammatory pathways may represent a key link between oral and cardiovascular health.

These findings highlight the potential importance of periodontal health in cardiovascular risk assessment and management. Healthcare providers should consider the systemic implications of periodontal disease, and collaborative approaches between dental and medical professionals may enhance comprehensive cardiovascular risk management. Although our cross-sectional study cannot establish causality, the observed associations, supported by biological plausibility and previous intervention studies, suggest that maintaining periodontal health may represent a modifiable factor in the prevention of cardiovascular disease.

Future longitudinal studies and intervention trials with hard cardiovascular endpoints are needed to elucidate further the temporal relationships between periodontal disease and cardiovascular health and to determine the potential cardiovascular benefits of periodontal treatment. Such research may contribute to the development of integrated approaches to cardiovascular disease prevention that incorporate oral health as a component of overall cardiovascular risk management.

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