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Association Between Periodontal Disease and Blood Biomarkers in U.S. Adults: A Cross-Sectional Study

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Abstract

(1) **Background**: Periodontal disease (PD) is a chronic inflammatory condition with potential systemic manifestations. This study examined the association between PD and selected blood biomarkers—white blood cell (WBC) count, serum albumin, and mean corpuscular hemoglobin concentration (MCHC)—using nationally representative data from the 2013–2014 National Health and Nutrition Examination Survey (NHANES). (2) **Methods**: Cross sectional data from the 2013–2014 National Health and Nutrition Examination Survey (NHANES) were analyzed. Periodontitis was defined per CDC/AAP. Three weighted multivariable logistic regression models determined the association between blood benzene levels and periodontal severity, adjusting for potential confounders. Among 4669 participants, 37.2% had PD (3) **Results**: In multivariable-adjusted models, individuals with higher white blood cell counts (OR = 1.08; 95% CI: 1.04–1.11; $p < 0.001$) and higher MCHC values (OR = 1.14; 95% CI: 1.06–1.22; $p < 0.001$) exhibited greater odds of periodontal disease, whereas lower serum albumin levels were independently associated with PD (OR = 0.76; 95% CI: 0.62–0.93; $p = 0.011$), after adjustment for demographic, socioeconomic, and behavioral covariates. (4) **Conclusions**: These findings suggest a statistical association between PD and systemic hematologic alterations in U.S. adults. However, due to the cross-sectional nature of this study, causal relationships cannot be inferred, and further longitudinal studies are needed to understand the mechanisms between PD and blood biomarkers.

Keywords: periodontal disease; blood biomarkers; WBC; Serum albumin; MCHC

1. Introduction

Periodontal disease (PD) is a prevalent chronic inflammatory condition that affects the supporting structures of the teeth, including the gingiva, periodontal ligament, and alveolar bone [1–3]. It is one of the most common oral diseases globally and is a leading cause of tooth loss in adults [1–3]. According to the Centers for Disease Control and Prevention (CDC), about 42% of U.S. adults aged 30 years and older exhibit signs of periodontal disease, with prevalence increasing with age [4]. Research has shown that PD has been a potential contributor to systemic inflammation and has been linked to various chronic conditions, including diabetes, cardiovascular disease, and chronic kidney disease [5].

The pathogenesis of PD is initiated by sub-gingival microbial biofilms that trigger a host immune response, resulting in tissue destruction when left unresolved [6]. This immune response is not only confined to the oral cavity but also may elicit systemic alterations in inflammatory and metabolic markers detectable in peripheral blood [7,8]. As such, blood-based biomarkers have gained attention as non-invasive indicators of the systemic impact of PD [7,8]. These biomarkers are routinely measured in clinical practice, making them accessible for population-level screening and research [7,8].

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Among these, white blood cell (WBC) count is a widely used measure of systemic inflammation and immune activation [9,10]. Elevated WBC counts have been linked to periodontal tissue destruction, reflecting the mobilization of leukocytes in response to chronic microbial challenge [11,12]. Serum albumin, the most abundant plasma protein, serves as a negative acute-phase reactant, and its levels may reflect both nutritional depletion and the severity of systemic inflammation [13,14]. Studies have shown that serum albumin levels may decrease during systemic inflammation due to cytokine-mediated suppression of hepatic synthesis [15]. Additionally, lower serum albumin concentrations have been reported in individuals with chronic inflammatory diseases, including periodontitis [16]. Mean corpuscular hemoglobin concentration (MCHC), which represents the average hemoglobin concentration within red blood cells, provides insight into erythrocyte hemoglobinization and iron metabolism [17,18]. Elevated MCHC may reflect subtle shifts in iron handling and redox balance, as hemoglobin concentration within red cells is influenced by systemic iron metabolism and inflammatory signals [17,18]. Alterations in MCHC are observed in anemia of chronic disease, a condition influenced by sustained inflammatory cytokine activity, and have been associated with periodontitis in clinical studies [19].

