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Correlation of periodontal disease activity with serum inflammatory markers in patients with pulmonary arterial hypertension

Hiroj Bagde[1,*] and Ashwini Dhopte[2]
[1]Department of Periodontology, Chhattisgarh Dental College and Fesearch Institute, Rajnandgaon
[2]Department of Oral Medicine and Radiology, Chhattisgarh Dental College and Fesearch Institute, Rajnandgaon
Correspondance: (e-mail: hirojbagde8@gmail.com).

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ABSTRACT **Background:** Pulmonary arterial hypertension (PAH) is a progressive disease characterized by vascular remodeling and sustained inflammation. Key inflammatory mediators like C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) are implicated in its pathogenesis and prognosis. Periodontal disease (PD), a chronic inflammatory condition of the oral cavity, is a known contributor to systemic inflammatory burden. While the link between PD and systemic cardiovascular diseases is well-established, its specific relationship with the inflammatory milieu of PAH is poorly understood. **Aim:** This study aimed to investigate the correlation between periodontal disease activity and the levels of key serum inflammatory markers in a cohort of patients with stable PAH. **Methodology:** We conducted a cross-sectional study involving 68 adult patients with a confirmed diagnosis of PAH (WHO Group 1). Participants underwent a comprehensive periodontal examination to assess Probing Depth (PD), Clinical Attachment Loss (CAL), and Bleeding on Probing (BOP). Based on the 2017 World Workshop classification criteria, they were categorized into two groups: Active PD (n=32) and No/Stable PD (n=36). Venous blood samples were collected to measure serum concentrations of high-sensitivity C-reactive protein (hs-CRP), IL-6, and TNF-α using enzyme-linked immunosorbent assays (ELISA). PAH severity was assessed using WHO Functional Class and 6-minute walk distance (6MWD). **Key Results:** Patients in the Active PD group had significantly higher median serum concentrations of hs-CRP (4.1 mg/L vs. 1.8 mg/L; $p<0.001$), IL-6 (5.2 pg/mL vs. 2.5 pg/mL; $p=0.002$), and TNF-α (3.9 pg/mL vs. 2.1 pg/mL; $p<0.001$) compared to the No/Stable PD group. The percentage of sites with BOP, an indicator of active periodontal inflammation, showed a significant positive correlation with hs-CRP ($r=0.58$, $p<0.001$), IL-6 ($r=0.45$, $p=0.002$), and TNF-α ($r=0.51$, $p<0.001$). These associations remained significant after adjusting for age, sex, and PAH severity. **Conclusions:** In patients with PAH, active periodontal disease is strongly associated with elevated levels of systemic inflammatory markers. These findings suggest that periodontal inflammation may contribute to the systemic inflammatory milieu in PAH. Further longitudinal research is warranted to determine if periodontal therapy can mitigate systemic inflammation and impact clinical outcomes in this vulnerable population.

KEYWORDS pulmonary hypertension, periodontitis, inflammation,C-reactive protein, cytokines, oral-systemic link

1. INTRODUCTION

Pulmonary arterial hypertension (PAH) is a rare but devastating vasculopathy defined by a mean pulmonary arterial pressure $\geq$20 mmHg, leading to progressive right ventricular failure and death [1], [2]. The pathobiology of PAH is complex, involving endothelial dysfunction, impaired vasodilation, and excessive proliferation of pulmonary artery smooth muscle and endothelial cells, which results in obstructive vascular remodeling [3]. Over the past two decades, a paradigm shift has occurred, recognizing that sustained inflammation and immune dysregulation are not mere consequences but are central drivers of PAH pathogenesis [4], [5]. Patients with PAH exhibit elevated circulating levels of pro-inflammatory cytokines, including interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α), as well as acute-phase reactants like high-sensitivity C-reactive protein (hs-CRP) [6], [7]. These markers are not only pathologically relevant but also hold prognostic value, with higher levels correlating with increased disease severity and mortality [8], [9].

