Journal of Dental Sciences 20 (2025) 1499–1505

Available online at www.sciencedirect.com

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journal homepage: www.e-jds.com

Original Article

Potential association between periodontitis and liver function test abnormalities: Results from the National Health and Nutrition Examination Survey (NHANES) 2009–2014

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Received 27 December 2024; Final revision received 5 January 2025
Available online 14 January 2025

KEYWORDS
Periodontitis;
Liver function test;
Liver abnormality;
NHANES

Abstract *Background/purpose:* Previous studies have indicated that periodontitis was associated with various liver diseases; however, few large-scale population-level studies were available. This study aimed to conduct a comprehensive investigation into the associations between periodontitis and liver function test (LFT) indexes.

Materials and methods: Data were sourced from 2009 to 2014 the National Health and Nutrition Examination Survey (NHANES) databases, and the study population included 10139 participants. LFTs included indicators of total protein (TP), albumin (ALB), globulin (GLB), alanine transaminase (ALT), aspartate transaminase (AST), gamma-glutamyl transferase (γ-GGT), and alkaline phosphatase (ALP). Propensity score matching (PSM) was used to increase the comparison. Multiple logistic regressions were used to examine the associations between periodontitis and LFT abnormalities in the total sample and age subgroups.

Results: After PSM adjustments, logistic regression results indicated that periodontitis was significantly associated with an increased risk of TP (adjusted odds ratio (AOR) 1.46; 95 % confidence internal (CI): 1.02, 2.10), GLB (AOR 2.02; 95 % CI: 1.18, 3.45), γ-GGT (AOR 1.32; 95 % CI: 1.02, 1.70), and ALP (AOR 2.00; 95 % CI: 1.05, 3.84). In the subgroup aged 45–64 years, there was elevated odds of ALT levels (AOR 1.73; 95 % CI: 1.03, 2.9); in the subgroup aged 65 years or above, we identified a statistically significant association in ALP (AOR 5.39; 95 % CI: 1.62, 17.99).

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https://doi.org/10.1016/j.jds.2025.01.005

Conclusion: Periodontitis is associated with abnormal LFTs. Particularly, periodontitis may increase risks for elevated γ-GGT, ALP, and GLB levels. Furthermore, the relationship between periodontitis and LFTs showed significant heterogeneity across different age groups.

Introduction

Periodontitis is a chronic non-specific inflammatory disease. Globally, it is a major and neglected public health problem. Severe periodontitis was the sixth-most prevalent condition in the world, and the global age-standardized prevalence of severe periodontitis was stable at around 11 % between 1990 and 2010.[1] Among Chinese adults aged 55—64 years, the prevalence of periodontitis was as high as 69 %, and the frequency of participants with severe periodontitis (stage III or IV) was 37.3 %.[2] However, for the public, periodontitis is prone to be overlooked and its treatment is given relatively low priority compared to other health problems. In recent decades, there has been an increasing focus on the relationship between periodontitis and systemic diseases, such as type II diabetes, cardiovascular disease, inflammatory bowel disease, and rheumatoid arthritis.[3—7]

Accumulating evidence from epidemiological studies suggested that periodontitis may be associated with liver diseases. Approximately two million people die from liver disease annually across the globe, accounting for 4 % of all deaths,[8] and it poses a heavy global health burden. A large-scale cross-sectional study involving 4272 individuals in South Korea indicated that the fatty liver index (FLI), a non-invasive surrogate marker for non-alcoholic fatty liver disease (NAFLD), was associated with periodontitis.[9] A nationally representative cohort study in Finland, which followed 6165 patients with periodontitis, demonstrated that periodontitis was associated with an increased risk of incident severe liver diseases, particularly among patients with severe periodontitis.[10]

However, more population-level studies are needed to confirm the relationship between periodontitis and liver status. And that these existing studies have not comprehensively assessed the association between periodontitis and liver function test (LFT) results, representing the most feasible and practical method for evaluating liver health.

