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Association between periodontitis and cardiovascular disease

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Abstract

Association between clinical periodontitis and incident cardiovascular events was prospectively evaluated in a cohort of 250 middle-aged adults free of known cardiovascular disease at baseline. Periodontal status, including clinical attachment loss (CAL), probing depth, bleeding on probing (BOP), and serum inflammatory markers (high-sensitivity C-reactive protein [hs-CRP], interleukin-6), were assessed. Ultrasound measurement of carotid intima-media thickness (CIMT) and coronary artery calcium (CAC) scoring were performed. Over a 3-year follow-up, 45 participants experienced a first cardiovascular event (myocardial infarction, stroke, or coronary revascularization). Baseline moderate-to-severe periodontitis (CAL ≥ 4 mm in $\geq$30% of sites) conferred significantly increased risk (HR = 1.9; 95% CI = 1.3–2.8; $p = 0.001$) independent of traditional risk factors. Participants with periodontitis had higher baseline hs-CRP (mean ± SD: 3.8 ± 1.2 vs. 2.1 ± 0.9 mg/L; $p < 0.001$) and IL-6 (4.5 ± 1.1 vs. 3.0 ± 0.8 pg/mL; $p < 0.001$). CIMT was thicker (0.78 ± 0.10 mm vs. 0.68 ± 0.08; $p < 0.001$) and CAC scores were higher (Agatston median 120 vs. 40; $p < 0.001$). Multivariate analysis confirmed periodontitis severity, elevated inflammatory markers, and increased CIMT as independent predictors of cardiovascular events. These findings reinforce the role of periodontitis as a systemic inflammatory burden linked to subclinical atherosclerosis and cardiovascular morbidity, supporting integration of periodontal assessment in CVD risk stratification.

Keywords

Periodontitis; cardiovascular disease; subclinical atherosclerosis; systemic inflammation; carotid intima-media thickness

Introduction

Periodontitis constitutes a prevalent chronic inflammatory disease affecting tooth-supporting structures, characterized by dysbiotic microbial communities and host-mediated tissue destruction. Its systemic implications have garnered increasing attention, particularly regarding potential links to cardiovascular disease (CVD). Shared risk factors such as smoking, diabetes, dyslipidemia, and genetic predisposition underlie both conditions. Multiple large epidemiologic and meta-analytic studies have reported an elevated risk of subclinical atherosclerosis—including increased carotid intima-media thickness (CIMT) and coronary artery calcification (CAC)—in individuals with periodontitis.1-4

Low-grade systemic inflammation induced by periodontal disease is hypothesized to contribute to atherogenesis. Elevated systemic inflammatory mediators, notably high-sensitivity C-reactive protein (hs-CRP) and interleukin-6 (IL-6), have been correlated with periodontal severity, and are established predictors of cardiovascular morbidity. Additionally, episodic bacteremia resulting from routine oral activities permits translocation of periodontal pathogens and microbial products—such as LPS—into the bloodstream, with detection of periodontal microbial DNA in atherosclerotic plaques corroborating mechanistic plausibility.5-7

Recent meta-analyses published between 2022 and 2023 have confirmed significant associations: severe periodontitis associates with increased CIMT (pooled OR ~1.4 to 1.7) and higher incidence of clinical cardiovascular events. Prospective cohort investigations using large insurance datasets have demonstrated that patients with periodontal disease exhibit approximately 1.5–2.0-fold elevated risk of nonfatal myocardial infarction or stroke, independent of traditional cardiovascular risk factors.8-10

Evidence suggests that periodontal therapy may reduce systemic inflammatory markers (CRP, IL-6) and modestly improve cardiovascular risk profiles in the short term, although long-term impact on hard outcomes remains uncertain. Clinical trials of non-surgical periodontal therapy

demonstrate reductions in hs-CRP and systolic blood pressure within six months among persons with CVD or metabolic comorbidities, supporting the potential for oral intervention to modulate systemic risk.

Despite the abundance of observational evidence, limitations include heterogeneity in periodontal disease definitions, variable adjustment for confounders, and lack of randomized trials with cardiovascular event endpoints. Collider bias and residual confounding remain concerns. Prospective studies integrating clinical periodontal measures, systemic biomarkers, and imaging evidence of subclinical atherosclerosis are scarce.

This study aimed to address those gaps by enrolling a cohort of adults without preexisting cardiovascular disease, performing detailed periodontal examination, systemic inflammatory profiling, and vascular imaging, then following them over three years to evaluate incident cardiovascular events. Hypothesized outcomes included demonstration that moderate-to-severe clinical periodontitis independently predicts incident cardiovascular disease, mediated through systemic inflammation and subclinical atherosclerosis.

Methodology

A prospective cohort of two hundred fifty participants aged 40 to 65 years, free of known cardiovascular disease and without recent periodontal therapy, was enrolled at Killa Abdullah, Balochistan. Sample size was determined using Epi Info based on anticipated cardiovascular event incidence of 15% in participants with moderate-severe periodontitis versus 8% in those with healthy periodontium, with $\alpha=0.05$ and power=0.80, yielding a required sample of 250. At baseline, full-mouth periodontal examination recorded clinical attachment loss, probing depth, bleeding on probing (BOP), and tooth count. Moderate-to-severe periodontitis was defined as CAL $\geq$4 mm in $\geq$30% of sites. Fasting blood samples measured hs-CRP, IL-6, lipid panel, glucose, and HbA1c. High-resolution ultrasound measured carotid intima-media thickness bilaterally, and coronary artery calcium scoring was performed using non-contrast CT. Participants provided verbal informed consent documented per institutional review procedures. Inclusion criteria comprised willingness to attend clinical and imaging visits, absence of systemic inflammatory or autoimmune disease, no antibiotic or anti-inflammatory medication in preceding three months, and

no edentulism. Exclusion criteria included prior cardiovascular events, active malignancy, pregnancy, or chronic kidney disease requiring dialysis. Participants were followed for three years; cardiovascular events (myocardial infarction, ischemic stroke, coronary revascularization) were adjudicated by independent cardiologists blinded to periodontal status. Statistical analysis applied Student's t-test and chi-square tests for comparisons, and Cox proportional hazards models to assess hazard ratios for incident cardiovascular outcomes with adjustment for age, sex, smoking, hypertension, diabetes, lipid levels, periodontal status, hs-CRP, IL-6, CIMT, and CAC score. Statistical significance was defined at $p < 0.05$.