Despite multiple studies linking periodontal status to systemic inflammatory markers, these investigations typically assess isolated indices (e.g., leukocyte counts or CRP) in convenience or disease-specific cohorts. To our knowledge, few studies—particularly those leveraging nationally representative datasets such as NHANES—have jointly evaluated white blood cell count, serum albumin, and MCHC in relation to periodontal disease [20,21]. In addition, although several reviews and studies have explored the pathophysiology of anemia of chronic disease, disturbances in iron metabolism, and the relationship between anemia and periodontitis, most have focused on broader hematologic parameters such as hemoglobin, hematocrit, and red blood cell count, without specifically addressing MCHC [22,23].

To address this gap, the present study aims to investigate the association between periodontal disease and three systemic blood biomarkers, including WBC count, serum albumin, and MCHC using data from the 2013–2014 National Health and Nutrition Examination Survey (NHANES). This analysis looks to better understand the systemic inflammatory and metabolic profile of individuals with periodontal disease, and to explore whether these biomarkers may serve as potential indicators of oral-systemic health interaction in the general U.S. adult population. We hypothesize that individuals with periodontal disease exhibit higher WBC counts, lower serum albumin levels, and altered MCHC values, potentially due to systemic inflammatory and hematologic responses associated with chronic periodontal inflammation.

2. Materials and Methods

2.1. Study Population

In this cross-sectional study, data was utilized from the 2013–2014 NHANES, a nationally representative survey of the non-institutionalized civilian population in the United States. The NHANES, conducted by the National Center for Health Statistics, Centers for Disease Control and Prevention, employs a complex probability sampling design involving multiple stages, stratification, and clustering. The NHANES sampling strategy includes stratification by demographic and geographic characteristics, cluster sampling within primary sampling units (PSUs), oversampling of specific population subgroups (e.g. non-Hispanic Black, Hispanic, Asian, and older adults) to ensure statistical reliability for these groups and use of sampling weights in analyses to adjust for unequal probabilities of selection, nonresponse, and post-stratification.

The NHANES collects data on various health outcomes and explanatory variables through a combination of interviews, laboratory tests, and clinical examinations. As a component of the NHANES, trained and calibrated dental professionals conducted comprehensive periodontal examinations on survey participants aged 30 years and older within the Mobile Examination Centers. All participants provided written informed consent. This study used publicly available, de-identified

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NHANES data and was therefore classified as secondary data analysis, exempt from Institutional Review Board (IRB) review. The study followed the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines. Nationally representative estimates were obtained by incorporating NHANES sample weights, strata, and primary sampling units (PSUs) in all analyses.

2.2.1. Eligibility Criteria

Inclusion Criteria:

1. Adults aged ⩾ 30 years, consistent with NHANES eligibility for full-mouth periodontal examinations.
2. Participants with complete periodontal clinical data, including probing depth (PD) and clinical attachment loss (CAL).
3. Participants with available data on the biomarkers of interest: white blood cell count, serum albumin, and mean corpuscular hemoglobin concentration
4. Individuals with available data on key covariates: age, sex, race/ethnicity, education level, smoking, any disease.

Exclusion Criteria:

1. Participants under 30 years old, since they were not eligible for the FMPE (Full-Mouth Periodontal Examination).
2. Individuals with missing periodontal examination data (non-examined or incomplete exam).
3. Individuals with missing values for biomarkers (WBC, serum albumin, MCHC).
4. Individuals with conditions requiring antibiotic prophylaxis prior to dental exams (excluded by NHANES protocols).
5. Participants with missing key covariates (e.g., demographic or health-related confounders).
6. Pregnant women (NHANES typically excludes them from some blood measures due to physiologic changes, and many biomarker analyses remove them to avoid bias).

2.2. Periodontal Examination

The NHANES study of 2013 to 2014 was conducted using a full-mouth periodontal examination (FMPE) among individuals aged ⩾ 30 years who did not have a health condition that required antibiotic prophylaxis before periodontal testing. The FMPE was conducted with the intent to produce gold-standard assessments for clinical attachment loss (AL). For this reason, direct measurements of both the distance between the cemento-enamel junction and the free gingival margin (CEJ-FGM) and the probing depth (PD) were measured at each site. All measurements were taken at six sites (mesiobuccal, midbuccal, distobuccal, mesiolingual, midlin-gual, and distolingual) of all teeth with the exclusion of third molars. All calculations were rounded to the lower whole millimeter. Clinical AL was calculated based on these two measurements.

