Scientific Research Report

The Relationship Between Alkaline Phosphatase and Periodontitis: The Mediating Role of Cranial Bone Mineral Density

Qiuling Tang [#], *Miao Yang* [#], *Qingfeng Xiao* [*], *Chaojie Cheng* [*]

Department of Stomatology, Xiangyang Central Hospital, Affiliated Hospital of Hubei University of Arts and Sciences, Xiangyang, Hubei, China

ARTICLE INFO

Article history:
Received 28 October 2024
Received in revised form
6 March 2025
Accepted 18 March 2025
Available online xxx

Key words:
Alkaline phosphatase
Cranial bone mineral density
Mediation
NHANES
Periodontitis

ABSTRACT

Background: Periodontitis is a common chronic disease characterized by the destruction of periodontal tissues and the resorption of alveolar bone, which severely impacts the quality of life of patients. Alkaline phosphatase (ALP), as a crucial marker of bone metabolism, is involved in the bone formation process. However, the mechanisms linking ALP to periodontitis remain unclear. Bone mineral density (BMD) of the skull is an important indicator reflecting bone mineral content and bone strength, yet its mediating role in the relationship between ALP and periodontitis has not been thoroughly investigated.

Objective: This study aimed to explore the association between serum ALP and the risk of periodontitis and to evaluate the potential mediating role of cranial BMD in this relationship, with the goal of providing new insights into the etiology of periodontitis and informing treatment strategies.

Methods: Data from periodontitis patients from the National Health and Nutrition Examination Survey (NHANES) from 2011 to 2014 were utilized with ALP as the independent variable, periodontitis as the dependent variable, and cranial BMD as the mediating variable. A logistic regression model was used to analyse the relationship between ALP and periodontitis, and subgroup analyses were conducted to explore the association between ALP and periodontitis in different subgroups. Restricted cubic splines (RCS) were used to explore the nonlinear relationship between the two. Additionally, mediation analysis was employed to study the potential mediating role of cranial BMD on the association between ALP and periodontitis.

Results: After adjusting for confounding variables, ALP showed a significant positive association with periodontitis (OR: 1.006, 95% CI: 1.002-1.011, $P < .05$). Subgroup analyses showed that this association was particularly pronounced in males, drinkers, and individuals lacking physical activities. RCS analysis revealed a nonlinear relationship between ALP and periodontitis (*P-non-linear* = 0.0006), with a threshold level of 68 U/L. The mediation analysis revealed that cranial BMD played a mediating role of 2.71% in the relationship between ALP and periodontitis ($P = .006$). Furthermore, ALP was significantly negatively correlated with cranial BMD ($\beta = -0.0016$, 95% CI: −0.0024 to −0.0007, $P < .001$).

Conclusion: Elevated serum ALP levels were positively associated with an increased risk of periodontitis, and cranial BMD partially mediated this association. Monitoring ALP levels may contribute to the early diagnosis and intervention of periodontitis, while targeting bone metabolism regulation could offer a novel direction for the treatment of periodontitis.

[*] *Corresponding author*. Department of Stomatology, Xiangyang Central Hospital, Affiliated Hospital of Hubei University of Arts and Science, 39 Jingzhou Street, Xiangcheng District, Xiangyang, Hubei, 441000, China.
E-mail addresses: qingfengxiaoqfx@163.com (Q. Xiao), ChaojieCheng1004@163.com (C. Cheng).
[#] Qiuling Tang and Miao Yang contributed equally to this work.

https://doi.org/10.1016/j.identj.2025.03.016

Introduction

According to the 2019 Global Burden of Disease Study, up to 1.1 billion people worldwide suffer from severe periodontitis, placing a heavy burden on healthcare systems throughout the world; this indicates that periodontitis is prevalent worldwide, with a 50% prevalence rate.[1] Periodontitis is a chronic inflammatory disease induced by dental plaque, characterized by dysregulated host immune responses and excessive release of inflammatory mediators, leading to the destruction of periodontal tissues and resorption of alveolar bone.[2,3] Notably, the systemic impact of periodontitis extends beyond the oral cavity and is closely associated with conditions such as diabetes, chronic kidney disease, and cardiovascular disease (CVD).[4,5] Periodontal treatment strategies, such as quadrant-wise subgingival debridement and full-mouth subgingival debridement, not only improve local clinical parameters (eg, probing depth and bleeding index) but may also indirectly influence systemic health by reducing systemic inflammation and pathogen load.[6] Furthermore, the potential improvement of arterial stiffness indicators (eg, flow-mediated dilation and carotid intima-media thickness) through nonsurgical periodontal treatment (NSPT) highlights the possibility of periodontal intervention as an important adjunct in reducing CVD risk.[7]

In the field of bone metabolism, alkaline phosphatase (ALP), a key marker of bone formation, plays a significant role in the mineralization processes of bones and alveolar bone.[8] ALP levels in saliva and gingival crevicular fluid are significantly elevated in periodontitis patients and are positively correlated with probing depth and clinical attachment loss.[9] Although evidence linking serum ALP to periodontitis remains insufficient, Gibert et al found that serum ALP activity in periodontitis patients may reflect local bone resorption status.[10]

Both periodontitis and osteoporosis are characterized by enhanced bone resorption, manifested as reduced bone mineral density (BMD).[11,12] Traditional BMD measurements often focus on the lumbar spine or femur, but alveolar bone, as part of the cranium, exhibits bone loss directly related to periodontitis progression. Dual-energy X-ray absorptiometry (DXA) measurements of cranial BMD not only avoid interference from degenerative lumbar changes or hip heterotopic calcification but also provide a more precise assessment of localized bone changes associated with periodontitis.[13,14] Additionally, the negative correlation between serum ALP and BMD[15] suggests that ALP may influence periodontitis progression by regulating bone metabolism.

Based on the above background, this study proposed the following scientific hypothesis: elevated serum ALP levels may mediate the development and progression of periodontitis by reducing cranial BMD. To test this hypothesis, we utilized data from the National Health and Nutrition Examination Survey (NHANES) database (2011-2014) and employed logistic regression models to analyse the relationship between serum ALP levels and periodontitis risk. Furthermore, a mediation effect model was used to explore the potential mediating role of cranial BMD in this relationship, aiming to provide new evidence for the bone metabolism mechanisms of periodontitis and systemic health management.