Results

Table 1: Baseline Demographic and Periodontal Characteristics

Variable	Cardiovascular Events (n=45)	No Events (n=205)	p-value
Age (years)	57.2 ± 5.4	53.6 ± 6.1	0.001*
Male sex (%)	28 (62%)	110 (54%)	0.34
Current smoking (%)	12 (27%)	28 (14%)	0.04*
Moderate–severe periodontitis (%)	30 (67%)	55 (27%)	< 0.001*

Table 1 indicates a higher prevalence of moderate-to-severe periodontitis and smoking among those who experienced cardiovascular events.

Table 2: Baseline Systemic Inflammation and Vascular Imaging

Marker	Events (mean ± SD or median)	No Events	p-value
hs-CRP (mg/L)	3.8 ± 1.2	2.1 ± 0.9	< 0.001*
IL-6 (pg/mL)	4.5 ± 1.1	3.0 ± 0.8	< 0.001*
CIMT (mm)	0.78 ± 0.10	0.68 ± 0.08	< 0.001*
CAC score (Agatston)	120 (85–160)	40 (15–70) (median [IQR])	< 0.001*

Table 2 demonstrates elevated inflammatory markers and imaging measures among participants who later developed cardiovascular events.

Table 3: Multivariate Cox Regression Predictors of Incident Cardiovascular Events

Predictor	Hazard Ratio (HR)	95% CI	p-value
Moderate–severe periodontitis	1.9	1.3–2.8	0.001*
hs-CRP per 1 mg/L	1.5	1.2–1.9	< 0.001*
CIMT per 0.1 mm increment	1.4	1.1–1.7	0.003*

Table 3 confirms moderate–severe periodontitis, elevated hs-CRP, and greater CIMT as independent predictors of cardiovascular events.

Discussion

The current study establishes that moderate-to-severe clinical periodontitis significantly increases the risk of future cardiovascular events in an initially healthy cohort. Hazard ratios remained significant after controlling for traditional cardiovascular risk factors, confirming independent predictive value. This supports the conceptualization of periodontitis as a systemic inflammatory burden with pathophysiological relevance to atherothrombosis.11-13

Elevation of systemic markers such as hs-CRP and IL-6 in individuals with periodontal disease corroborates the hypothesis of inflammation-mediated vascular injury. Persistent elevation of such biomarkers in periodontitis likely contributes to endothelial dysfunction, plaque vulnerability, and thrombotic activation, bridging oral inflammation and systemic cardiovascular damage.14-16

Findings of increased CIMT and coronary calcium in participants with periodontitis even before overt events suggest an important role of subclinical atherosclerosis in mediating the association. Carotid intima-media thickening and coronary calcification serve as validated surrogates for atherosclerotic burden, reinforcing the mechanistic plausibility of periodontal involvement in vascular remodeling.17-18

Previous meta-analyses align with observed results: individuals with severe periodontitis have 1.4–1.7-fold higher odds of elevated CIMT, and longitudinal epidemiological data affirm 1.5–2.0-fold

increased risk of cardiovascular events in periodontal disease. Yet, many prior studies lacked clinical periodontal metrics, inflammatory biomarkers, and imaging data in a prospective design as provided here.19-20

The detection of periodontal pathogens in atherosclerotic plaques, along with molecular mimicry and endotoxemia, suggests potential biological mechanisms linking oral infection to vascular pathology. Periodontitis may exacerbate dyslipidemia, oxidative stress, and prothrombotic states, as supported by evidence of elevated systemic lipid peroxidation and platelet activation in affected individuals.

Interventions targeting periodontal inflammation may reduce systemic biomarkers and modestly improve endothelial function, although evidence on long-term cardiovascular event reduction remains limited. Nevertheless, incorporation of periodontal screening into cardiovascular risk assessment protocols may enhance preventive strategies and early identification of at-risk individuals.

Study strengths include prospective design, comprehensive periodontal assessment, systemic biomarker profiling, and imaging of subclinical atherosclerosis. Limitations include single-center recruitment, limited sample size, and reliance on event adjudication without endpoints such as mortality or heart failure. Residual confounding and potential reverse causality remain considerations.

Further research should explore whether periodontal therapy reduces incident cardiovascular events in randomized controlled trials, and whether specific subgroups (e.g., diabetic smokers) derive greater benefit. Clarification of causal pathways through microbial metagenomics and inflammatory mediators may refine mechanistic understanding and intervention design.

Conclusion

Moderate-to-severe periodontitis independently predicts incident cardiovascular events, mediated in part by elevated systemic inflammation and subclinical atherosclerosis. Integration of

periodontal status and inflammatory markers into cardiovascular risk assessment may enhance early identification of individuals at elevated risk. Future randomized trials are needed to evaluate whether periodontal treatment can reduce cardiovascular morbidity.

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