2.3. Definition of the Dependent Variable: Periodontal disease

Periodontitis was used as a categorical variable with four categories: no periodontitis, mild periodontitis, moderate periodontitis, and severe periodontitis. The categorization was based on clinical attachment loss (CAL) and probing pocket depth (PPD) in accordance with the latest guidelines from the American Academy of Periodontology (AAP) and the Centers for Disease Control and Prevention (CDC) [24]. Severe periodontitis was defined as having two or more interproximal sites with CAL of 6 mm or greater and one or more interproximal sites with PPD of 5 mm or greater. Moderate periodontitis was characterized by having two or more interproximal sites with CAL of 4 mm or greater or two or more interproximal sites with PPD of 5 mm or greater. Mild periodontitis was defined as having two or more interproximal sites with CAL of 3 mm or greater

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and two or more interproximal sites with PPD of 4 mm or greater (not on the same tooth) or one or more sites with PPD of 5 mm or greater. No periodontitis was defined If none of the above thresholds are met.

2.3. Description of Independent Variable: Blood biomarkers

2.3.1. White Blood Cell Count

White blood cell (WBC) count was obtained from the NHANES Complete Blood Count (CBC) laboratory component (variable IBXWBCSI). WBC was treated as continuous variable, reported in 10^3 cells/μL of whole blood. Measurements were performed using an automated hematology analyzer (Coulter® DxH 800).

2.3.2. Serum Albumin

Serum albumin was obtained from the NHANES Biochemistry Profile laboratory component (variable IBXSAL). It was treated as a continuous variable, reported in grams per deciliter (g/dL). Measurements were performed using a colorimetric bromocresol purple dye–binding method on a Roche/Hitachi Modular P Chemistry Analyzer.

2.3.3. Mean Corpuscular Hemoglobin Concentration

Mean corpuscular hemoglobin concentration (MCHC) was obtained from the NHANES Complete Blood Count (CBC) laboratory component (variable IBXMC). It was treated as a continuous variable, reported in grams per deciliter (g/dL). MCHC was calculated by the Coulter® DxH 800 Hematology Analyzer as part of the automated complete blood count.

2.4. Potential Confounding Variable

In this study, several demographic and health-related variables were categorized for analysis. Age was grouped into four categories: 30–34 years, 35–49 years, 50–64 years, and 65 years or older. Sex was classified as a binary variable (male or female) while race was treated as a nominal variable with categories including "Non-Hispanic White", "Non-Hispanic Black", "Hispanic", "Non-Hispanic Asian", and "Other" races. Education level was divided into three categories: less than high school, high school graduate or equivalent (including GED), and more than high school education.

2.5. Statistical Methods

Descriptive statistics were used to summarize the study population. Categorical variables were compared using chi-square tests, and continuous variables using t-tests. A stepwise multivariate logistic regression approach was then employed to identify routine blood biomarkers associated with periodontal disease. Demographic variables and established risk factors (age, sex, race/ethnicity, education, income-to-poverty ratio, smoking, and comorbidities including diabetes) were retained in all models to control for confounding. Candidate biomarkers were entered using a liberal entry criterion ($p < 0.20$) and excluded if ≥ 0.20, ensuring comprehensive evaluation while maintaining parsimony. Multicollinearity was assessed using Pearson correlations, with highly correlated variables ($r > 0.5$) evaluated and redundant measures removed based on biological rationale. The final weighted model incorporated NHANES sampling weights, strata, and primary sampling units (PSUs) to account for the complex multistage probability sampling design, producing nationally representative estimates. Associations between biomarkers and periodontal disease were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). A two-sided p value < 0.05 was considered statistically significant. All analyses were performed using STATA 17.0 (StataCorp LLC., College Station, TX, USA).