Methods

Data source and study population

Aiming to evaluate the physical and nutritional health of American adults and children, the NHANES is a biennial cross-sectional survey that is done on an annual basis on around 5000 inhabitants of the United States. The NCHS Research Ethics Review Board has approved this survey, and each respondent has given written, informed permission. You may get more specific statistics data at http://www.cdc.gov/nchs/nhanes.htm.

Using NHANES data covering two cycles, from 2011 to 2014, this study performed a cross-sectional analysis on serum ALP and periodontitis. A total of 19,931 Americans took part throughout this time. The inclusion criteria for this study were as follows: (1) Participants had to complete a periodontal health examination (based on the Center for Disease Control and Prevention (CDC)/American Academy of Periodontology (AAP) standards); (2) Participants had to have available serum ALP and cranial BMD data; (3) Participants had to provide complete covariate information (eg, age, gender, BMI, etc.).

The exclusion criteria included: (1) Total 10,897 participants with missing periodontitis data; (2) 4319 participants with missing cranial BMD data; (3) 224 participants with missing ALP data; (4) 341 participants with missing other covariate data; (5) To avoid analytical bias caused by outliers, one participant with ALP values above the 99th percentile was excluded. Ultimately, 4149 participants were included in the study. The detailed screening and inclusion/exclusion process is illustrated in Figure 1.

ALP measurement

The DxC800 device is used in the NHANES database to quantify the activity of ALP in serum or plasma using a kinetic rate approach and a 2-amino-2-methyl-1-propanol buffer. Nitrophenol and phosphate, a yellow result of the reaction, are produced when ALP catalyses the hydrolysis of a colourless organic phosphate ester substrate. This reaction happens at a pH of 10.3, which is alkaline. At predetermined intervals, the system tracks the rate of absorbance change at 410 nm. The serum ALP activity is directly correlated with the rate of absorbance change.[15]

Assessment of periodontitis

Using the gold standard established by the CDC/AAP, a thorough examination was carried out in this study. The protocol used for the partial mouth periodontal examination[16,17] was the primary method used. The lack of signs of mild, moderate, or severe periodontitis was referred to as non-periodontitis. Clinical attachment loss (CAL) ≥3 mm at ≥2 interproximal sites and probing pocket depth (PPD) ≥4 mm at ≥2 interproximal sites (not on the same tooth), or PPD ≥5 mm at one site were considered indicators of mild periodontitis. CAL ≥4 mm at ≥2 interproximal sites (not on the same tooth), or PPD ≥5 mm at ≥2 interproximal sites (not on the same tooth) were indicators of moderate periodontitis. The criteria for severe

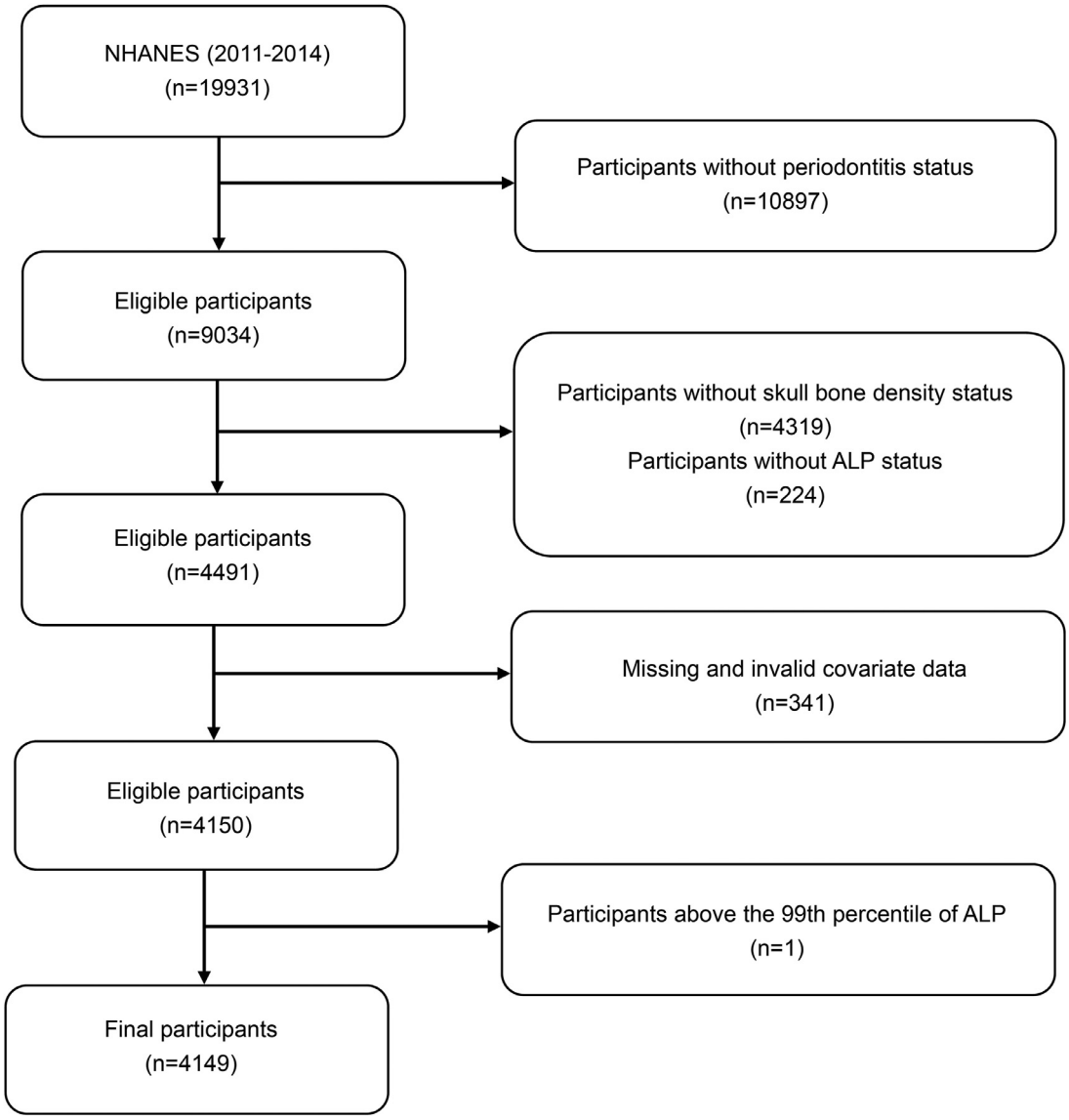

Fig. 1 – The flowchart of participants.

