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Vitamin B6 status, type 2 diabetes mellitus, and periodontitis: evidence from the NHANES database 2009–2010

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Abstract

Background Periodontitis is a chronic inflammatory disease that seriously affects the quality of patients' life. Diabetes mellitus (DM) is the independent risk factor of periodontitis. The association between vitamin B_6 with several inflammatory diseases have been reported in previous studies. However, the effect of vitamin B_6 on the association of T2DM and periodontitis remains unclear. This study aimed to explore the effect of vitamin B_6 [evaluated by serum pyridoxal 5'-phosphate (PLP)] on the association of T2DM and periodontitis in American population.

Methods Data of this cross-sectional study were extracted from the National Health and Nutrients Examination Survey (NHANES) 2009–2010. Serum PLP level was the indicator of vitamin B_6 status in *vivo* and measured by enzymatic assay. Covariates included demographic information, physical examination, lifestyle characteristics, laboratory parameters and complications. The weighted univariate and multivariate logistics regression models were conducted to explore the association of PLP, T2DM and periodontitis, with the odds ratios (ORs) and 95% confidence intervals (CIs). Subgroup analyses were further performed to explore these associations based on age, body mass index (BMI), cardiovascular disease (CVD) and dental decay.

Results Finally, 3,491 eligible adults with the information of periodontitis measurement, T2DM diagnosis and PLP detection were included. Among them, 1,999 (57.26%) had periodontitis. After adjusted confounders, we found adults with T2DM had high odds of periodontitis (OR = 1.45, 95%CI: 1.04–2.02); while no significant association between PLP and periodontitis was observed. Adults with low PLP level (< 67.20 nmol/L) and combined with T2DM had high odds of periodontitis (OR = 1.82, 95%CI: 1.29–2.55), no significant association was found between T2DM and periodontitis in adults with high PLP level (≥ 67.20 nmol/L). These results suggested that serum PLP levels may have the modulatory effect on the association of T2DM and periodontitis. This modulatory effect remains robust in subgroup analysis, especially in adults aged ≥ 60 years (OR = 4.54, 95%CI: 2.15–9.62), with obese (OR = 3.06, 95%CI: 1.31–7.18), without the history of CVD (OR = 2.25, 95%CI: 1.06–4.79) and without dental decay (OR = 2.93, 95%CI: 1.51–5.68) (all $P < 0.05$).

Conclusion Our study suggested that adults with T2DM had the high odds of periodontitis, and serum PLP may plays a modulatory effect in this association. T2DM patients maintaining a higher intake of vitamin B_6 may have potential benefits in reducing the periodontitis risk.

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Keywords Vitamin B_6, Pyridoxal 5'-phosphate (PLP), Type 2 diabetes mellitus (T2DM), Periodontitis, National health and nutrition examination surveys (NHANES) database

Introduction

Periodontitis, resulted from a disorder in the interaction between oral microbes and the host inflammatory response, is a complicated chronic condition causing a huge disease burden worldwide [1]. Nowadays, periodontitis has become the sixth prevalent disease in the world, and the estimated global prevalence of periodontitis is as high as 50% [2]. Epidemiological studies reported that there was an obvious positive association between the level of hyperglycaemia and severity of periodontitis [3], and compared with the general population, patients with diabetes mellitus (DM) are approximately three times more susceptible to periodontitis [4]. Although the exact mechanisms between these two diseases have not yet been elucidated, current knowledge suggests that involving the aspects of immune function, neutrophil activity, and cytokine biology [5].

Exploring modifiable factors that involving the association of DM and periodontitis is important to reduce the diseases burden. Vitamin B_6, including pyridoxine, pyridoxal, and pyridoxamine, is an essential water-soluble vitamin of the B vitamins acting a vital effect in normal brain development and immune system health [6]. Pyridoxal 5'-phosphate (PLP) is the most widely used biomarker of vitamin B_6 with more reliable and representative [7]. Previous studies have shown that serum PLP level was associated with several inflammatory conditions including cardiovascular disease (CVD), inflammatory bowel disease and rheumatoid arthritis (RA) [8–11]. A review of Mascolo et al. [12] reported that the deficiency of vitamin B_6 significantly increases the risk of occurring and developing of DM and its complications [12]. Moreover, the that study also concluded that there existed a vicious circle between vitamin B_6 and DM. Vitamin B_6 levels can impact different types of DM through various physiological pathways, mainly concerning inflammatory responses, the metabolism of tryptophan (TRP) and lipid [13, 14]. The beneficial role of vitamins in maintaining oral health has also been widely discussed, and moderate and severe vitamin deficiencies may lead to systemic complications, including oral diseases [15, 16]. A previous review pointed out that insufficient intake of vitamin B is associated with decreased oral epithelial development, impaired tooth formation, hypomineralized enamel, and periodontitis [17]. However, less is known, the role of serum PLP on the risk of periodontitis driven by DM.