LFTs can help identify patterns of liver injury, and facilitate differential diagnosis. LFTs typically include the following indexes: total protein (TP), albumin (ALB), globulin (GLB), alanine transaminase (ALT), aspartate transaminase (AST), gamma-glutamyl transferase (γ-GGT), and alkaline phosphatase (ALP).[11,12] ALB is synthesized exclusively in the liver. A decline in ALB levels typically indicates chronic rather than acute liver diseases due to its long half-life of approximately 21 days.[13] Comprising of α1, α2, β, and γ globulins, GLB is recognized as immunoglobulin because of its immune functions. However, elevated GLB levels can sometimes signify severe liver disease.[14] ALT and AST are the most commonly used indicators of hepatocellular injury. Hepatocellular damage triggers the release of these enzymes into circulation. ALT is considered more specific for liver diseases, since it is predominantly found in the liver, whereas AST is present not only in the liver, but also in skeleton, kidney, and cardiac muscle. ALP and γ-GGT serve as indicators of cholestasis. ALP lacks specificity due to its widespread distribution across various tissues including the liver, bone, intestine, and placenta.[15] γ-GGT primarily catalyzes the transfer of a gamma-glutamyl group from peptides to other amino acids. Its upregulation suggests hepatobiliary conditions such as alcoholic hepatitis and cirrhosis. Compared to ALP, γ-GGT exhibits greater specificity for cholestasis because it is absent from bone tissue.

Therefore, this study aimed to examine the associations between periodontitis and abnormalities in comprehensive LFTs using data from a nationally representative largescale sample. This research may provide more evidence regarding the impact of periodontitis on liver health.

Materials and methods

Data sources and study population

The National Health and Nutrition Examination Survey (NHANES) was conducted by the U.S. CDC's National Center for Health Statistics on a biennial cycle. The NHANES employs a stratified, multi-stage probability cluster sampling method to obtain a sample representative of the U.S. population, and it collects the data on demographics, socioeconomic status, diet, lifestyle, and health conditions. It received ethical approval from the Ethics Review Board of the National Center for Health Statistics. This study used data from three consecutive NHANES cycles (2009—2010, 2011—2012, and 2013—2014), which included the periodontitis examinations.

Inclusion criteria for this study included participants aged 30 years old or older who underwent both full-mouth periodontal examinations and liver function tests. According to the NHANES guidelines, participants were required to have two or more natural permanent teeth eligible for periodontal examination, and a following full-mouth periodontal examination was performed at six sites per tooth (i.e., mesiobuccal, buccal, distobuccal, mesiolingual, lingual, and distolingual) by trained and calibrated examiners. Detailed information regarding the technical aspects of methodologies for periodontal data collection as well as data usability can be found in the

NHANES documentation. The total sample size of this study was 10,139 (Fig. 1).

In order to increase the comparability, propensity score matching (PSM) was performed to reduce or eliminate the interference of confounding variables by matching periodontitis and non-periodontitis groups. PSM facilitates fine individual matching based on predicted propensity scores, thereby enhancing similarity between disease and control groups concerning confounding factors, and allowing for more accurate estimation of causal effects. For each case with periodontitis, one healthy control was selected (ratio 1:1). After PSM, 2647 participants were included in each group. The study population post-PSM was then reanalyzed to further assess the validity and robustness of our findings.

Study variables

Periodontitis status

Participants were categorized into non-periodontitis and periodontitis groups based on the definition of periodontitis established by the Centers for Disease Control/American Academy of Periodontology (CDC/AAP). In detail, periodontitis refers to participants with two or more interproximal sites with clinical attachment loss (CAL) $\geq$3 mm, two or more interproximal sites with probing pocket depth (PPD) $\geq$4 mm (not occurring on the same tooth), or a single site with PPD $\geq$5 mm. Non-periodontitis was defined if there was no evidence indicating the presence of periodontitis.

LFT abnormalities

LFT abnormalities were defined according to the NHANES III criteria: TP $<$ 6.4 g/dL, ALB$<$3.7 g/dL, GLB$>$4.0 g/dL, ALT$>$47 IU/L in males, and $>$30 IU/L in females, AST$>$33 IU/L, γ-GGT$>$65 IU/L in males and $>$36 IU/L in females, and ALP$>$113 IU/L.