periodontitis were PPD ≥5 mm at one interproximal location and CAL ≥6 mm at ≥2 interproximal sites (not on the same tooth).[18] We divided periodontitis into two groups in this study: non-periodontitis and periodontitis (which includes moderate/severe and mild cases).[19]

Mediating variable

Cranial BMD (g/cm^2) data was obtained using the Apex 3.2 software on the Hologic Discovery A densitometer (Hologic, Inc, Bedford, Massachusetts).[14]

Covariates

(1) Covariates included age, gender (male and female), race (other Hispanic, Mexican American, non-Hispanic white, non-Hispanic black, and others), and body mass index (BMI) (underweight/normal: <25 kg/m^2, overweight: 25-30 kg/m^2, obese: ≥30 kg/m^2).[20] Additionally, smoke (defined as having smoked at least 100 cigarettes in one's lifetime),[14] alcohol (yes, no),[21] physical activities (none, moderate, vigorous),[22] and sleeping time (<7 h, ≥7 h)[14] were included as covariates. Activities that resulted in a small rise in heart rate or respiration, or perspiration, were classified as moderate physical activities. Tasks that resulted in a noticeable rise in heart rate or respiration, or considerable perspiration, were classified as vigorous physical activities. (2) Biochemical parameters: blood urea nitrogen (BUN), total bilirubin, and uric acid.

Statistical analysis

With R (V4.4.1), statistical analysis was carried out. The baseline tables were created using the 'tableone' package. Based on population-wide variables related to periodontitis prevalence, participants were divided into groups. Sample sizes and percentages (n [%]) were used to represent categorical variables, while means and standard deviations (mean [sd])

were used to represent continuous variables (n: unweighted sample size, n (%): weighted percentage, mean: weighted mean, sd: weighted standard deviation). Weighted logistic regression models were built using the 'survey' package to investigate the link between ALP and its tertiles with periodontitis. Subgroup analyses were then conducted to investigate the relationship between ALP and periodontitis in various subgroups. Restricted cubic splines (RCS) were constructed using the 'rms' package to examine the nonlinear association between ALP and periodontitis. For threshold effect analysis, generalized linear models were employed to assess the dose-response association between ALP and periodontitis. Using weighted logistic regression analysis, the 'mediation' package was employed to examine the possible mediating influence of cranial BMD on the relationship between ALP and periodontitis. This study used the following models: unadjusted (crude); adjusted for age, gender, and race (Model 1); adjusted for BMI, smoke, alcohol, physical activities, sleeping time, uric acid, total bilirubin, BUN, age, gender, and race (Model 2).

Results

Baseline characteristics of the study population

This study comprised 4149 people, whose mean age was 44.89 ± 8.63 years, from the NHANES database between 2011 and 2014. Table 1 presents baseline characteristics. Depending on whether they had periodontitis or not, participants were split into 2 groups: 1364 had a diagnosis of periodontitis and 2785 did not. In addition, those in the periodontitis group were generally older, non-Hispanic white, and smokers with a BMI of ≥30 kg/m^2, with a significant low cranial BMD (2.19 ± 0.37 vs 2.24 ± 0.37, P = .027) and high ALP values (69.05 ± 20.99 vs 63.95 ± 20.88, P < .001).

Stratified analysis

The association between ALP and periodontitis is seen in Table 2. ALP and periodontitis had a positive connection in Model 2, after adjusting for all confounding factors (OR: 1.006, 95% CI: 1.002-1.011, P < .01). ALP was further stratified into tertiles, and all models revealed that higher tertiles were associated with a greater risk of periodontitis (P_{trend} < 0.05). In Model 2, the risk of periodontitis was 38.5% greater in those in T3 of ALP compared to those in T1 (OR: 1.385, 95% CI: 1.031-1.860, P < .05) (Table 2).

Subgroup analysis

ALP and periodontitis were investigated in relation to several subgroups using subgroup analysis. Table 3 illustrates the results of the adjustment for all confounding variables, which revealed a significant correlation between elevated ALP levels and a greater prevalence of periodontitis. This correlation was particularly strong in men, drinkers, and those with low levels of physical activities (P < .05).

Nonlinear association between ALP and periodontitis risk

RCS analysis of the association between the risk of periodontitis and ALP is shown in Figure 2. The RCS curve findings showed a significant overall trend between ALP and periodontitis in the weighted logistic regression model that adjusted for all confounding variables (*P-overall* < 0.0001). ALP and periodontitis were shown to have a strong nonlinear connection (*P-non-linear* = 0.0006).

ALP had a threshold level that we determined to be 68 U/L (Table 4). There was no significant correlation between the incidence of periodontitis and ALP levels more than 68 U/L (OR = 0.999, 95% CI: 0.994-1.004, P = .7). Nonetheless, an increase in ALP levels was substantially linked to a higher risk of periodontitis when ALP was less than 68 U/L (OR = 1.021, 95% CI: 1.013-1.030, P < .001).

Mediation analysis

For each participant, we assessed the mediating function of cranial BMD in the association between ALP and periodontitis using the mediation analysis (Figure 3). A substantial negative connection (β = −0.0016 (−0.0024, −0.0007), P < .001) was identified between ALP and cranial BMD after adjusting for all confounding variables. Greater levels of ALP were associated with a higher risk of periodontitis (OR > 1, P < .05), according to the overall influence of ALP on the disease. Cranial BMD mediated around 2.71% of the overall impact of ALP on periodontitis (P = .006).

Discussion

The findings of this study revealed that elevated serum ALP levels were significantly nonlinearly associated with an increased risk of periodontitis, and this association was more pronounced in males, individuals who consume alcohol, and those with a lack of physical activity. Additionally, cranial BMD partially mediated the relationship between ALP and periodontitis, with a mediation effect of 2.71%. These results provide new insights into the bone metabolism mechanisms underlying periodontitis and offer potential targets for clinical intervention.