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3. Results

Table 1 summarizes the weighted characteristics of the study population by periodontal disease status. Of the 4669 participants, 1739 (37.2%) had periodontal disease. The prevalence of periodontal disease varied by sex ($p < 0.001$), with 45.0% of males compared to 30.3% of females affected. Across age groups ($p < 0.001$), prevalence ranged from 29.3% among those aged 30–34 years to 38.8% among those aged 65 years or older. Differences were also observed by race/ethnicity ($p < 0.001$), with higher prevalence among Hispanics (43.7%) and non-Hispanic Blacks (43.1%) compared to non-Hispanic Whites (31.3%). By education level ($p < 0.001$), prevalence was 45.9% among those with less than a high school education, 43.4% among high school/GED, and 31.2% among those with college or more. Smoking status ($p < 0.001$) showed 43.0% prevalence among smokers compared to 32.4% among non-smokers. Household income relative to the Federal Poverty Level ($p < 0.001$) showed higher prevalence in the lowest income group (<138% FPL: 43.9%) compared to 39.0% in the 138–399% group and 29.0% in those with ≥400% of FPL. The prevalence of periodontal disease did not differ meaningfully by comorbidity status ($p = 0.356$), with 38.0% among those reporting any disease and 36.7% among those without.

Table 1. Descriptive summary of population characteristics: Comparison with and without periodontal disease.

Covariate	No Periodontal Disease N=2930	Periodontal Disease N=1739	Total N=4669	P-Value
Sex				
male	1221 (29.1%)	995 (18.5 %)	2216 (47.6%)	
female	1709 (38.5%)	744 (13.8%)	2453 (100%)	<0.001
Age				
30-34	354 (8.1%)	147 (2.8%)	501 (52.3%)	
35-49	982 (23.4%)	485 (9.9%)	1467 (10.9%)	
50-64	817 (20.76%)	619 (11.85%)	1436 (33.3%)	<0.001
65+	777 (15.3%)	488 (7.7 %)	1265 (23%)	
Race				
Non-Hispanic White	1402 (48.4%)	638 (19.5%)	2040 (67.9%)	
Non-Hispanic Black	539 (6.5%)	409 (4.5%)	948 (11%)	
Hispanic	574 (7.8%)	445 (5.5 %)	1019 (13.3%)	
Non-Hispanic Asian	341 (3.3%)	206 (2 %)	547 (5.3%)	<0.001
Other	74 (64.35%)	41 (0.85%)	115 (2.3%)	
Education				
< High School	563 (8.7%)	479 (6.7 %)	1042 (15.4%)	
High School/GED	593 (12.7%)	454 (8.6%)	1047 (21.4%)	<0.001
College or More	1772 (46.1%)	804 (16.9%)	2576 (63%)	
Smoking				
No	1716 (39.6%)	824 (14.8 %)	2540 (54.4%)	
Yes	1214 (28%)	915 (17.5%)	2129 (45.5%)	<0.001
Family Income Ratio to FPL				
<138%	826 (12.6%)	646 (9.3%)	1472 (21.9%)	
138%-399%	1012 (23.5)	646 (13.2%)	1658 (36.7%)	<0.001
>400%	1092 (31.4)	447 (9.8)	1539 (41.2)	
Any disease				
No	1626 (37.5%)	942 (17.1%)	2568 (54.6%)	
Yes	1294 (30%)	793 (15.2 %)	2087 (45.3%)	0.356

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Table 2 presents the comparison of routine blood parameters between participants with and without periodontitis. Positive differences were observed, with higher white blood cell counts and mean corpuscular hemoglobin concentration (MCHC), but lower serum albumin levels among individuals with periodontitis compared with those without.

Table 2. Comparison of routine blood parameters between participants with and without periodontitis.

Variable (Total N)	No Periodontitis (n, Mean ± SD)	Periodontitis (n, Mean ± SD)	P-Value
White Blood Cells (10^3 cells/μL) (N = 4504)	2,817, 7.18 ± 2.21	1,687, 7.49 ± 2.53	<0.001
Serum Albumin (g/dL) (N=4449)	2,776, 4.23 ± 0.33	1,673, 4.20 ± 0.32	0.0067
MCHC (g/dL) (N = 4,504)	2,817, 33.71 ± 0.95	1,687, 33.84 ± 1.37	0.0003