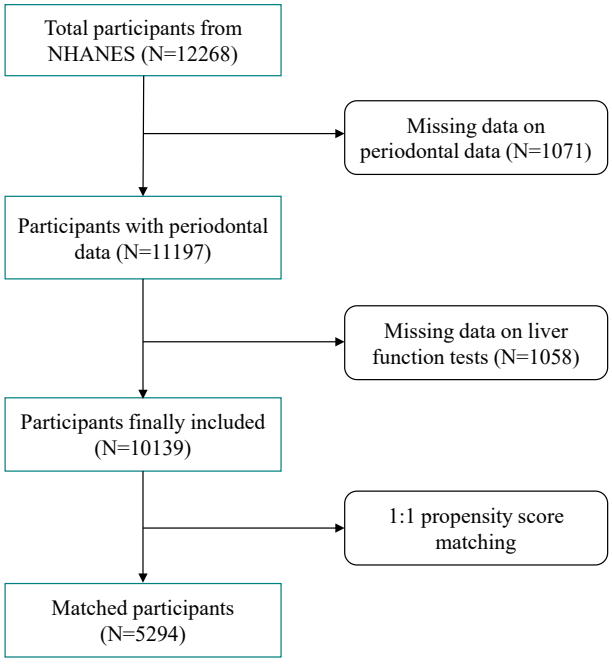

Figure 1 Process map for sample collection from NHANES.

The liver function indices were measured via different methods on a Beckman Coulter DxC800 Synchronous Clinical System. Specifically, the concentration of TP was assessed via a timed rate biuret method; the ALB concentration was determined via a bichromatic digital endpoint method; GLB was calculated by subtracting ALB from TP; ALT and ALP activities in blood were measured through a kinetic rate method; and AST and γ-GGT activities were evaluated via an enzymatic rate method. Detailed measurement protocols are publicly available from the NHANES Analysis Guide (https://wwwn.cdc.gov/Nchs/Nhanes/2013-2014/BIOPRO_H.htm).

Covariates

Multiple confounding variables potentially associated with periodontitis and liver diseases were obtained in the survey, including sociodemographics (i.e., age group, sex, race/ethnicity, education, marital status, annual household income, and body mass index [BMI]), lifestyle factors (i.e., alcohol abuse, and smoking status), health conditions (i.e., hypertension, high cholesterol, diabetes, cardiovascular disease, stomach or intestinal illness, rheumatoid arthritis, chronic kidney disease, Chronic bronchitis, cancer or malignancy, congestive heart failure).

Data analysis

First, descriptive statistics were used to describe the demographic characteristics of the study population. Second, the prevalence of LFT abnormalities among the total sample, non-periodontitis and periodontitis subgroups were calculated, respectively. Third, we compared the mean values of liver function indexes between periodontitis and non-periodontitis subgroups before and after PSM. Finally, multiple logistic regression models were utilized to examine the associations between periodontitis status and LFT abnormalities among the total sample and age subgroups. Continuous variables are presented as means with standard deviation, while categorical variables are described as a percentage. Differences between groups were evaluated using either a weighted Student's t-test (for continuous variables) or weighted chi-square test (for categorical variables). Two-sided levels of significance were set at 0.05. All the statistical analyses accounted for NHANES's complex survey designs, including primary sampling units, strata, and weights, and were performed using R software (Version 4.3.0. https://www.R-project.org).

Results

Characteristics of the study population

Among the total sample, 49.5 % were diagnosed with periodontitis. The majority were aged 45–64 years older (45.48 %), female (51.25 %), non-Hispanic white (69.13 %), with a college degree or above (64.16 %), married (63.72 %), and $25,000-$75,000 annual household income (39.37 %) (Table 1). Also, 13.5 % reported alcohol abuse, and 17.23 % reported smoke use. The most prevalent health conditions included high cholesterol (37.22 %), hypertension (34.30 %),

Table 1 Characteristics of the study sample, stratified by periodontal status: NHANES 2009—2014.