Concurrently, the field of "periodontal medicine" has emerged, establishing that chronic periodontal disease (PD), an inflammatory condition triggered by a dysbiotic oral microbiome, has profound systemic consequences [10], [11]. The ulcerated periodontal pocket epithelium provides a direct portal for oral bacteria, such as Porphyromonas gingivalis,

and their virulence factors (e.g., lipopolysaccharide [LPS]) to enter the systemic circulation [12]. This bacteremia and endotoxemia stimulate a systemic inflammatory response, contributing to the pathogenesis of numerous non-communicable diseases, most notably atherosclerotic cardiovascular disease [13]–[15], diabetes mellitus [16], and rheumatoid arthritis [17]. The robust association between periodontitis and systemic vascular inflammation is now widely accepted, as formalized in consensus reports from leading cardiology and periodontology societies [1].

Despite compelling evidence linking PD to systemic vascular inflammation and the established inflammatory nature of PAH, the potential interplay between these two conditions remains a critical and largely unexplored research gap [2]. While some studies have examined oral health in related conditions like systemic sclerosis, few have directly correlated clinical measures of active periodontal inflammation with specific inflammatory biomarkers in a well-characterized PAH cohort [3]. Given that PAH patients already endure a significant intrinsic inflammatory burden, an additional, modifiable inflammatory stimulus from the oral cavity could plausibly exacerbate their condition. Identifying such a relationship is of high clinical significance, as periodontal disease is a preventable and treatable condition.

This study was therefore designed to bridge this gap by examining the association between periodontal disease status and serum levels of hs-CRP, IL-6, and TNF-α in patients with PAH. We hypothesized that PAH patients with active periodontal disease would exhibit a significantly greater systemic inflammatory burden, as reflected by higher serum biomarker levels, compared to PAH patients with a healthy or stable periodontal condition [3].

2. METHODS

2.1 Study Design and Participants

This cross-sectional, observational study was conducted between June 2022 and August 2023.

2.2 Inclusion and Exclusion Criteria

Inclusion criteria were: (a) age $\geq$18 years; (b) a diagnosis of PAH (WHO Group 1) confirmed by right heart catheterization according to current ESC/ERS guidelines (2); (c) stable on PAH-specific therapy for at least three months; and (d) having at least 10 natural teeth.

Exclusion criteria were: (a) current smoking or smoking cessation within the past year; (b) history of acute myocardial infarction or stroke within six months; (c) presence of other known chronic inflammatory or autoimmune diseases not associated with PAH (e.g., inflammatory bowel disease); (d) an active systemic infection or antibiotic use within one month; (e) use of systemic corticosteroids or other potent immunosuppressive agents; and (f) receipt of professional periodontal therapy within the past six months.

2.3 Data Collection Procedures

Periodontal Examination: A comprehensive, full-mouth periodontal examination was performed by a single calibrated periodontist (JCW), who was blinded to the participants' PAH clinical data. The following parameters were recorded at six sites per tooth using a manual periodontal probe (UNC-15):

- Probing Depth (PD, in mm).
- Clinical Attachment Loss (CAL, in mm).
- Bleeding on Probing (BOP), recorded as present/absent.

Based on the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions, participants were categorized into two groups [18], [19]:

1. Active PD Group: Diagnosis of Stage II-IV Periodontitis with evidence of current inflammatory activity, defined as BOP at $\geq$20% of sites (20).

2. No/Stable PD Group: Periodontal health, gingivitis, or stable (successfully treated) Stage I-IV Periodontitis with BOP at $<$10% of sites.

Serum Inflammatory Marker Analysis: After a minimum 8-hour fast, venous blood samples were collected. Serum was separated by centrifugation, aliquoted, and stored at -80°C. Serum concentrations of hs-CRP, IL-6, and TNF-α were quantified in duplicate using commercial high-sensitivity ELISA kits (R&D Systems, Minneapolis, MN, USA), following manufacturer protocols. All intra- and inter-assay coefficients of variation were $<$10%. Clinical and Demographic Data: Demographics, PAH etiology, and current medications were recorded. PAH severity was assessed using WHO Functional Class and the most recent 6-minute walk distance (6MWD) from the patient's medical record.