Table 3 displays the results from the weighted multiple Poisson regression model showing the association between periodontal disease and WBC, serum albumin, and MCHC in the United States, 2013–2014. Positive associations were observed for higher white blood cell counts (OR = 1.08, 95% CI: 1.04–1.11, p < 0.001), higher mean corpuscular hemoglobin concentration (MCHC; OR = 1.14, 95% CI: 1.06–1.22, p < 0.001), and race/ethnicity, with greater odds among non-Hispanic Black (OR = 1.93, 95% CI: 1.60–2.32, p < 0.001), Hispanic (OR = 1.69, 95% CI: 1.42–2.01, p < 0.001), and non-Hispanic Asian participants (OR = 1.81, 95% CI: 1.46–2.25, p < 0.001) compared with non-Hispanic Whites. Participants aged 45–64 (OR = 1.95, 95% CI: 1.53–2.49, p < 0.001) and ≥65 years (OR = 1.74, 95% CI: 1.35–2.26, p < 0.001) also had higher odds of periodontitis compared with those aged 30–34 years. Lower odds were observed for serum albumin (OR = 0.76, 95% CI: 0.62–0.94, p = 0.011), higher income levels (OR = 0.61, 95% CI: 0.51–0.72, p < 0.001 for ≥400% FPL), and those with some college education or more (OR = 0.73, 95% CI: 0.61–0.87, p = 0.001). Female sex was also associated with lower odds compared with males (OR = 0.55, 95% CI: 0.48–0.63, p < 0.001). Smoking showed a positive association with periodontitis (OR = 1.31, 95% CI: 1.15–1.50, p < 0.01).

Table 3. Multiple Logistic regression model for the association between PD and WBC count, serum albumin and MCHC.

Covariate	Odds Ratio	Composite		p Value
		Confidence Interval		
		Lower	Upper	
White blood cells	1.075	1.044	1.107	<0.001
Serum albumin	0.760	0.615	0.939	0.011
MCHC	1.138	1.062	1.219	<0.001
Sex (reference: Male)	0.551	0.481	0.631	<0.001
Education (reference: <high school)				
High school/GED	1.006	0.832	1.217	0.947
Some college or more	0.734	0.616	0.874	0.001
Poverty (reference: <138 FPL)				
138%-399%	0.883	0.754	1.035	0.127
>400%	0.608	0.511	0.724	<0.001
Race (reference: Non-Hispanic White)				
Non-Hispanic Black	1.927	1.600	2.321	<0.001
Hispanic	1.689	1.416	2.014	<0.001
Non-Hispanic Asian	1.811	1.455	2.253	<0.001
Other	1.338	0.909	2.118	0.128

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Smoking (reference: No Smoking)	1.311	1.146	1.500	<0.01
Any Disease (reference: No Disease)	0.906	0.781	1.050	0.190

4. Discussion

In this nationally representative analysis of U.S. adults, we observed positive associations between three selected blood biomarkers (WBC, serum albumin, and MCHC) and periodontal disease. Higher WBC counts and increased MCHC were positively associated with periodontal disease, suggesting heightened systemic immune activation and altered erythropoiesis in affected individuals. Conversely, serum albumin was inversely associated with periodontal disease, with lower levels observed among those with the condition, consistent with its role as a negative acute-phase reactant.

Our findings for white blood cell (WBC) count and serum albumin are consistent with previous population-based studies that have demonstrated robust associations between systemic blood biomarkers and periodontal disease. Specifically, we observed higher WBC counts and lower serum albumin concentrations among individuals with periodontitis, in agreement with earlier population data. In contrast, our analysis identified elevated mean corpuscular hemoglobin concentration (MCHC) values in association with periodontitis—a result that diverges from most prior reports, which have commonly described reduced MCHC in chronic inflammatory conditions. This discrepancy may be attributable to population-specific characteristics, residual confounding, or biological variability in erythrocyte indices, and therefore warrants further investigation.