Studies show that inflammatory indicators including white blood cell count and C-reactive protein (CRP) levels are favorably linked with serum ALP levels on their own.[23,24] Patients with periodontitis may have higher serum CRP and white blood cell count due to locally generated pro-inflammatory substances that reach the systemic circulation throughout the disease.[25] As a result, increased blood ALP levels might indicate gingival inflammation. Moreover, serum ALP, which is mostly present in osteoblasts, is a sign of bone production. Bone healing mechanisms are activated during periodontitis due to the breakdown of the periodontal ligament and alveolar bone resorption. By releasing organic phosphates and hydrolysing inorganic pyrophosphates, ALP is released from osteoblasts and aids in the process of bone mineralization, ultimately contributing to periodontal regeneration.[8,10] Patients with chronic severe periodontitis had greater blood ALP levels, according to studies by Cauĸla

Table 1 – Characteristics of NHANES participants between 2011 to 2014.

Characters	Total	Non-periodontitis	Periodontitis	*P* value
Overall	4149	2785 (72.9)	1364 (27.1)	
Age	44.89 (8.63)	44.38 (8.59)	46.29 (8.57)	<.001
Race				<.001
Mexican American	532 (9.1)	293 (6.9)	239 (14.8)	
Other Hispanic	375 (5.8)	249 (5.3)	126 (7.3)	
Non-Hispanic White	1715 (66.8)	1277 (71.7)	438 (53.7)	
Non-Hispanic Black	881 (10.7)	510 (8.7)	371 (16.2)	
Other race	646 (7.5)	456 (7.4)	190 (8.0)	
Gender				<.001
Male	2110 (51.3)	1286 (47.1)	824 (62.7)	
Female	2039 (48.7)	1499 (52.9)	540 (37.3)	
BMI (kg/m^2)				<.001
<25	1092 (25.0)	775 (26.7)	317 (20.2)	
25-30	1423 (36.3)	951 (36.4)	472 (35.9)	
≥30	1634 (38.8)	1059 (36.9)	575 (43.9)	
Alcohol				.423
No	979 (17.6)	668 (18.1)	311 (16.3)	
Yes	3170 (82.4)	2117 (81.9)	1053 (83.7)	
Smoke				<.001
No	2328 (55.4)	1698 (60.3)	630 (42.2)	
Yes	1821 (44.6)	1087 (39.7)	734 (57.8)	
Physical activities				.247
None	1704 (43.0)	1166 (43.4)	538 (42.1)	
Moderate	1303 (32.3)	888 (32.7)	415 (31.1)	
Vigorous	1142 (24.7)	731 (23.9)	411 (26.8)	
Sleeping time				.001
<7h	1776 (39.7)	1156 (37.4)	620 (45.7)	
≥7h	2373 (60.3)	1629 (62.6)	744 (54.3)	
Cranial bone mineral density	2.23 (0.37)	2.24 (0.37)	2.19 (0.37)	.027
Uric acid (mg/dL)	5.39 (1.36)	5.33 (1.35)	5.55 (1.39)	.001
Total bilirubin (mg/dL)	0.68 (0.29)	0.68 (0.29)	0.66 (0.29)	.142
BUN (mg/dL)	12.46 (4.43)	12.50 (4.42)	12.34 (4.45)	.277
ALP (U/L)	65.33 (21.03)	63.95 (20.88)	69.05 (20.99)	<.001

Note: Categorical variables are expressed as n (%) and continuous variables are expressed as mean (sd); n is unweighted and n (%), mean, and sd are weight-adjusted.

et al.[26] Our results corroborate this, adding to the body of data linking higher blood ALP levels to a higher risk of periodontitis.

Through mediation analysis, this study found that cranial BMD played a mediating role of 2.71% in the relationship between ALP and periodontitis. This effect size is relatively low compared to other studies in the field of bone metabolism. For example, ALP mediated the effect of whole egg intake on femoral BMD with a mediation proportion as high as 71.8%,[27] suggesting that cranial BMD may not be the core mechanism linking ALP and periodontitis. However, this study is the first to reveal the supplementary role of cranial BMD in the bone metabolism of periodontitis. As a direct indicator of alveolar bone structural integrity, its reduction may

Table 2 – Associations between ALP and odds ratios (95% CI) for periodontitis.

Participants	OR (95% CI)		
	Crude model	Model 1	Model 2
ALP (continuous)	1.011 (1.007-1.015)***	1.009 (1.004-1.013)***	1.006 (1.002-1.011)**
ALP (categorical)			
T1 (< 55 U/L)	Ref.	Ref.	Ref.
T2 (55-71U/L)	1.505 (1.157-1.957)**	1.374 (1.036-1.821)*	1.322 (0.993-1.759)
T3 (≥ 71U/L)	1.800 (1.405-2.305)***	1.539 (1.169-2.027)**	1.385 (1.031-1.860)*
P_{trend}	<0.001	0.001	0.018

Note: Crude not adjusted; Model 1 adjusted for age, race, and gender; Model 2 adjusted for age, gender, race, BMI, smoke, alcohol, physical activities, cranial BMD, sleeping time, uric acid, total bilirubin, and blood urea nitrogen.

* *P* value <.05.
** *P* value <.01.
*** *P* value <.001.

Table 3 – Relationship between ALP and periodontitis by subgroup (95% CI).

Participants	OR (95% CI)		
	Crude	Model 1	Model 2
ALP			
Gender			
Male	1.013 (1.007-1.020)***	1.010 (1.002-1.017)**	1.008 (1.000-1.017)*
Female	1.011 (1.006-1.015)***	1.008 (1.003-1.013)**	1.004 (0.999-1.008)
Smoke			
No	1.014 (1.008-1.019)***	1.010 (1.004-1.017)**	1.009 (1.002-1.016)**
Yes	1.007 (1.002-1.013)**	1.006 (1.001-1.011)*	1.005 (1.000-1.011)*
Alcohol			
No	1.003 (0.997-1.009)	1.001 (0.995-1.007)	1.000 (0.993-1.007)
Yes	1.013 (1.008-1.019)***	1.011 (1.006-1.017)***	1.009 (1.003-1.015)**
Physical activities			
None	1.015 (1.007-1.023)***	1.011 (1.003-1.019)**	1.008 (1.000-1.016)*
Moderate	1.011 (1.003-1.018)**	1.009 (1.001-1.016)*	1.006 (0.998-1.014)
Vigorous	1.006 (0.998-1.014)	1.006 (0.997-1.014)	1.005 (0.995-1.015)

Note: Crude not adjusted; Model 1 adjusted for age, race, and gender; Model 2 adjusted for age, gender, race, BMI, smoke, alcohol, physical activities, cranial BMD, sleeping time, uric acid, total bilirubin, and blood urea nitrogen.

