Original Article

Association between serum vitamin D and depression among non-alcoholic fatty liver disease

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Background and Objectives: While previous population-based studies have suggested a link between serum vitamin D levels and depression in individuals with non-alcoholic fatty liver disease (NAFLD), the exact correlation between serum vitamin D and depression among NAFLD patients remains controversial and disputed. Thus, we conducted this study to evaluate the relationship between serum vitamin D and depression in NAFLD participants diagnosed via transient elastography. **Methods and Study Design:** This cross-sectional study was extracted from the latest NHANES 2017–2018 dataset. Depression was assessed using the Patient Health Questionnaire-9 (PHQ-9) score of ≥10. NAFLD phenotype was identified by vibration-controlled transient elastography (VCTE) examination based on diagnostic criteria. Binary logistic regression models were applied to estimate the impact of increased serum vitamin D on the reduced risk of depression based on sample weights. **Results:** A total of 1339 participants with NAFLD were included in this investigation, of which 127 (8.58%) were diagnosed with depression according to PHQ-9 scores. Binary logistic regression analysis presented that high serum vitamin D level was a protective factor for depression in NAFLD (OR=0.61, 95% CI: 0.37–0.99, *p*=0.048) after adjusting for all confounding factors. In subgroup analyses, these associations were more pronounced among men (OR=0.32, 95% CI: 0.13-0.81, *p*=0.024) and obese population (OR=0.53, 95% CI: 0.33-0.86, *p*=0.019). **Conclusions:** Increased serum vitamin D was negatively associated to the prevalence of depression in males and obese individuals with NAFLD diagnosed by VCTE.

Key Words: depression, vitamin D, NAFLD, cross-sectional study

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is described as a chronic liver disorder characterized by hepatic steatosis without excessive alcohol use or other known causes of fatty liver.[1] Non-alcoholic fatty liver (NAFL), non-alcoholic steatohepatitis (NASH) and hepatic fibrosis are subgroups of NAFLD that may lead to adverse clinical, economic and patient-reported outcomes.

Depression is considered a major psychological comorbidity of NAFLD, with an estimated prevalence between 7% and 27% among individuals with the condition.[2, 3] Depression leads to poor adherence to lifestyle and dietary modifications, which are the cornerstone of NAFLD management and recommended as the first line treatment.[4] More than half of depression cases in patients with NAFLD are not correctly diagnosed, and very few receive adequate antidepressant treatment. Therefore, exploring suitable and effective treatments for depression in NAFLD patients has become increasingly imminent.

There is mounting evidence of the significant impact of vitamin D on calcium absorption, phosphorus digestibility and bone structure.[5] In addition, a growing number of *in vivo* and *in vitro* studies establish an extra-skeletal link between vitamin D insufficiency and a range of medical issues.[6] Vitamin D insufficiency is prevalent worldwide, with an estimated one billion individuals throughout the world have low vitamin D levels (i.e., hypovitaminosis D; serum 25-hydroxyvitamin D [25(OH)D] concentration <20ng/mL or 50nmol/L).[7] It is generally accepted that the cutoff range of 25 (OH) D is between 30-60 ng/mL and with 'insufficiency' defined as <20ng/mL or 50nmol/L. However, determining the optimal critical value to define vitamin D deficiency or insufficiency remains a controversial issue.[7, 8]

Many researchers have reported that patients with low blood levels of vitamin D had a high probability of moderate-severe steatosis and liver fibrosis, implying that vitamin D insufficiency might contribute to the occur-

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rence and development of hepatic diseases.[9, 10] In the context of depression, some animal studies have shown that vitamin D can be effective in treating depressive disorders, while several population-based studies have not reached a consensus on whether vitamin D has antidepressant effects.[11-17] Based on previous observations, the exact correlation between serum vitamin D levels and depression in NAFLD individuals remains controversial and disputed. Therefore, we conducted this study to evaluate the relationship between serum vitamin D [25(OH)D] and depression among American participants with NAFLD, as defined by transient elastography in the NHANES 2017–2018 cycle survey dataset.