Several previous studies have reported similar trends in other populations. A recent cross-sectional study conducted in Germany found that patients with poor periodontal health exhibited higher systemic leukocyte counts and lower serum albumin levels, even in the absence of acute systemic inflammation [25]. Likewise, Tonetti et al., using data from the National Health and Nutrition Examination Survey (NHANES), reported that increasing periodontal disease severity corresponded with higher circulating neutrophil counts, suggesting an extension of local inflammation into systemic circulation [26]. Furthermore, multiple investigations have demonstrated that serum albumin, a negative acute-phase reactant, declines with increasing periodontal inflammation and probing depth, likely reflecting systemic inflammatory activity [27,28]. Conversely, cross-sectional studies have shown that reduced MCHC levels were present among individuals with periodontal disease, indicating a potential link between anemia-related hematologic alterations and periodontal pathology [29,30]. The consistent direction observed across most populations supports the concept that decreased MCHC aligns with anemia of chronic disease rather than hyperchromic changes [29,30].

Several mechanistic pathways may explain the association between blood-based biomarkers and periodontal disease. Research has shown that PD is initiated by a dysbiotic oral microbiota, particularly gram-negative anaerobes such as *Porphyromonas gingivalis, Treponema denticola, and Tannerella forsythia* [31]. These pathogens may stimulate pattern recognition receptors (PRRs), including Toll-like receptors (TLRs), on resident immune and epithelial cells such as neutrophils, monocytes, and lymphocytes [32,33]. Activation of these receptors may trigger the release of pro-inflammatory cytokines (C-reactive protein, IL-6, IL-1β, TNF-α), which may drive chemotactic signaling and attract neutrophils to the periodontal sulcus [32,33].

The bone marrow may also respond with increased production and release of segmented neutrophils, elevating their percentage in peripheral blood and numbers in the gingival crevicular fluid (GCF) [34]. Studies have shown that upon arrival at the periodontal site, neutrophils may attempt to phagocytose periodontal pathogens, initiate the oxidative burst, produce reactive oxygen species (ROS) [35]. Furthermore, in healthy periodontium, once the microbial threat is cleared, neutrophils may undergo apoptosis and are removed by macrophages, leading to resolution of inflammation [36]. However, in periodontitis, neutrophils may exhibit delayed apoptosis or hyper-responsiveness, resulting in prolonged activation at the site [37]. This chronic activation may lead to sustained release of ROS and proteolytic enzymes, which may contribute to tissue destruction, pocket

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formation, and bone loss [35,38]. Additionally, elevated neutrophils count in peripheral blood may represent a systemic spillover of local periodontal inflammation and a pro-inflammatory systemic phenotype [39,40]. This is particularly relevant for individuals with comorbidities such as diabetes or cardiovascular disease [39,40].

Previous studies have demonstrated that during periodontitis, monocytes migrating into gingival tissues can differentiate into pro-inflammatory macrophages (M1 type) and osteoclast precursors [41–43]. On one hand, M1 macrophages may secrete high levels of IL-1β, TNF-α, and matrix metalloproteinases (MMPs), which may degrade extracellular matrix, destroy connective tissue, and exacerbate alveolar bone loss [41–43]. On the other hand, monocytes may also differentiate into osteoclasts in the presence of RANKL (Receptor Activator of Nuclear Factor κB Ligand) and M-CSF (Macrophage Colony Stimulating Factor), driving bone resorption in periodontitis [41–43]. This mechanism is crucial for the irreversible alveolar bone loss that characterizes stage III and IV in advanced periodontal disease [41–43].

Research has demonstrated that in chronic periodontitis, some activated monocytes may spill into systemic circulation, contributing to low-grade systemic inflammation [44,45]. These circulating monocytes may also express high levels of adhesion molecules and infiltrate vascular tissues, and link periodontal inflammation to comorbidities such as cardiovascular disease and diabetes mellitus [44,45]. Recent evidence further suggests that periodontal pathogens may epigenetically reprogram monocytes, promote "trained immunity," and generate hyper-responsive monocytes upon secondary stimulation [46]. Such reprogramming may amplify systemic inflammation, worsen immune aggressiveness at distant sites, and exacerbate systemic comorbidities [47].

Studies have shown that pro-inflammatory cytokines such as IL-6, TNF-α, and IL-1β, released from inflamed periodontal tissues, may downregulate hepatic synthesis of albumin [48,49]. This may result in lower serum albumin concentrations in patients with PD compared to periodontally healthy individuals [48,49].