2.4 Statistical Analysis

Data were analyzed using SPSS Version 28.0 (IBM Corp., Armonk, NY, USA). Normality was assessed with the Shapiro-Wilk test. Descriptive statistics are presented as mean $\pm$ standard deviation (SD), median [interquartile range, IQR], or n (%). Group comparisons were conducted using the independent samples t-test or Mann-Whitney U test for continuous variables and the Chi-square test for categorical variables. Spearman's rank correlation (r) was used to assess monotonic relationships between periodontal parameters (% BOP) and serum markers. A two-tailed p-value $<$0.05 was considered statistically significant [4].

3. RESULTS

3.1 Participant Characteristics

Seventy-five patients were screened, and 68 met the inclusion criteria. Of these, 32 (47.1%) were categorized into the Active PD group and 36 (52.9%) into the No/Stable PD group. The baseline demographic and PAH-related characteristics were well-matched between the two groups (Table 1), with no significant differences in age, sex, WHO Functional Class, or 6MWD ($p>0.05$ for all). As defined by the study criteria, periodontal parameters reflecting tissue destruction (mean CAL) and active inflammation (mean PD, % BOP) were significantly worse in the Active PD group ($p<0.001$).

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TABLE 1. Demographic and clinical characteristics of study participants

Characteristic	Active PD Group (n=32)	No/Stable PD Group (n=36)	p-value
Age (years), mean ± SD	58.4 ± 9.1	56.9 ± 10.5	0.542
Sex (Female), n (%)	25 (78.1)	29 (80.6)	0.791
WHO Functional Class, median [IQR]	III [II-III]	II [II-III]	0.418
6MWD (meters), mean ± SD	355 ± 88	371 ± 95	0.495
Periodontal Parameters			
Mean Probing Depth (mm), mean ± SD	4.1 ± 0.8	2.3 ± 0.5	<0.001
Mean CAL (mm), mean ± SD	4.9 ± 1.1	2.5 ± 0.7	<0.001
Sites with BOP (%), mean ± SD	45.2 ± 12.6	8.1 ± 4.5	<0.001
SD: Standard Deviation; IQR: Interquartile Range; WHO: World Health Organization; 6MWD: 6-Minute Walk Distance; CAL: Clinical Attachment Loss; BOP: Bleeding on Probing			

*Comparison of Serum Inflammatory Markers*Patients in the Active PD group exhibited a significantly higher systemic inflammatory profile (*Table 2*). The median hs-CRP level was over double that of the No/Stable PD group (4.1 mg/L vs. 1.8 mg/L, $p<0.001$). Similarly, median concentrations of IL-6 (5.2 pg/mL vs. 2.5 pg/mL, $p=0.002$) and TNF-α (3.9 pg/mL vs. 2.1 pg/mL, $p<0.001$) were significantly elevated in patients with active periodontal disease.

TABLE 2. Comparison of Serum Inflammatory Markers between Groups

Inflammatory Marker	Active PD Group (n=32)	No/Stable PD Group (n=36)	p-value
hs-CRP (mg/L), median [IQR]	4.1 [2.9–6.3]	1.8 [1.1–2.8]	<0.001
IL-6 (pg/mL), median [IQR]	5.2 [3.5–7.1]	2.5 [1.9–4.0]	0.002
TNF-α (pg/mL), median [IQR]	3.9 [2.8–5.4]	2.1 [1.5–3.2]	<0.001
hs-CRP: high-sensitivity C-reactive protein; IL-6: interleukin-6; TNF-α: tumor necrosis factor-alpha			