METHODS

Depression score

Depression score is determined by the Patient Health Questionnaire-9 (PHQ-9). The PHQ-9 form is completed during the face-to-face interview at the mobile examination center and is designed to assess the frequency of depression symptoms over the past two weeks. Each item on the questionnaire is scored from 0 to 3, resulting in a total PHQ-9 score range of 0 to 27. In this study, a PHQ-9 score of ≥ 10 is defined as indicating depression, based on previous studies, which have reported a specificity and sensitivity of 88% for this cutoff.[18, 19]

Definition of NAFLD

"Previously used methods, such as liver enzyme tests and liver ultrasound examinations, were not reliable for assessing hepatic steatosis and fibrosis. For the first time, the NHANES 2017–2018 survey used VCTE to detect liver fat, due to its higher sensitivity (80%) and specificity (70%) as indicated by a controlled attenuation parameter (CAP) score of ≥285 dB/m, compared to liver enzymograms or liver ultrasound examinations.[20,21]

Sample sources and study population

NHANES is a population-based survey designed to provide representative samples of the U.S. population. The dataset from the 2017–2018 cycle was used for this analysis because it was the only cycle with information on essential parameters, including PHQ-9 scores, blood vitamin D levels, and liver VCTE.

A total of 9,254 participants were enrolled in this cycle of the investigation. Of these, 3,036 participants did not receive a VCTE examination, 1,379 lacked blood vitamin D level data, and PHQ-9 data were omitted for some. After excluding 1,071 participants with excessive alcohol use, other causes of fatty liver, or missing key parameters, 3,498 participants remained. Other causes of fatty liver included viral hepatitis (Hepatitis B or C), autoimmune hepatitis, and liver cancer. Important parameters considered were age, sex, race, glycosylated hemoglobin (HbA1c), moderate activity status, body mass index (BMI), and relevant blood biochemical values. Ultimately, the study population comprised 1,339 NAFLD participants with CAP scores ≥285 dB/m, among whom 127 were identified as having depression based on PHQ-9 scores (Figure 1).

Covariates

Sociodemographic information and lifestyles were obtained from NHANES 2017-2018 survey cycle. Daily alcohol consumption was assessed using two 24-hour dietary recall interviews. Participants consuming ≥20 g/day of alcohol for males or ≥10 g/day for females were classified as heavy drinkers. If a participant completed both 24-hour recall and food intake frequency interviews, average alcohol intake was calculated based on this data.[22] Otherwise, alcohol intake was determined from the first 24-h recall and food intake frequency interview. Obesity was categorized as non-obesity (BMI<30 kg/m^2) and obesity (BMI≥30 kg/m^2).[23] The serum concentration

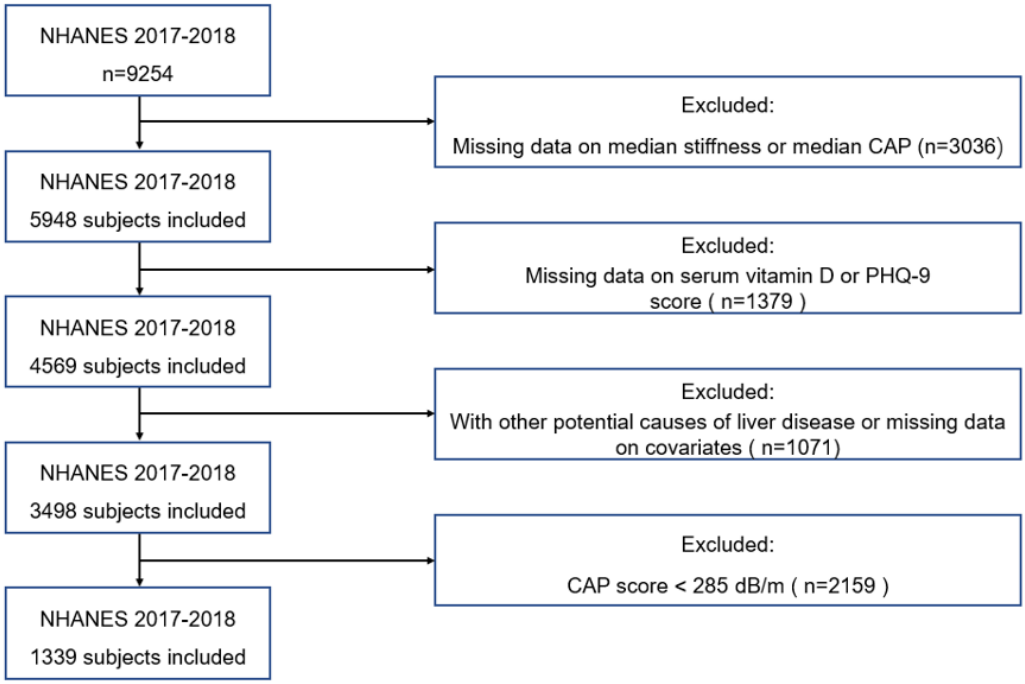

Figure 1. Flowchart of the sample selection in the 2017–2018 NHANES.

of 25-hydroxyvitamin D [25(OH)D] was determined by liquid chromatography. Participants with insufficient vitamin D had serum concentrations of less than 20 ng/mL or 50 nmol/L, while those with sufficient vitamin D had serum concentrations of 20 ng/mL or greater (50 nmol/L), according to the guidelines from the Food and Nutrition Board.