Based on previous studies, we speculated that serum PLP level may associated with the periodontitis driven by DM. Therefore, we performed this cross-sectional analysis to explore the role of serum PLP level on the association between DM and periodontitis using the data from the National Health and Nutrition Examination Surveys (NHANES) database, aiming to provide some insights into the prevention and treatment of DM-related periodontitis.

Methods

Study design and participants

Based on the NHANES database 2009–2010, a cross-sectional study was conducted to explore the role of serum PLP level on the association of T2DM and periodontitis. The NHANES database is a survey conducted by the Centers for Disease Control and Prevention, a part of National Center for Health Statistics (NCHS). It aims to evaluate the health and nutritional status of non-institutional population of the United States (U.S.). The participants were recruited through a multistage, complex and probability sampling methods based on broad population distributions. All participants provided the written informed consent, and the study was approved by the NCHS Research Ethics Review Board. More information was obtained from: https://www.cdc.gov/nchs/nhanes/index.htm.

Total 3,752 participants aged ≥ 30 years old and with the periodontitis assessment were initial included from the NHANES 2009–2010. Among them, 260 adults without the measurement of PLP and 1 participant with edentulous were further excluded. Finally, 3,491 eligible adults were included for further analysis. The flow chart of participant selection for the study population were shown in Fig. 1. The requirement of ethical approval for this was waived by the Institutional Review Board of Affiliated Hospital of Nantong University, because the data was accessed from NHANES (a publicly available database). The need for written informed consent was waived by the Institutional Review Board of Affiliated Hospital of Nantong University due to retrospective nature of the study. All methods were performed in accordance with the relevant guidelines and regulations.

Assessment of periodontitis

Oral health including the number of teeth, periodontal pockets, gum recession, and bleeding on probing (BOP). The recession, attachment loss (AL), and BOP were examined by the seasoned measurer using mobile screening facilities. As the part of the NHANES 2009–2010 Oral Health-Periodontal Exam, six sites for each tooth for up to 28 teeth were measured.