Unweighted sample size	Total n = 10139	Non-periodontitis n = 5118		Periodontitis n = 5021		P-value
Weighted column %	% (SE)	%	(95 % CI)	%	(95 % CI)	
Age group, years						
30 - 44	37.20 (1.53)	45.32	(40.69, 49.94)	25.19	(22.40, 27.98)	<0.001***
45- 64	45.48 (2.11)	42.58	(37.34, 47.83)	49.75	(44.96, 54.54)	
Above 65	17.33 (0.94)	12.10	(10.43, 13.77)	25.06	(27.71, 28.41)	
Sex						<0.001***
Male	48.75 (1.94)	42.42	(37.97, 46.88)	58.28	(53.11, 63.44)	
Female	51.25 (2.07)	57.58	(51.70, 63.45)	41.72	(37.42, 46.02)	
Race/Ethnicity						<0.001***
Non-Hispanic white	69.13 (4.35)	75.05	(65.05, 85.06)	60.61	(51.02, 70.19)	
Hispanic	13.38 (1.27)	10.56	(8.83, 12.30)	17.62	(13.80, 21.44)	
Non-Hispanic African American	10.29 (0.70)	7.75	(6.75, 8.74)	13.86	(11.54, 16.19)	
Others	7.21 (0.55)	6.63	(5.55, 7.71)	7.92	(6.30, 9.53)	
Education						<0.001***
Under 11th grade	15.08 (0.84)	9.10	(7.85, 10.34)	23.92	(21.06, 26.79)	
High school graduate/AA degree	20.76 (1.20)	17.34	(14.88, 19.80)	25.78	(22.72, 28.85)	
College graduate or above	64.16 (2.97)	73.57	(65.30, 81.83)	50.29	(45.41, 55.18)	
Marital status						<0.001***
Unmarried	36.28 (1.18)	31.53	(29.14, 33.92)	43.15	(38.59, 47.72)	
Married	63.72 (3.05)	68.47	(60.40, 76.55)	56.85	(51.26, 62.43)	
Annual household income						<0.001***
<$25,000	23.88 (1.00)	18.01	(16.21, 19.82)	32.05	(29.13, 35.99)	
$25,000 -$75,000	39.37 (1.90)	35.44	(31.44, 39.45)	45.10	(39.67, 50.52)	
Above $75,000	36.75 (2.23)	46.54	(40.37, 52.72)	22.34	(19.40, 25.28)	
Alcohol abuse						<0.001***
No	86.50 (3.54)	89.55	(80.17, 98.92)	81.84	(74.42, 89.25)	
Yes	13.50 (0.68)	10.45	(8.92, 11.98)	18.16	(16.03, 20.29)	
Smoking						<0.001***
No	82.67 (3.40)	88.71	(79.77, 97.65)	73.78	(66.78, 80.79)	
Yes	17.23 (0.69)	11.29	(9.90, 12.68)	26.22	(23.64, 28.79)	
BMI						
<25	26.19 (1.31)	28.50	(24.87, 32.12)	25.29	(22.62, 27.97)	<0.001***
25 - 30	35.73 (1.62)	35.61	(31.67, 39.55)	35.64	(31.96, 39.32)	
≥30	37.08 (1.47)	35.89	(32.28, 39.50)	39.07	(35.07, 43.06)	
Health conditions						
Hypertension	34.30 (1.58)	30.05	(27.04, 33.07)	40.36	(35.38, 45.34)	<0.001***
High cholesterol	37.22 (1.80)	35.76	(31.57, 39.96)	39.14	(34.91, 43.36)	<0.001***
Diabetes	9.61 (0.47)	6.60	(5.65, 7.54)	13.61	(11.89, 15.34)	<0.001***
Cardiovascular diseases	16.33 (0.75)	14.31	(12.21, 16.42)	19.32	(17.49, 21.15)	<0.001***
Stomach or intestinal illness	6.08 (0.47)	6.02	(4.76, 7.28)	6.16	(5.17, 7.16)	<0.001***
Rheumatoid arthritis	3.61 (0.23)	3.13	(2.60, 3.66)	4.25	(3.58, 4.93)	<0.001***
Chronic kidney disease	2.08 (0.19)	1.57	(1.09, 2.05)	2.87	(2.29, 3.46)	<0.001***
Chronic bronchitis	4.97 (0.42)	4.46	(3.61, 5.31)	5.67	(4.41, 6.93)	<0.001***
Cancer or malignancy	10.48 (0.64)	9.78	(8.28-, 1.29)	11.51	(9.62, 13.51)	<0.001***
Congestive heart failure	1.77 (0.17)	0.85	(0.58, 1.13)	3.18	(2.44, 3.91)	<0.001***