* *P* value < .05.
** *P* value < .01.
*** *P* value < .001.

indirectly promote the progression of periodontitis by weakening the stability of periodontal supporting tissues. Additionally, it is noteworthy that the anatomical specificity of cranial BMD allows it to reflect localized bone metabolic disturbances, whereas systemic BMD studies (eg, lumbar spine or femur) may fail to capture such subtle changes.[28] Although the 2.71% mediation effect has limited clinical translational significance, its value in mechanistic exploration should not be overlooked, especially given the scarcity of related research. It provides direction for subsequent analyses of multifactorial synergistic effects, such as combining inflammatory mediators or microbial load. Future studies should validate this effect in larger samples or specific subgroups (eg, patients with severe periodontitis) and explore the interactions between cranial BMD and other bone metabolism markers.

We discovered that drinking alcohol is a significant risk factor for periodontitis in our subgroup analysis. Alcohol use may worsen alveolar bone loss and reduce alveolar BMD.[29-31] Periodontitis is linked to compromised neutrophil phagocytic activity,[32,33] and alcohol use can exacerbate the severity of periodontitis by impairing neutrophil function and increasing bacterial penetration into periodontal tissues.[34,35] According to a prior study, drinking alcohol raises blood ALP levels,

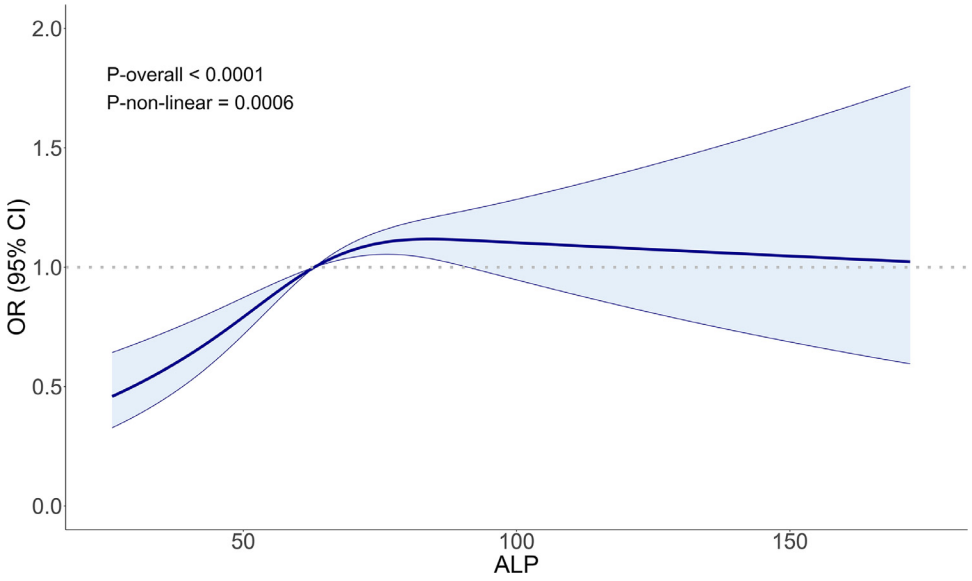

Fig. 2 – The OR of ALP and periodontitis adjusted by covariates, NHANES 2011 to 2014. The OR is represented by the blue line and the shaded part represents 95% CI. CI, confidence interval; OR, odds ratio.

Table 4 – Threshold analysis for ALP and periodontitis.

Outcome	OR (95% CI)	P
Model 1 Fitting model by standard linear regression	1.006 (1.002-1.011)	.004
Model 2 Fitting model by two-piecewise linear regression		
Inflection point		
<68	1.021 (1.013-0.030)	<.001
>68	0.999 (0.994-1.004)	.700
P for likelihood ratio test	<0.001	

Note: Adjusted for age, gender, race, BMI, smoke, alcohol, physical activities, cranial BMD, sleeping time, uric acid, total bilirubin, blood urea nitrogen.

which exacerbates periodontitis.[36] Thus, preserving bone health and lowering the risk of periodontitis can be achieved by leading a healthy lifestyle and consuming less alcohol.

The results of this investigation showed a strong positive association between serum ALP levels and periodontitis, which was more pronounced in inactive people. Reading, using a computer, and driving are examples of sedentary behaviours that might result in poor eating habits such snacking and eating in between meals. This can exacerbate periodontitis by increasing the risk of acidic teeth exposure.[37,38] Furthermore, a lack of physical activity tends to activate systemic inflammatory responses, increasing levels of inflammatory markers such as CRP, which is closely associated with periodontitis.[39-41] Therefore, increasing physical activity may improve periodontal health by mitigating inflammatory responses. In 2020, the World Health Organization released the Guidelines on Physical Activity and Sedentary Behaviour, strongly recommending that adults engage in at least 150 to 300 minutes of moderate-intensity aerobic activity or at least 75 to 150 minutes of vigorous-intensity aerobic activity per week to reduce the risk of various diseases.[42]

Gender variations may potentially impact the severity of periodontitis.[43-45] According to our findings, there is a stronger correlation between men's periodontitis prevalence and higher ALP levels. The function of androgens in controlling the ratio of osteoblasts to osteoclasts in the processes of inflammation and bone turnover are some possible explanations.[46,47] According to research, dihydrotestosterone, an androgen metabolite, increases blood ALP activity[48,49] and stimulates osteoblast proliferation and differentiation, which inhibits alveolar bone resorption and lessens the severity of periodontitis. Males are also more likely than females to smoke, and long-term nicotine use can cause the body to generate pro-inflammatory chemicals, which in turn activate osteoclast activity and exacerbate alveolar bone resorption—a condition that is frequently linked to the start and progression of periodontitis.[36]