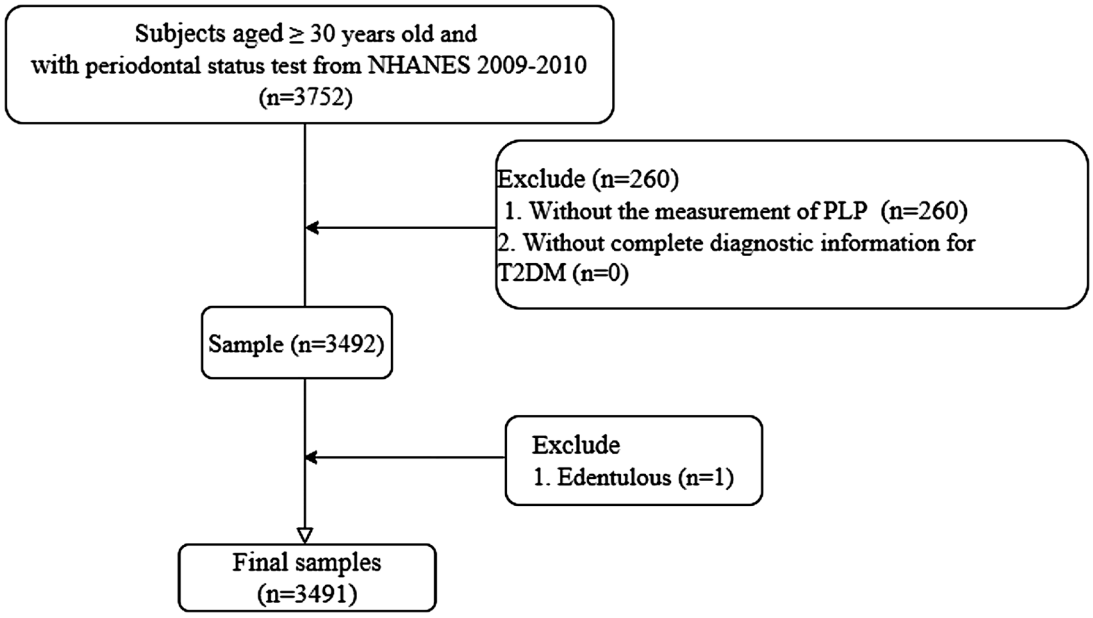

Fig. 1 Flowchart of the study population

Calculated AL (CAL) and probing depth (PD) were used to evaluate the periodontal health. According to the 2012 revision of the periodontitis classification criteria proposed by Eke et al. [18]. The presence of at least two interproximal sites with CAL ≥ 3 mm and at least two interproximal sites with PD ≥ 4 mm (not at the same tooth) or one site with PD ≥ 5 mm were defined as mild periodontitis. Moderate periodontitis was featured by the presence of at least two interproximal sites with CAL ≥ 4 mm or at least two interproximal sites PD ≥ 5 mm (both the sites were not on one tooth). Severe periodontitis was featured by the presence of at least two interproximal sites with CAL ≥ 6 mm and at least one interproximal site with PD ≥ 5 mm. In present study, in order to eliminate the bias caused by the over prevalence of mild periodontitis in the population, we grouped non-periodontitis and mild periodontitis into one category, and moderate, and severe periodontitis in another [19].

Definition of T2DM

Participants were defined as T2DM if their met the criteria as following: glycosylated hemoglobin (HbA1c) ≥ 6.5%, serum fasting glucose ≥ 126 mg/dL or 2 h oral glucose tolerance test (OGTT) ≥ 200 mg/dL, any self-reported diagnosis of T2DM by clinician, or any self-reported take of insulin or other diabetes medication [20].

Measurement of serum PLP level

The detailed laboratory procedures for measuring the serum PLP level were described in the NHANES documentation (https://wwwn.cdc.gov/nchs/data/nhanes/2003-2004/labmethods/l43_c_met_plp.pdf).

Serum PLP level (nmol/L) was measured by a homogeneous, nonradioactive, enzymatic assay (A/C Diagnostics, San Diego, CA, USA). The average intra-assay coefficient of variation (CV) was 7.8–8.3% and the average inter-assay CV from 12.0 to 13.1% were reported. Assay value below the limit of detection were replaced with 7.1 nmol/L (the detection limit of 10.9 nmol/L divided by the square root of 2) [21]. The present study was divided the PLP levels into two groups according to its upper tertile [22].

Potential covariates

Sociodemographic information [age, gender, race, education level, poverty-to-income ratio (PIR) and married status], lifestyle (smoking, drinking and physical activity), physical examination [height, weight, BMI, diastolic blood pressure (DBP) and systolic blood pressure (SBP)], laboratory parameters [serum PLP, HbA1c, fasting glucose, OGTT, triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), c reactive protein (CRP), serum creatinine, urine creatinine and albumin], and complications [dental implants, dental decay, diabetes retinopathy, chronic kidney diseases (CKD), hypertension, dyslipidemia and CVD] were extracted from the NHANES.

PIR was divided into ≤ 1.3 (poor or near poor), 1.3–3.5 (medium income) and > 3.5 (high income) according to the federal poverty level (FPL) [23]. Smoking status was defined as smoking at least 100 cigarettes in life (yes/no). Drinking status was defined as < 1 time/week and ≥ 1 time/week. Dental decay was defined as untreated

caries or restorative needs. CKD was defined as urine albumin-to-creatinine ratio > 30 mg/g or eGFR (estimated glomerular filtration rate) < 60 [24]. Physical activity was described as the metabolic equivalent (MET) and calculated as the following formula: physical activity (met·min/week) = recommended MET exercise time for corresponding activities (min/day) the number of exercise days per week (day) [25]. Diabetic retinopathy was assessed by the participants answered yes to question "Has a doctor ever told you that diabetes has affected your eyes or that you had retinopathy?" Participants were defined as hypertension if they met the flowing criteria: (1) SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg, (2) diagnosed as hypertension by the clinician, (3) taking hypotensive drugs. Dyslipidemia was defined as TC ≥ 200 mmg/dL (5.2 mmol/L) or TG ≥ 150 mg/dL (3.4 mmol/L) or HDL-C ≤ 40 mg/dL (1.0 mmol/L), or self-reported as dyslipidemia or receiving cholesterol-lowering therapy. CVD was assessed by the question "Ever told you had angina or heart failure/heart attack/coronary heart disease/stoke/congestive heart failure?" The drug coding of periodontitis medication was 1–9 to 1–18.