SE: standard error, CI: confidence interval.
***Significant difference at $P < 0.001$ by chi-square test.

cardiovascular diseases (16.33 %), and cancer (10.48 %). Periodontitis and non-periodontitis subgroups exhibited distinct distributions in sociodemographic, lifestyle, and health conditions. For instance, compared to the non-periodontitis subgroup, the periodontitis subgroup demonstrated higher proportions of hypertension (40.36 % vs. 30.05 %) and high cholesterol (39.14 % vs. 35.76 %).

Prevalence of abnormal liver function

In the periodontitis group, the prevalence of abnormal liver function was 3.45 % for ALB, 5.90 % for TP, 1.70 % for GLB, 10.98 % for ALT, 12.95 % for AST, 10.97 % for γ-GGT, and 1.48 % for ALP. In the non-periodontitis group, the prevalence of abnormal liver function was 3.06 % for

ALB, 4.54 % for TP, 0.50 % for GLB, 11.38 % for ALT, 10.61 % for AST, 8.63 % for γ-GGT, and 0.92 % for ALP (Fig. 2 & S1).

Mean values of liver function indexes before and after PSM

Higher GLB and ALP values and lower ALB level were consistently observed in the periodontitis group than those in the non-periodontitis group before and after PSM (Fig. 3).

Adjusted analyses of associations between periodontitis status and LFT abnormalities after PSM

Logistic regressions controlling for age, sex, race, education, marital status, annual household income, alcohol abuse, smoking status, BMI, health conditions indicated there was a positive association between periodontitis and abnormal liver function. After PSM, periodontitis was associated with increased odds of abnormal GLB (AOR 2.02, 95 % CI: 1.18, 3.45), abnormal ALP (AOR 2.00, 95 % CI: 1.05, 3.84), abnormal TP (AOR 1.46, 95 % CI: 1.02, 2.10), and abnormal γ-GGT (AOR 1.32, 95 % CI: 1.02, 1.70) (Fig. 4).

The associations between periodontitis and LFT abnormalities showed a significant heterogeneity across different age groups (Fig. 5). Specifically, among ages 30–44 years old, periodontitis was significantly associated with an elevated risk of abnormal GLB (AOR 4.19, 95 % CI: 1.59, 10.99); among ages 45–64 years old, periodontitis was significantly associated with an elevated risk of abnormal ALT (AOR 1.73, 95 % CI: 1.03, 2.91); among ages ≥65 years old, there was a relatively strong association of abnormal ALP (AOR 5.39, 95 % CI: 1.62, 17.99).

Discussion

To our knowledge, this study is among the first to comprehensively examine the associations between periodontitis and liver function indexes. Our findings indicate that there were significant associations between periodontitis and LFT abnormalities in TP, GLB, γ-GGT and ALP. Notably, this study presents patterns of liver diseases that may be affected by periodontitis: immune hyperfunction, or cholestatic liver diseases. These results suggest that periodontitis may have an impact on liver function indicators to inform paying more attention to the liver conditions among patients with periodontitis.

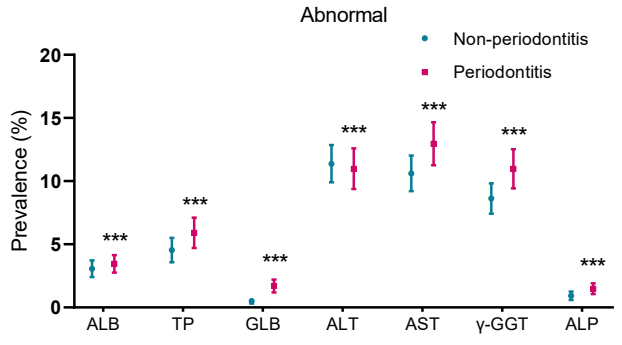

Figure 2 Prevalence of liver function test abnormalities among non-periodontitis and periodontitis group. Data are presented as percentage ±95%CI. ***Significant difference, at $P < 0.001$ by chi-square test.