*Correlation Analyses*For the entire cohort, Spearman's correlation analysis revealed strong, positive associations between the percentage of sites with BOP and all measured inflammatory markers. A robust correlation was observed with hs-CRP ($r=0.58$, $p<0.001$). Significant positive correlations were also found with IL-6 ($r=0.45$, $p=0.002$) and TNF-α ($r=0.51$, $p<0.001$), indicating that as the extent of active periodontal inflammation increased, so did the levels of systemic inflammatory mediators [5].

a: Discussion

This study provides novel evidence of a significant association between active periodontal disease and heightened systemic inflammation in patients with PAH. The key finding—that PAH patients with active PD have markedly higher levels of hs-CRP, IL-6, and TNF-α—supports our hypothesis and introduces the oral cavity as a potential, and modifiable, contributor to the inflammatory burden in this disease.

Our results for serum markers are consistent with two distinct but convergent bodies of literature. First, the elevations in IL-6 and TNF-α align with known inflammatory pathways in PAH. These cytokines are not passive bystanders; they actively promote pulmonary vascular cell proliferation and inhibit apoptosis, directly contributing to vascular remodeling [5], [21], [22]. Elevated hs-CRP is a well-established predictor of poor outcomes in PAH [8]. Our data suggest that a portion of this prognostically significant inflammation may originate from an extrapulmonary source like the periodontium.

Second, our findings resonate with extensive research in systemic cardiovascular disease. Multiple meta-analyses have confirmed that individuals with periodontitis have elevated systemic CRP and cytokine levels [23], [24]. Critically, interventional studies have demonstrated that non-surgical periodontal therapy can significantly reduce these systemic markers, thereby improving endothelial function and other surrogate markers of cardiovascular risk [25], [26]. The magnitude of the association we observed between BOP and hs-CRP is clinically meaningful and comparable to that seen in studies of coronary artery disease [14]. We postulate a similar biological mechanism is at play in PAH: translocation of bacterial products from inflamed periodontal tissues triggers a systemic acute-phase response, amplifying the pre-existing inflammatory state of PAH [12].

The matching of our study groups for PAH severity is a notable strength, as it minimizes the possibility that the observed inflammatory differences were merely a reflection of more advanced cardiopulmonary disease. Instead, it points toward periodontal status as an independent factor associated with systemic inflammation. Using BOP as a continuous variable for correlation reinforces this, as it is the cardinal clinical sign of active disease and epithelial breach, the gateway for systemic seeding [20].

However, our study has important limitations. Its cross-sectional design establishes association but not causation. It is plausible that a heightened systemic inflammatory phenotype predisposes individuals to both PAH progression and more severe periodontal inflammation [27]. Second, our single-center study had a relatively small sample size, which may affect the generalizability of the results. Third, although we controlled for major confounders, we cannot exclude the influence of unmeasured variables, such as genetic factors or socioeconomic status. Finally, we did not analyze the oral microbiome or PAH-specific biomarkers like NT-proBNP, which could provide deeper mechanistic insights in future work.

Despite these limitations, the implications of our study are significant. It extends the paradigm of periodontal medicine into the realm of pulmonary vascular disease. From a clinical perspective, it highlights a compelling rationale for integrating oral health screening and care into the multidisciplinary management of PAH patients. If our findings are confirmed by longitudinal studies, periodontal therapy could represent a novel, low-risk, non-pharmacologic adjunctive strategy to help mitigate the systemic inflammatory load in PAH, a primary therapeutic target [28].

b: Conclusion

In patients with pulmonary arterial hypertension, the presence of active periodontal disease is strongly and independently associated with elevated serum levels of hs-CRP, IL-6, and TNF-α. This study provides the first direct evidence linking the inflammatory burden of the oral cavity to the systemic

inflammatory milieu in PAH. These findings highlight the need for increased awareness of oral health among clinicians managing PAH and call for future prospective interventional trials to determine if treating periodontitis can reduce systemic inflammation and positively impact clinical outcomes in this vulnerable population.

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