Statistical analysis

Continuous variates were described as mean and standard error (S.E.), and weighted t-test were used for comparison between two groups. Categorical variates were represented as number and percentage [n (%)], and weighted chi-square test were used for comparison between two groups. Sensitivity analysis were performed to evaluate the robustness before and after imputation of missing data (Table S1). The weighted univariate logistics regression analysis was performed to screen the potential covariates related to T2DM and periodontitis (Table S2). The weighted multivariate logistics regression models were utilized to explore the association of serum PLP levels, T2DM and periodontitis, with odds ratios (ORs) and 95% confidence intervals (CIs). Mediation effect analysis was performed to explore the mediation effect of serum PLP between diabetes and periodontitis. The mediation effect was mainly tested through the interaction product of the mediation variable (serum PLP) *independent variable (diabetes) to evaluate the mediation effect of the mediation variable on the independent variable and the outcome variable (periodontitis). Model 1 was a crude model; model 2 adjusted common sociodemographic factors including age, gender, education level and PIR; in addition to these variates, model 3 further adjusted smoking, CKD, and dental decay. Subgroup analysis stratified by age, BMI, CVD and dental decay was further conducted to evaluate whether these associations between serum PLP level, T2DM and periodontitis remain steady.

All statistical analyzes were performed using R v 4.20 (R Foundation for Statistical Computing, Vienna, Austria) and SAS v. 9.4 (SAS Institute, Cary, North Carolina). Two-sided $P < 0.05$ was considered statistically significant. The final sample size was weighted with SDMVPSU, SDMVSTRA and WTMEC2YR.

Results

Characteristic of study populations

The baseline information of all study populations were shown in Table 1. Finally, 3,491 participants were included, with the mean age of 50.42 ± 0.39 years old. Among these populations, 1,999 (57.26%) had periodontitis. In non-periodontitis groups, the proportion of T2DM was significant lower than in periodontitis groups (9.24 vs. 18.41). The difference was found in age, gender, race, marital status, smoking, dental decay, the level of education, PIR and physical activity, and the history of CKD, hypertension, dyslipidemia and CVD (all $P < 0.05$).

Association of T2DM, PLP and periodontitis

The results from the logistics regression analysis regarding the association of T2DM, PLP and periodontitis were reported in Table 2. After adjusted confounders, we observed that patients with T2DM may have a 45% increases odds of periodontitis (OR = 1.45, 95%CI: 1.04–2.02, $P = 0.031$). No significant association was observed in the PLP level and periodontitis ($P > 0.05$).

The modulatory effect of serum PLP on the association of T2DM and periodontitis

Then, the modulatory effect of serum PLP on the association of T2DM and periodontitis was evaluated via the interaction term T2DM × PLP. After adjusted confounders, we found the modulatory effect of PLP on the association of T2DM and periodontitis was prominent (OR = 2.29, 95%CI: 1.47–3.57, $P = 0.001$) (Table 3).

The association of T2DM and periodontitis based on different PLP levels

Table 4 shown the association of T2DM and periodontitis based on different PLP levels (≥ 67.20 nmol/L and < 67.20 nmol). After adjusted age, gender, education level, PIR, smoking, CKD, and dental decay, we found in low PLP level group (< 67.20 nmol/L), participants with T2DM had high odds of periodontitis (OR = 1.82, 95%CI: 1.29–2.55). However, in higher serum PLP concentration group (≥ 67.20 nmol/L), no significant association was observed between participants with and without T2DM and the odds of periodontitis ($P = 0.523$). These findings suggested that higher serum PLP may regulate the odds of periodontitis in patients with T2DM to some extent, that was, serum PLP may play a moderating role between T2DM and the odds of periodontitis.