In recent years, the optimization of periodontal treatment strategies has not only focused on improving local clinical parameters (eg, probing depth and bleeding index) but has also increasingly emphasized their comprehensive impact on patients' systemic health and quality of life. For example, full-mouth subgingival debridement (FM-SI) has been shown to significantly reduce periodontal pathogen load compared to traditional quadrant-wise treatment (Q-SI) and indirectly improve cardiovascular health by decreasing systemic inflammatory markers (eg, CRP, IL-6).[6] Additionally, nonsurgical periodontal treatment (NSPT) has been proven to directly enhance patients' oral health-related quality of life (OHRQoL) by restoring periodontal tissue function, alleviating chewing pain, and reducing tooth mobility.[7] The association between elevated serum ALP levels and periodontitis risk identified in this study further highlights the potential value of bone metabolism regulation in periodontal treatment. Interventions targeting the ALP-BMD pathway (eg, anti-resorptive drugs or nutritional supplements) may serve as adjuncts to traditional mechanical debridement, synergistically improving alveolar bone stability and optimizing long-term treatment outcomes. Moreover, ALP levels in saliva and gingival crevicular fluid warrant further investigation. These local samples can directly reflect the inflammatory and bone metabolic status of periodontal tissues and offer the advantage of non-invasive collection.[9,50] Future studies should combine serum, saliva, and GCF ALP measurements to provide a more comprehensive assessment of the bone metabolism

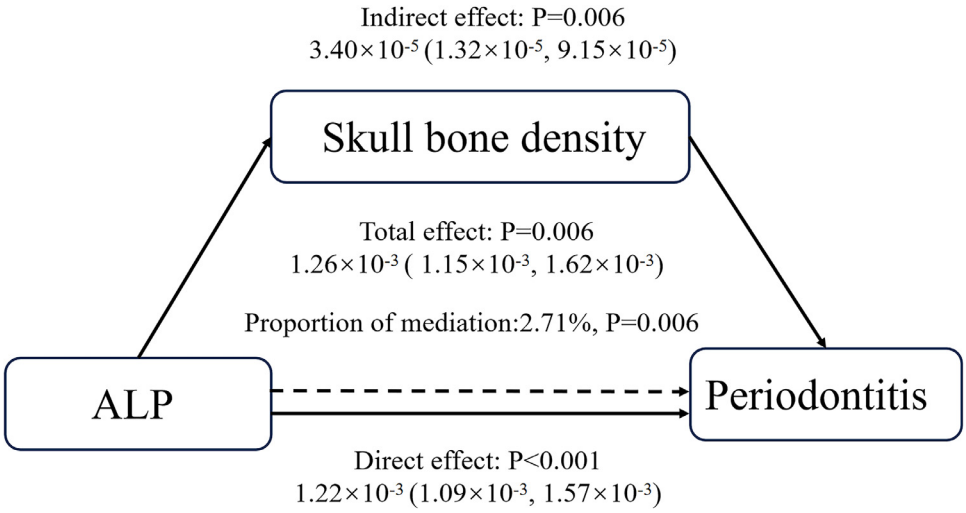

Fig. 3 – Results of cranial BMD-mediated ALP and periodontitis.

mechanisms in periodontitis and offer a basis for non-invasive diagnosis and personalized treatment.

In summary, this study not only reveals the association between serum ALP and periodontitis but also emphasizes the mediating role of cranial BMD in this relationship. Although the mediation effect is modest, its clinical significance lies in suggesting the potential role of bone metabolism in the progression of periodontitis. There are certain restrictions, though. Firstly, since this is a cross-sectional research, causality cannot be established. Secondly, because the study was limited to the U.S. population, further research in various cohorts is required to improve the generalizability of findings. Finally, because periodontitis is a complex illness with a wide range of influencing factors, this study's adjusted confounding variables are small, and other possible influencing factors were left out, which may have prejudiced the results.

Conclusion

This study reveals a significant association between elevated serum ALP levels and the risk of periodontitis and, for the first time, proposes the supplementary mediating role of cranial BMD in this relationship. Although the mediation effect is modest, its anatomical specificity provides a new perspective for understanding the local bone metabolism mechanisms underlying periodontitis. In light of recent research, periodontal treatments (eg, NSPT or FM-SI) not only alleviate symptoms by improving clinical parameters but may also enhance patients' quality of life by regulating bone metabolism and inflammatory pathways. Future studies should explore multimodal treatment strategies (eg, combined ALP-targeted interventions) to more comprehensively improve periodontal health and systemic outcomes.

CRediT authorship contribution statement

Qiuling Tang, Miao Yang conceived and designed the study. Qiuling Tang, Miao Yang wrote the manuscript. Qingfeng Xiao, Chaojie Cheng reviewed and edited the manuscript. All authors read and approved the final manuscript.

Consent for publication

All of the authors have given their consent to submit the manuscript for publication.

Availability of date and materials

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest

None disclosed.