Research has found that hypoalbuminemia may reflect malnutrition or frailty, which may compromise oral health and exacerbate periodontal disease [50,51]. Conversely, chronic periodontitis may impair chewing efficiency and nutrient intake, aggravate nutritional deficits and reduce serum albumin levels [52]. As such, albumin may act as a bi-directional marker, linking poor nutrition and periodontal inflammation [52].

Recent evidence has shown that albumin has a major role as a plasma antioxidant, binding free radicals, heavy metals, and advanced glycation end-products (AGEs) [53]. In periodontitis, oxidative stress may elevate due to overactivation of neutrophils and chronic infection [54]. As a result, consumption of albumin as an antioxidant defense mechanism may deplete its levels in circulation [54]. Recent evidence highlight that antioxidant therapies may help in inflammation resolution [55]. Additionally, studies have shown that low serum albumin is associated with vascular dysfunction, atherosclerosis, and chronic kidney disease, which may share inflammatory pathways with periodontal disease [56]. Moreover, periodontitis may amplify systemic endothelial injury, indirectly lowering albumin via the acute-phase response [57]. This may contribute to the oral-systemic connection, where albumin decline mirrors broader inflammatory burden [56,57].

According to recent evidence, pro-inflammatory cytokines produced in periodontitis may disrupt iron homeostasis by upregulating the negative iron-regulating hormone hepcidin [58–60]. Elevated hepcidin levels may reduce intestinal iron absorption and promote iron sequestration within macrophages, thereby limiting iron availability for hemoglobin synthesis [58–60]. This mechanism may contribute to decreased MCHC and the development of iron deficiency anemia in individuals with chronic periodontitis [58–60]. Studies have shown that chronic inflammation may suppress erythropoietin production and bone marrow activity, producing RBCs with lower hemoglobin content relative to their volume [58–60]. This is commonly seen in anemia of chronic disease, which has been reported in patients with periodontitis [58,60].

Research has revealed that excessive production of reactive oxygen species (ROS) by activated neutrophils may promote hypochromia [61–64]. Oxidative stress may impair red blood cell (RBC)

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integrity by damaging cell membranes and hemoglobin, thereby shortening RBC lifespan and promoting the formation of dysfunctional erythrocytes with reduced hemoglobin content [61–64]. Consequently, these alterations may be reflected as lower MCHC levels [61–64]. In addition, PD may impair chewing efficiency and nutrient intake, leading to dietary deficiencies (iron, folate, vitamin B12) that may compromise hemoglobin synthesis [65]. Several clinical and population-based studies have reported lower hemoglobin levels, hematocrit, and MCHC values in patients with periodontitis compared to periodontally healthy individuals [66,67]. These hematological alterations are consistent with low-grade chronic inflammation and iron-restricted erythropoiesis [66,67]. Furthermore, treatment of PD has been associated with improved hematological parameters, supporting this systemic link [68]. As such, MCHC may serve as an indirect biomarker of systemic inflammatory load in patients with periodontitis [65–68].

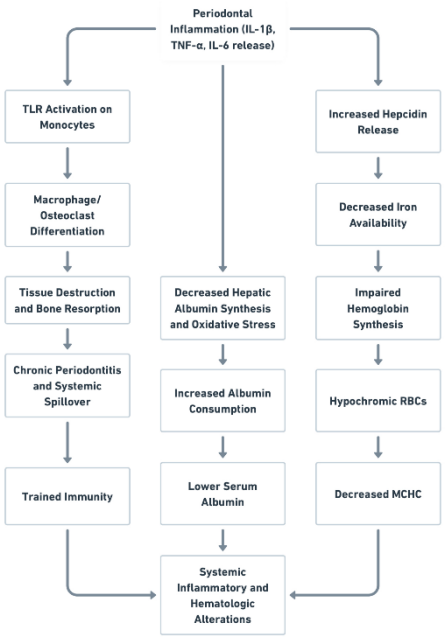

Figure 1. Proposed mechanistic pathways linking periodontal inflammation to systemic hematologic and biochemical alterations. Note: The causal relationship cannot be inferred from this cross-sectional figure.