Table 1 Characteristics of participants

Variables	Total (*n* = 3491)	Non-periodontitis (*n* = 1492)	Periodontitis (*n* = 1999)	*P*
PLP, nmol/L, Mean (S.E)	75.55 (2.22)	78.25 (3.57)	72.93 (2.47)	0.214
PLP, nmol/L, n (%)				0.444
≥67.20	1014 (33.38)	462 (34.06)	552 (32.72)	
<67.20	2477 (66.62)	1030 (65.94)	1447 (67.28)	
T2DM, n (%)				< 0.001
No	2849 (86.10)	1318 (90.76)	1531 (81.59)	
Yes	642 (13.90)	174 (9.24)	468 (18.41)	
Age, years, Mean (S.E)	50.42 (0.39)	45.61 (0.25)	55.09 (0.55)	< 0.001
Age, years, n (%)				< 0.001
<60	2354 (75.07)	1212 (85.37)	1142 (65.09)	
≥60	1137 (24.93)	280 (14.63)	857 (34.91)	
Gender, n (%)				< 0.001
Male	1750 (49.30)	559 (39.80)	1191 (58.50)	
Female	1741 (50.70)	933 (60.20)	808 (41.50)	
Race, n (%)				< 0.001
Non-Hispanic White	1707 (70.53)	817 (75.17)	890 (66.04)	
Non-Hispanic Black	619 (10.74)	244 (9.71)	375 (11.74)	
Others	1165 (18.73)	431 (15.12)	734 (22.22)	
Education, n (%)				< 0.001
High school and below	1714 (38.74)	574 (31.26)	1140 (45.98)	
College and above	1777 (61.26)	918 (68.74)	859 (54.02)	
PIR, n (%)				< 0.001
≤1.3	1003 (17.27)	347 (13.02)	656 (21.38)	
1.3–3.5	1313 (35.35)	541 (33.29)	772 (37.35)	
>3.5	1175 (47.38)	604 (53.69)	571 (41.27)	
Marital status, n (%)				< 0.001
Married	2052 (64.81)	904 (68.17)	1148 (61.56)	
Never married	364 (9.47)	190 (10.36)	174 (8.60)	
Others	1075 (25.72)	398 (21.47)	677 (29.83)	
Smoking, n (%)				< 0.001
No	1913 (56.93)	945 (64.41)	968 (49.69)	
Yes	1578 (43.07)	547 (35.59)	1031 (50.31)	
Drinking, n (%)				0.244
< once /week	2340 (61.64)	1023 (62.89)	1317 (60.43)	
≥once/week	1151 (38.36)	469 (37.11)	682 (39.57)	
Physical activity, met*minutes/week, n (%)				< 0.001
<450	345 (9.50)	156 (10.16)	189 (8.87)	
≥450	2233 (68.81)	999 (70.78)	1234 (66.89)	
Unknown	913 (21.69)	337 (19.06)	576 (24.24)	
Dental implants, n (%)				0.804
No	3417 (98.07)	1459 (98.15)	1958 (98.00)	
Yes	74 (1.93)	33 (1.85)	41 (2.00)	
Dental decay, n (%)				< 0.001
No	2508 (78.44)	1227 (86.29)	1281 (70.84)	
Yes	983 (21.56)	265 (13.71)	718 (29.16)	
Diabetic retinopathy, n (%)				0.935
No	3427 (98.82)	1469 (98.80)	1958 (98.84)	
Yes	64 (1.18)	23 (1.20)	41 (1.16)	
CKD, n (%)				< 0.001
No	3081 (90.96)	1379 (94.17)	1702 (87.85)	
Yes	410 (9.04)	113 (5.83)	297 (12.15)	
Hypertension, n (%)				< 0.001

Table 1 (continued)

Variables	Total (*n* = 3491)	Non-periodontitis (*n* = 1492)	Periodontitis (*n* = 1999)	*P*
No	1915 (59.84)	969 (67.54)	946 (52.38)	
Yes	1576 (40.16)	523 (32.46)	1053 (47.62)	
Dyslipidemia, n (%)				< 0.001
No	807 (23.77)	417 (27.61)	390 (20.05)	
Yes	2684 (76.23)	1075 (72.39)	1609 (79.95)	
CVD, n (%)				< 0.001
No	2833 (83.14)	1306 (87.99)	1527 (78.44)	
Yes	658 (16.86)	186 (12.01)	472 (21.56)	
BMI, kg/m^2, Mean (S.E)	29.05 (0.15)	29.21 (0.21)	28.89 (0.22)	0.332
Obese, kg/m^2, n (%)				0.210
<30	2106 (63.01)	877 (61.56)	1229 (64.41)	
≥30 kg/m^2	1385 (36.99)	615 (38.44)	770 (35.59)	
CRP, mg/dL, Mean (S.E)	0.36 (0.02)	0.36 (0.03)	0.36 (0.02)	0.947
Total energy, kcal, Mean (S.E)	2171.15 (32.57)	2142.56 (32.89)	2198.85 (45.72)	0.224
Vitamin B_6 intake, mg, Mean (S.E)	5.82 (0.27)	5.54 (0.40)	6.09 (0.41)	0.356
Frequency of using dental floss, n (%)				0.255
< three times/week	1761 (47.51)	689 (46.00)	1072 (48.97)	
≥three times/week	1730 (52.49)	803 (54.00)	927 (51.03)	
Antibiotics, n (%)				0.221
No	3387 (96.70)	1440 (96.26)	1947 (97.13)	
Yes	104 (3.30)	52 (3.74)	52 (2.87)	

T2DM: type 2 diabetes mellitus; PLP: pyridoxal 5′-phosphate; PIR: poverty-to-income ratio; met: metabolic equivalent; CKD: chronic kidney disease; CVD: cardiovascular disease; BMI: body mass index; CRP: c-reactive protein