REFERENCES

1. Chen MX, Zhong YJ, Dong QQ, Wong HM, Wen YF. Global, regional, and national burden of severe periodontitis, 1990-2019: an analysis of the global burden of disease study 2019. J Clin Periodontol 2021;48(9):1165–88. doi: 10.1111/jcpe.13506 From NLM Medline.
2. Kinane DF, Stathopoulou PG, Papapanou PN. Periodontal diseases. Nat Rev Dis Primers 2017;3:17038. doi: 10.1038/nrdp.2017.38 From NLM Medline.
3. Todorovic T, Dozic I, Vicente-Barrero M, Ljuskovic B, Pejovic J, Marjanovic M, et al. Salivary enzymes and periodontal disease. Med Oral Patol Oral Cir Bucal 2006;11(2):E115–9.
4. Baeza M, Morales A, Cisterna C, et al. Effect of periodontal treatment in patients with periodontitis and diabetes: systematic review and meta-analysis. J Appl Oral Sci 2020;28:e20190248. doi: 10.1590/1678-7757-2019-0248 From NLM Medline.
5. Parsegian K, Randall D, Curtis M, Ioannidou E. Association between periodontitis and chronic kidney disease. Periodontol 2000 2022;89(1):114–24. doi: 10.1111/prd.12431 From NLM Medline.
6. Isola G, Polizzi A, Santonocito S, Alibrandi A, Pesce P, Kocher T. Effect of quadrantwise versus full-mouth subgingival instrumentation on clinical and microbiological parameters in periodontitis patients: a randomized clinical trial. J Periodontal Res 2024;59(4):647–56. doi: 10.1111/jre.13279 From NLM Medline.
7. Polizzi A, Nibali L, Tartaglia GM, Isola G. Impact of nonsurgical periodontal treatment on arterial stiffness outcomes related to endothelial dysfunction: a systematic review and meta-analysis. J Periodontol 2024. doi: 10.1002/JPER.24-0422 From NLM Publisher.
8. Vimalraj S. Alkaline phosphatase: structure, expression and its function in bone mineralization. Gene 2020;754:144855. doi: 10.1016/j.gene.2020.144855 From NLM Medline.
9. Sanikop S, Patil S, Agrawal P. Gingival crevicular fluid alkaline phosphatase as a potential diagnostic marker of periodontal disease. J Indian Soc Periodontol 2012;16(4):513–8. doi: 10.4103/0972-124X.106889 From NLM PubMed-not-MEDLINE.
10. Gibert P, Tramini P, Sieso V, Piva MT. Alkaline phosphatase isozyme activity in serum from patients with chronic periodontitis. J Periodontal Res 2003;38(4):362–5. doi: 10.1034/j.1600-0765.2003.00388.x From NLM Medline.
11. Wang CJ, McCauley LK. Osteoporosis and periodontitis. Curr Osteoporos Rep 2016;14(6):284–91. doi: 10.1007/s11914-016-0330-3 From NLM Medline.
12. Peng J, Chen J, Liu Y, Lyu J, Zhang B. Association between periodontitis and osteoporosis in United States adults from the national health and nutrition examination survey: a cross-sectional analysis. BMC Oral Health 2023;23(1):254. doi: 10.1186/s12903-023-02990-4 From NLM Medline.
13. Turner AS, Maillet JM, Mallinckrodt C, Cordain L. Bone mineral density of the skull in premenopausal women. Calcif Tissue Int 1997;61(2):110–3. doi: 10.1007/s002239900305 From NLM Medline.
14. Jin F, Song J, Luo Y, et al. Association between skull bone mineral density and periodontitis: using the national health and nutrition examination survey (2011-2014). PLoS One 2022;17(12):e0271475. doi: 10.1371/journal.pone.0271475 From NLM Medline.