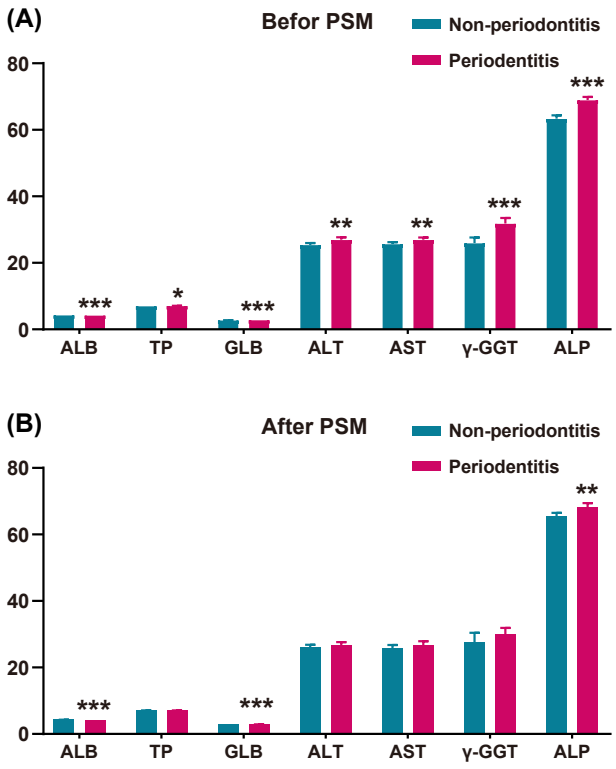

Figure 3 Values of liver function indexes in non-periodontitis and periodontitis group before and after PSM. Data are presented as mean ± SD. Group difference was determined by two sample T test or Wilcoxon test as appropriate. PSM: propensity score matching. ***Significant difference at $P < 0.001$; **Significant difference at $P < 0.01$; *Significant difference at $P < 0.05$.

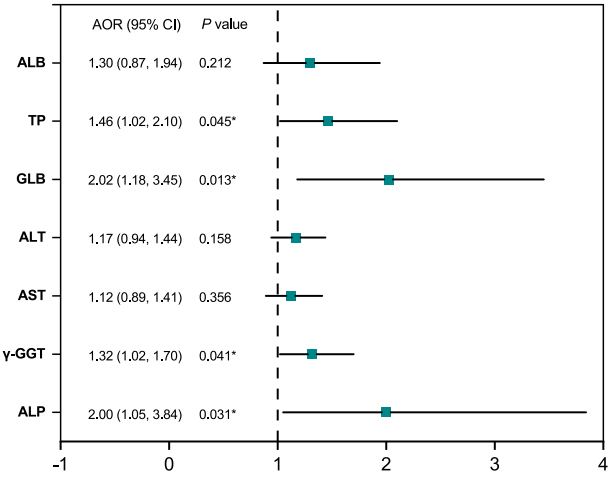

Figure 4 Logistic regression forest plot of the associations of periodontitis with liver function tests abnormalities after PSM. AOR: adjusted odds ratio. CI: confidence interval.