Table 2 Association of PLP, T2DM and periodontitis

Variates	Crude Model		Model 1		Model 2	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
T2DM						
No	Ref		Ref		Ref	
Yes	2.22 (1.59–3.09)	< 0.001	1.58 (1.15–2.18)	0.008	1.45 (1.04–2.02)	0.031
PLP, nmol/L						
≥ 67.20	Ref		Ref		Ref	
< 67.20	1.06 (0.90–1.25)	0.452	1.03 (0.87–1.23)	0.685	0.92 (0.78–1.09)	0.328

OR: odds ratio; CI: confidence interval

Crude model: adjusted nothing

Model 1: adjusted age, gender, education level and PIR

Model 2: adjusted age, gender, education level, PIR, smoke, CKD and dental decay

Table 3 The moderate effect of PLP on the association of diabetes and periodontitis

Variates	Crude Model*		Model 3		Model 4	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
T2DM	1.43 (0.89–2.30)	0.131	0.89 (0.54–1.46)	0.611	0.80 (0.48–1.34)	0.375
PLP	0.96 (0.80–1.14)	0.606	0.92 (0.77–1.11)	0.376	0.83 (0.69–0.99)	0.038
Diabetes * PLP	1.84 (1.09–3.08)	0.025	2.22 (1.38–3.58)	0.003	2.29 (1.47–3.57)	0.001

OR: odds ratio; CI: confidence interval

Model 3: adjusted age, gender, education level and PIR

Model 4: adjusted age, gender, education level, PIR, smoking, CKD and dental decay

Subgroup analysis

The subgroup analysis based on age, obese, CVD, and dental decay were further conducted to explore the modulatory effect of PLP on the association between T2DM and periodontitis. The results suggested that the modulatory effect of PLP on the association between T2DM and periodontitis remain robust, especially in participants aged ≥ 60 years (OR = 4.54, 95CI: 2.15–9.62), obese (OR = 3.06, 95%CI: 1.31–7.18), without the history

Table 4 The association of diabetes and periodontitis at different PLP levels

Variates	Crude Model**		Model 3		Model 4	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
PLP ≥ 67.20 nmol/L (*n* = 1014)						
Non-diabetes	Ref		Ref		Ref	
T2DM	1.43 (0.89–2.30)	0.131	0.91 (0.55–1.51)	0.703	0.86 (0.53–1.40)	0.523
PLP < 67.20 nmol/L (*n* = 2477)						
Non-diabetes	Ref		Ref		Ref	
T2DM	2.62 (1.79–3.84)	< 0.001	1.98 (1.42–2.75)	< 0.001	1.82 (1.29–2.55)	0.002

OR: odds ratio; CI: confidence interval; T2DM: type 2 diabetes mellitus; PLP: pyridoxal 5′-phosphate

Model 3: adjusted age, gender, education level and PIR

Model 4: adjusted age, gender, education level, PIR, smoking, CKD and dental decay

Table 5 Subgroup analysis based on age, BMI, CVD and dental decay

Subgroup & variable	Model			
	OR (95%CI)	*P*	OR (95%CI)	*P*
Subgroup I: Age	< 60 (*n* = 2354)		≥ 60 (*n* = 1137)	
T2DM	1.38 (0.52–3.69)	0.497	0.48 (0.21–1.09)	0.077
PLP	0.87 (0.68–1.11)	0.246	0.68 (0.44–1.06)	0.082
Diabetes * PLP	1.25 (0.49–3.21)	0.626	4.54 (2.15–9.62)	< 0.001
Subgroup II: BMI obese	BMI < 30 kg/m^2 (*n* = 2106)		BMI ≥ 30 kg/m^2 (*n* = 1385)	
T2DM	0.99 (0.46–2.12)	0.971	0.70 (0.28–1.75)	0.425
PLP	0.88 (0.71–1.10)	0.232	0.82 (0.49–1.35)	0.409
Diabetes * PLP	1.97 (0.68–5.72)	0.199	3.06 (1.31–7.18)	0.013
Subgroup III: CVD	No (*n* = 2833)		Yes (*n* = 658)	
T2DM	0.91 (0.46–1.79)	0.763	0.48 (0.14–1.61)	0.219
PLP	0.87 (0.72–1.05)	0.126	0.59 (0.35–0.99)	0.045
Diabetes * PLP	2.25 (1.06–4.79)	0.036	2.95 (0.85–10.18)	0.083
Subgroup IV: Dental decay	No (*n* = 2508)		Yes (*n* = 983)	
T2DM	0.73 (0.40–1.33)	0.287	1.10 (0.22–5.46)	0.899
PLP	0.80 (0.65–0.99)	0.040	0.94 (0.48–1.84)	0.841
Diabetes * PLP	2.93 (1.51–5.68)	0.003	1.00 (0.18–5.59)	0.999