15. Shu J, Tan A, Li Y, Huang H, Yang J. The correlation between serum total alkaline phosphatase and bone mineral density in young adults. BMC Musculoskelet Disord 2022;23(1):467. doi: 10.1186/s12891-022-05438-y From NLM Medline.
16. Romano F, Perotto S, Castiglione A, Aimetti M. Prevalence of periodontitis: misclassification, under-recognition or over-diagnosis using partial and full-mouth periodontal examination protocols. Acta Odontol Scand 2019;77(3):189–96. doi: 10.1080/00016357.2018.1535136 From NLM Medline.
17. Eke PI, Page RC, Wei L, Thornton-Evans G, Genco RJ. Update of the case definitions for population-based surveillance of periodontitis. J Periodontol 2012;83(12):1449–54. doi: 10.1902/jop.2012.110664 From NLM Medline.
18. Fu H, Zhang D, Li Y. NHANES-based analysis of the correlation between leisure-time physical activity, serum cotinine levels and periodontitis risk. BMC Oral Health 2024;24(1):466. doi: 10.1186/s12903-024-04141-9 From NLM Medline.
19. Sun J, Wang W, Li D, et al. Association between C-reactive protein and periodontitis in an obese population from the NHANES 2009-2010. BMC Oral Health 2023;23(1):512. doi: 10.1186/s12903-023-03189-3 From NLM Medline.
20. Guo W, Song Y, Sun Y, et al. Systemic immune-inflammation index is associated with diabetic kidney disease in type 2 diabetes mellitus patients: evidence from NHANES 2011-2018. Front Endocrinol (Lausanne) 2022;13:1071465. doi: 10.3389/fendo.2022.1071465 From NLM Medline.
21. Dong X, Li S, Sun J, Li Y, Zhang D. Association of coffee, decaffeinated coffee and caffeine intake from coffee with cognitive Performance in older adults: national health and nutrition examination survey (NHANES) 2011-2014. Nutrients 2020;12(3). doi: 10.3390/nu12030840 From NLM Medline.
22. Wang X, Mukherjee B, Park SK. Associations of cumulative exposure to heavy metal mixtures with obesity and its comorbidities among U.S. adults in NHANES 2003-2014. Environ Int 2018;121(Pt 1):683–94. doi: 10.1016/j.envint.2018.09.035 From NLM Medline.
23. Seo MS, Shim JY, Lee YJ. Relationship between serum alkaline phosphatase level, C-reactive protein and leukocyte counts in adults aged 60 years or older. Scand J Clin Lab Invest 2019;79(4):233–7. doi: 10.1080/00365513.2019.1585567 From NLM Medline.
24. Webber M, Krishnan A, Thomas NG, Cheung BM. Association between serum alkaline phosphatase and C-reactive protein in the United States National Health and Nutrition Examination Survey 2005-2006. Clin Chem Lab Med 2010;48(2):167–73. doi: 10.1515/CCLM.2010.052 From NLM Medline.
25. Cecoro G, Annunziata M, Iuorio MT, Nastri L, Guida L. Periodontitis, low-grade inflammation and systemic health: a scoping review. Medicina (Kaunas) 2020;56(6). doi: 10.3390/medicina56060272 From NLM Medline.
26. Caula AL, Lira-Junior R, Tinoco EM, Fischer RG. Serum creatinine and alkaline phosphatase levels are associated with severe chronic periodontitis. J Periodontal Res 2015;50(6):793–7. doi: 10.1111/jre.12266 From NLM Medline.
27. Shi D, Liu W, Hang J, Chen W. Whole egg consumption in relation to bone health of the US population: a cross-sectional study. Food Funct 2024;15(3):1369–78. doi: 10.1039/d3fo04248k From NLM Medline.
28. Chen R, Gong K, Chen W, et al. Association of serum alkaline phosphatase levels with bone mineral density, osteoporosis prevalence, and mortality in US adults with osteoporosis: evidence from NHANES 2005-2018. Osteoporos Int 2025;36(2):283–97. doi: 10.1007/s00198-024-07324-w From NLM Medline.
29. Malik P, Gasser RW, Kemmler G, et al. Low bone mineral density and impaired bone metabolism in young alcoholic patients without liver cirrhosis: a cross-sectional study. Alcohol Clin Exp Res 2009;33(2):375–81. doi: 10.1111/j.1530-0277.2008.00847.x From NLM Medline.
30. Kim MJ, Shim MS, Kim MK, et al. Effect of chronic alcohol ingestion on bone mineral density in males without liver cirrhosis. Korean J Intern Med 2003;18(3):174–80. doi: 10.3904/kjim.2003.18.3.174 From NLM Medline.
31. Dal-Fabbro R, Marques-de-Almeida M, Cosme-Silva L, Ervolino E, Cintra LTA, Gomes-Filho JE. Chronic alcohol consumption increases inflammation and osteoclastogenesis in apical periodontitis. Int Endod J 2019;52(3):329–36. doi: 10.1111/iej.13014 From NLM Medline.
32. Kim TS, Silva LM, Theofilou VI, et al. Neutrophil extracellular traps and extracellular histones potentiate IL-17 inflammation in periodontitis. J Exp Med 2023;220(9). doi: 10.1084/jem.20221751 From NLM Medline.
33. Hajishengallis G. New developments in neutrophil biology and periodontitis. Periodontol 2000 2020;82(1):78–92. doi: 10.1111/prd.12313 From NLM Medline.
34. Wang J, Lv J, Wang W, Jiang X. Alcohol consumption and risk of periodontitis: a meta-analysis. J Clin Periodontol 2016;43(7):572–83. doi: 10.1111/jcpe.12556 From NLM Medline.
35. Gay IC, Tran DT, Paquette DW. Alcohol intake and periodontitis in adults aged >/=30 years: NHANES 2009-2012. J Periodontol 2018;89(6):625–34. doi: 10.1002/JPER.17-0276 From NLM Medline.
36. Pinto KP, Fidalgo T, de Lima CO, et al. Chronic alcohol and nicotine consumption as catalyst for systemic inflammatory storm and bone destruction in apical periodontitis. Int Endod J 2024;57(2):178–94. doi: 10.1111/iej.13994 From NLM Medline.
37. Benatti FB, Ried-Larsen M. The effects of breaking up prolonged sitting time: a review of experimental studies. Med Sci Sports Exerc 2015;47(10):2053–61. doi: 10.1249/MSS.0000000000000654 From NLM Medline.
38. Zhang Z, Ding M, Ding H, et al. Understanding the consequences of leisure sedentary behavior on periodontitis: a two-step, multivariate mendelian randomization study. Heliyon 2023;9(12):e23118. doi: 10.1016/j.heliyon.2023.e23118 From NLM PubMed-not-MEDLINE.
39. Codella R, Della Guardia L, Terruzzi I, et al. Physical activity as a proxy to ameliorate inflammation in patients with type 2 diabetes and periodontal disease at high cardiovascular risk. Nutr Metab Cardiovasc Dis 2021;31(8):2199–209. doi: 10.1016/j.numecd.2021.04.022 From NLM Medline.
40. Lieske B, Moszka N, Borof K, et al. Association between an anti-inflammatory dietary score and periodontitis-evidence from the population-based Hamburg City Health Study. Nutrients 2023;15(14). doi: 10.3390/nu15143235 From NLM Medline.
41. Slots J. Periodontitis: facts, fallacies and the future. Periodontol 2000 2017;75(1):7–23. doi: 10.1111/prd.12221 From NLM Medline.
42. In *WHO Guidelines on Physical Activity and Sedentary Behaviour*, WHO Guidelines Approved by the Guidelines Review Committee. World Health Organization; 2020 https://www.ncbi.nlm.nih.gov/books/NBK566045.
43. Meisel P, Eremenko M, Holtfreter B, Volzke H, Kocher T. The sex paradox in the interplay between periodontitis, obesity, and serum C-reactive protein: data from a general population. J Periodontol 2019;90(12):1365–73. doi: 10.1002/JPER.18-0733 From NLM Medline.
44. Su X, Jin K, Zhou X, et al. The association between sex hormones and periodontitis among American adults: a cross-sectional study. Front Endocrinol (Lausanne) 2023;14:1125819. doi: 10.3389/fendo.2023.1125819 From NLM Medline.
45. Ghafouri-Fard S, Gholami L, Badrlou E, et al. Sex-based dysregulation of inflammation-related genes in periodontitis. Int J Mol Cell Med 2023;12(3):300–9. doi: 10.22088/IJMCM.BUMS.12.3.300 From NLM PubMed-not-MEDLINE.

46. Clarke BL, Khosla S. Androgens and bone. Steroids 2009;74 (3):296–305. doi: 10.1016/j.steroids.2008.10.003 From NLM Medline.
47. Michael H, Harkonen PL, Vaananen HK, Hentunen TA. Estrogen and testosterone use different cellular pathways to inhibit osteoclastogenesis and bone resorption. J Bone Miner Res 2005;20(12):2224–32. doi: 10.1359/JBMR.050803 From NLM Medline.
48. Davey RA, Hahn CN, May BK, Morris HA. Osteoblast gene expression in rat long bones: effects of ovariectomy and dihydrotestosterone on mRNA levels. Calcif Tissue Int 2000;67 (1):75–9. doi: 10.1007/s00223001100 From NLM Medline.
49. Davey RA, Morris HA. Effects of estradiol and dihydrotestosterone on osteoblast gene expression in osteopenic ovariectomized rats. J Bone Miner Metab 2005;23(3):212–8. doi: 10.1007/s00774-004-0586-z From NLM Medline.
50. Daltaban O, Saygun I, Bal B, Balos K, Serdar M. Gingival crevicular fluid alkaline phosphatase levels in postmenopausal women: effects of phase I periodontal treatment. J Periodontol 2006;77 (1):67–72. doi: 10.1902/jop.2006.77.1.67 From NLM Medline.