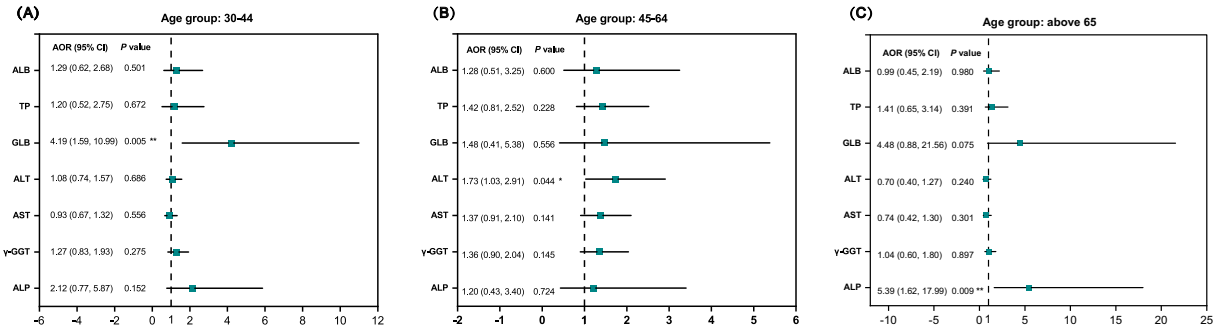

Figure 5 Forest plot depicting the associations between periodontitis and abnormal liver function indexes in different age groups. AOR: adjusted odds ratio. CI: confidence interval.

Our findings from large-scale population-level data indicated a positive association between periodontitis and certain abnormal liver function, which is in line with some studies. Periodontitis is characterized as a low-grade systemic inflammation.[16] The local invasion and long-distance translocation of periodontal pathogens can induce systemic inflammation, activate the immune response, and lead to elevated levels of immunoglobulin.[17,18] The liver is continuously exposed to various pathogenic factors originating from the oral cavity, including bacteria or their products, inflammatory cytokines, and reactive oxygen species, and these factors may play a vital role in the progression of liver diseases.[19] The increase of GLB levels could be partially associated with rise in serum antibody levels targeting specific periodontal pathogens.[20] Additionally, elevated serum immunoglobulins are also observed in certain liver diseases, such as autoimmune hepatitis (increased IgG), primary biliary cirrhosis (increased IgM), and alcoholic liver disease (increased IgA).[21,22] Moreover, elevated IgA have frequently been reported in patients with NAFLD and serve as an independent predictor of advanced fibrosis.[23] Therefore, further evaluation of serum immunoglobulin subtypes (IgA, IgG, and IgM) may assist in diagnosing various liver diseases. In this study, periodontitis was closely associated with TP and GLB levels, which suggests that periodontitis may contribute to the hyperactivity of the immune system.

Our findings indicate that periodontitis was associated with an increased risks of γ-GGT and ALP levels, suggesting a potential contribution of periodontitis to cholestatic liver abnormalities. Cholestasis refers to the impairment of bile formation and/or bile flow. γ-GGT, a type II transmembrane protein synthesized in the epithelial cells lining the intrahepatic bile duct, plays a crucial role as an enzyme in the catabolism of glutathione (GSH) and in cysteine metabolism.[24] The observed association between elevated γ-GGT levels and periodontitis aligns with previous research involving 1510 Japanese adults, which found that serum γ-GGT were associated with periodontal disease independent of alcohol consumption.[25]

However, the associations between periodontitis and LFT abnormalities across different age groups were inconsistent with those observed in the overall population. In the subgroup aged 45—64 years old, periodontitis was significantly associated with an increased risk of ALT elevation, potentially indicating hepatocellular impairment. In the subgroup aged 65 years or above, periodontitis was associated with a heightened risk of elevated ALP. This association may be attributed to cholestasis in older people or may result from other inflammatory condition.

This study has several limitations. First, the results may be limited to the U.S. population and may not be generalizable to broader populations. Next, due to the complexity of liver conditions, a single test cannot definitively diagnose liver diseases; it must be interpreted in conjunction with clinical manifestations. Furthermore, after PSM processing, the dataset was significantly reduced, which could result in loss of information. Last, the 2017 EFP/AAP new classification could not be applied because of missing relevant data in the NHANES database.[26,27]

In summary, periodontitis was associated with certain liver function abnormalities. It is noteworthy that we found that periodontitis was associated with an increased risk of γ-GGT, ALP, and GLB, which are indicators of cholestatic liver diseases and heightened immune activity. Additionally, periodontitis seems to have varying effects on liver status across different age groups. These findings need to be further confirmed with observational studies and animal experiments.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

Acknowledgement

This research was supported by research funds from the National Natural Science Foundation of China (Grant number 82071117), Beijing, China; the Special Funds for Basic Scientific Research of Central Universities (Grant Number: BMU2020YJ001, PI: H. Zhu), Beijing, China.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jds.2025.01.005.

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