OR: odds ratio; CI: confidence interval; BMI: body mass index; CVD: cardiovascular disease; PLP: pyridoxal 5′-phosphate; T2DM: type 2 diabetes mellitus

Subgroup I: adjusted gender, education, PIR, smoking, CKD, and dental decay

Subgroup II and III: adjusted age, gender, education, PIR, smoking, CKD, and dental decay

Subgroup IV: adjusted age, gender, education, PIR, smoking, and CKD

of CVD (OR = 2.25, 95%CI: 1.06–4.79) and without dental decay (OR = 2.93, 95%CI: 1.51–5.68) (all $P < 0.05$) (Table 5).

Discussion

In this nationally representative study, the associations of vitamin B_6 status (evaluated by serum PLP levels), T2DM and periodontitis in U.S. adults were explored. After adjusted all confounders, the findings were as follows: (1) adults with T2DM had high odds of periodontitis; while, no significant association was found between PLP and periodontist is; (2) adults with low PLP level and concomitant T2DM have high odds of periodontitis; while no association with periodontitis was observed in adults with high PLP level and T2DM; that was, PLP may have a modulatory effect on the association of T2DM and periodontitis; (3) this modulatory effect was robust in subpopulations, especially in adults aged ≥ 60 years, or obese, or without the history of CVD or dental decay.

Clinically, DM and periodontitis are two diseases with a "bidirectional relationship". Continuous high glucose state in DM patients provides rich nutrients to the bacteria in their gums, causing obstructed of the microvascular in the gum tissue, making it more susceptible to oral infection [26]. Besides, high glucose incudes reactive oxygen species (ROS) and increases oxidative stress (OS) level, aggravating periodontal tissue destruction [27]. Inflammatory mediator produces in periodontitis patients can inhibit glycogen synthesis, reduce insulin sensitivity, and be detrimental to glycemic control. Moreover, oral diseases can aggravate a variety of complications in DM patients, including angina, stroke and heart failure [4]. Several previous epidemiologic studies have reported this "bidirectional relationship" between DM and periodontitis [28–30]. Consistent with

previous studies, our study also found an increased odd of periodontitis in T2DM patients (OR = 1.45, 95%CI: 1.04–2.02). Our study provides new evidence for the association between T2DM and periodontitis. Patients with T2DM should be exhorted regarding their elevated risk of T2DM and vice versa. Therefore, it is necessary to explore the appropriate adjustable impact factors in order to reduce the burden of T2DM and periodontitis.

Vitamin B_6 is a type of water soluble vitamin that regulates approximately 150 physiological reactions, including the metabolism of glucose, lipids, amino acids, DNA, and neurotransmitters [31]. Moreover, vitamin B_6 plays the role of antioxidant by confronted the formation of ROS and advanced glycation end-products (AGEs) [6]. PLP is the biologically most active form of vitamin B_6, so, the term "PLP" is used interchangeably with "vitamin B_6" [32]. Epidemiological and experimental studies reported PLP level was significant inverse associated with DM and the clear protective of vitamin B_6 on the DM was suggested [12, 14, 33]. In experimental animals, the inverse relationship between vitamin B_6 and DM was also observed [34, 35]. However, it was still unknown whether vitamin B_6 has a regulatory effect on periodontitis related to T2DM. The result of modulatory effect shown that PLP had a significant modulatory effect on T2DM and periodontitis ($P < 0.001$). Then, we further validated this modulatory effect based on different PLP levels after adjusting for a series of confounding factors that affect the outcomes. The results suggested that T2DM patients with low PLP level also have high odds of periodontitis, while there was no significant increase in the odds of periodontitis in T2DM patients with higher PLP levels. These results suggested that higher levels of vitamin B_6 may partially reduce the odds of periodontitis in T2DM patients. Subgroup analyses suggested that this modulatory effect remains robust, especially among T2DM patients aged ≥ 60 years old, obese, without the history of CVD and dental decay.