1.4. Limitation of Research

Several limitations should be acknowledged. First, the cross-sectional design of NHANES precludes determination of causality between periodontal disease and systemic biomarker alterations; thus, the temporal sequence of these associations remains uncertain. Second, periodontal status was assessed at a single time point and may not fully capture disease progression, while partial-mouth protocols and the exclusion of third molars could introduce misclassification. Third, despite multivariable adjustment, residual confounding from unmeasured factors—such as dietary micronutrient intake, systemic inflammation, or medication use—cannot be excluded.

In contrast to most prior clinical and case–control studies that have reported lower mean corpuscular hemoglobin concentration (MCHC) in periodontitis, this nationally representative analysis identified a positive association between periodontal disease and higher MCHC values. This divergence may reflect differences in population characteristics, such as the generally good nutritional status of the NHANES cohort, or potential influences of erythrocyte dehydration, plasma volume contraction, or measurement variability on MCHC estimates. As this study is cross-sectional, these findings should be interpreted with caution and verified in longitudinal or mechanistic studies.

Finally, single laboratory measurements of WBC, serum albumin, and MCHC may be affected by short-term physiological variation, and the results may not be generalizable beyond the U.S. adult

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population. Future research in diverse cohorts and prospective designs will be essential to confirm these associations and elucidate their underlying biological mechanisms.

2.4. Future Perspectives

The findings of this study underscore the potential of routinely measured hematological and biochemical parameters—such as white blood cell count, serum albumin, and mean corpuscular hemoglobin concentration (MCHC)—as accessible indicators of systemic alterations associated with periodontal disease. Future research should build upon these observations by employing longitudinal or cohort designs to clarify the temporal direction and causal nature of these associations. Establishing whether systemic inflammatory and hematologic changes precede, coincide with, or follow the onset of periodontal disease will be essential to determine their diagnostic and prognostic utility.

Furthermore, integrative analyses incorporating inflammatory cytokines, oxidative stress biomarkers, and nutritional indicators could provide a more comprehensive understanding of the biological pathways linking oral and systemic health. Multi-omics approaches, including proteomics, metabolomics, and transcriptomics, may also help identify molecular signatures that mediate the interactions between systemic inflammation, erythropoiesis, and periodontal tissue destruction.

Given the cross-sectional nature of the present study, future investigations should also address potential residual confounding from unmeasured lifestyle, dietary, or metabolic variables. In addition, extending this line of inquiry to diverse and underrepresented populations will improve the generalizability of findings and reveal potential population-specific hematologic or inflammatory responses to periodontal pathology.

Lastly, clinical trials evaluating periodontal therapy and its impact on systemic biomarkers could help determine whether improvements in periodontal health translate into measurable hematologic and inflammatory benefits. Such evidence would strengthen the concept of periodontitis as a systemic condition and highlight the role of oral health management in overall disease prevention.

5. Conclusions

In summary, this cross-sectional analysis of nationally representative NHANES 2013–2014 data revealed positive associations between periodontal disease and systemic blood biomarkers. Individuals with periodontitis exhibited higher white blood cell counts and lower serum albumin levels, consistent with a heightened systemic inflammatory state. Interestingly, mean corpuscular hemoglobin concentration (MCHC) showed a positive association with periodontal disease, diverging from findings of smaller clinical studies that have typically reported reduced MCHC in chronic inflammation. These results reinforce the concept that periodontal disease extends beyond local tissue destruction and is linked to measurable systemic hematologic and biochemical alterations. Routine blood biomarkers, which are easily obtainable in clinical practice, may therefore serve as adjunct indicators of the systemic impact of periodontitis. Nonetheless, given the cross-sectional nature of the data, causal relationships cannot be inferred. Future longitudinal and interventional studies are warranted to clarify temporal dynamics, explore mechanistic pathways, and determine whether periodontal treatment can modulate these systemic biomarkers, ultimately improving both oral and general health outcomes.

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Data Availability Statement: The data used in this article are publicly available and can be found at the Centers for Disease Control and Prevention (CDC) National Center for Health Statistics: National Health and Nutrition Examination Survey (NHANES) Questionnaires, Datasets, and Related Documentation, available at the following website: Accessed 21 September 2025 (https://wwwn.cdc.gov/nchs/nhanes/).

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

PD	Periodontal disease
WBC	White blood cell
MCHC	Mean corpuscular hemoglobin concentration
ROS	Reactive oxygen species

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