The modulatory effect of vitamin B_6 levels on the odds of periodontitis related to T2DM may be mediated by its involvement in inflammatory immune response. Recently, vitamin B_6-dependent inflammatory pathways have been comprehensively researched. Du et al. [36] reported that vitamin B_6 may prevent excessive inflammation by reducing the accumulation of sphingosine-1-phosphate (S1P) in macrophages in an S1P lyase (SPL)-dependent manner. During inflammation, tissue-specific vitamin B_6 depletion leads to decreased PLP levels [37]. Reduced availability of vitamin B6 can also affect insulin resistance by increasing adipose tissue and lipogenesis [38]. In addition, studies have shown that vitamin B6 plays a key role in the production of T lymphocytes and interleukins, and vitamin B6 deficiency can lead to decreased immunity, including the formation of serum antibodies, reduced production of IL-2 and increased IL-4 [39, 40]. Interestingly, PLP also affects the formation of the microbiota, and the composition of the microbiota affects human immunity. Since mammals do not synthesize B6, they obtain food and some intestinal bacteria that constitute the pathway for B6 synthesis [41]. In summary, vitamin B_6 may be involved in a variety of physiological processes in T2DM patients, and inflammation and immune response are only some of the possible mechanisms. The mechanism between vitamin B_6 and T2DM and its complications needs to be further clarified.

T2DM and its implications are a global and complex public health challenge. In present study, complex, stratified, multistage probabilistic sampling method was used to obtained the study samples. The weighted univariate and multivariate logistics regression models were utilized to explore the effect of vitamin B6 levels on the odds of periodontitis among T2DM patients after adjusting various potential confounders. Subgroup analyses based on the characteristics of the study population also showed the robustness of the findings. Regarding the patients with T2DM, maintaining a higher intake of dietary vitamin B_6 and vitamin B_6 supplements may have potential benefits in reducing their risk of periodontitis. However, several limitations of our study also have to be pointed out. First, because this was a cross-sectional study, we can only observe the association between vitamin B_6 and the odds of periodontitis in T2DM patients and could not establish a causal relationship between them. Future well-designed, large-scale Mendelian randomization or randomized controlled trial studies are necessary to further explore the causal association between vitamin B6 and the risk of periodontitis in T2DM populations. In addition, in *vivo* and in *vitro* studies are also necessary to reveal the exact biological mechanisms of vitamin B_6 with T2DM and periodontitis. Second, due to the limitations of the NHANES database, although we considered as many confounding factors as possible that could affect the outcome, some periodontitis treatment information that was not recorded in NHANES, such as subgingival scaling, may have potentially biased the outcome. Last but not least, this study focused on the relationship between vitamin B_6 levels and periodontitis in the United States T2DM patients. Therefore, whether the conclusions of this study are applicable to other populations needs further exploration in future multi-center studies.

Conclusion

We analyzed 3,491 T2DM patients from the NHANES 2009–2010 and observed that high vitamin B_6 may play a modulatory effect on the association between the odds of periodontitis and T2DM. More large-scale, well-designed prospective studies are needed to further verify the modulatory effects of serum PLP on diabetes and

periodontitis, and its related physiological mechanisms also need to be further revealed through in *vivo* and in *vitro* researches.

Abbreviations

DM	Diabetes mellitus
PLP	Pyridoxal 5′-phosphate
CVD	Cardiovascular disease
TRP	Tryptophan
NHANES	National Health and Nutrition Examination Surveys
NCHS	National Center for Health Statistics
U. S.	United States
ERB	Ethics Review Board
BOP	Bleeding on probing
AL	Attachment loss
CAL	Calculated AL
PD	Probing depth
HbA1c	Glycosylated hemoglobin
OGTT	Oral glucose tolerance test
CV	Coefficient of variation
PIR	Poverty-to-income ratio
DBP	Diastolic blood pressure
SBP	Systolic blood pressure
TG	Triglyceride
HDL-C	High-density lipoprotein cholesterol
LDL-C	Low-density lipoprotein cholesterol
TC	Total cholesterol
CRP	C reactive protein
CKD	Chronic kidney diseases
FPL	federal poverty level
MET	Metabolic equivalent

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12903-025-05597-z.

Supplementary Material 1

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Not applicable.

Author contributions
Donghui Song designed the study, Jiang Zhu wrote the manuscript, Jiang Zhu, Wushuang Xu, and Senbin Wu collected, analyzed and interpreted the data, Yujie Li critically reviewed the manuscript, all authors read and approved the manuscript.

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Data availability
The datasets generated during and/or analyzed during the current study are available in the NHANES database, https://www.cdc.gov/nchs/nhanes/index.htm.

Declarations

Ethics approval and consent to participate
The requirement of ethical approval for this was waived by the Institutional Review Board of Affiliated Hospital of Nantong University, because the data was accessed from NHANES (a publicly available database). The need for written informed consent was waived by the Institutional Review Board of Affiliated Hospital of Nantong University due to retrospective nature of the study. All methods were performed in accordance with the relevant guidelines and regulations.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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