Statistics methods

Data information was analysed and processed by R package (version 3.5.1, https://www.r-project.org/) and SPSS software. p values of < 0.05 (two-sided) was statistically significant. Continuous variables were compared using Student's t-test, and categorical variables were compared using the chi-squared test. In accordance with NHANES guidelines, each sample was weighted accordingly.

Binary logistic regression models were constructed to assess odds ratios (ORs) and weighted percentages (95% CI) related to serum vitamin D concentration and depression. Model 1 did not adjust for any covariates. Model 2 adjusted for age and sex. Model 3 adjusted for age, race, sex, season of blood draw, and BMI. Additionally, we performed a subgroup analysis based on two variables: sex (male/female) and obesity (yes/no).

RESULTS

Baseline characteristics

Table 1 displays the baseline characteristics of the overall sample. A total of 1,339 individuals diagnosed with NAFLD were included in this investigation. Of these, 127 subjects were identified with depression, resulting in a depression rate of 8.58% (weighted prevalence, the same below). The mean age of the participants was 51.5 ± 16.1 years. Among these NAFLD patients, 55.9% were men, 44.1% were women, 64.1% were non-Hispanic White, 12.6% were Mexican-American, 7.77% were non-Hispanic Black, 5.61% were of other Hispanic descent, and 4.99% were non-Hispanic Asian. Compared to NAFLD participants in the non-depressed group, those with depression were more likely to have diabetes mellitus and higher levels of glycosylated hemoglobin (HbA1c) and BMI. There were no significant differences in gender, age, race, season of blood draw, aspartate aminotransferase (AST), total cholesterol, CAP, and LSM among the groups with and without depression. The proportion of vitamin D sufficiency was significantly lower in depressed participants ($p < 0.05$), though there was no significant difference in serum vitamin D levels ($p > 0.05$).

Table 1. Basic characteristics of participants with NAFLD (n = 1339) in the 2017–2018 NHANES by depression status[†‡]

	NAFLD (n=1339) Mean±SD (weight %)	Non-depressed (n=1212) Mean±SD (weight %)	Depressed (n=127) Mean±SD (weight %)
Gender			
Male	731 (55.94)	674 (56.79)	57 (46.93)
Female	608 (44.06)	538 (43.21)	70 (53.07)
Season of blood draw			
Cold season	646 (46.27)	585 (46.39)	61 (45.07)
Warm season	693 (53.73)	627 (53.61)	66 (54.93)
Age (years)	51.5 ± 16.1	51.5 ± 16.1	51.7 ± 16.1
Race			
Non-Hispanic white	500 (64.14)	448 (64.33)	52 (62.08)
Mexican-American	260 (12.61)	236 (12.78)	24 (10.8)
Non-Hispanic black	229 (7.77)	214 (7.95)	15 (5.86)
Non-Hispanic Asian	164 (4.99)	153 (5.1)	11 (3.77)
Other Hispanic	115 (5.61)	98 (5.18)	17 (10.11)
Other races	71 (4.89)	63 (4.66)	8 (7.39)
BMI (kg/m^2)	34.7 ± 7.36	34.5 ± 7.36	36.8 ± 7.09*
Diabetes			
Yes	457 (29.11)	406 (28.37)	51 (37.04)
No	882 (70.89)	806 (71.63)	76 (62.96)
Moderate activities			
Yes	478 (41.46)	447 (42.47)	31 (30.69)
No	861 (58.54)	765 (57.53)	96 (69.31)
HbA1c (%)	6.09 ± 1.21	6.08 ± 1.19	6.23 ± 1.45
Total cholesterol (mmol/L)	4.93 ± 1.09	4.94 ± 1.10	4.82 ± 0.92
AST (IU/L)	22.4 ± 10.4	22.4 ± 10.2	23.0 ± 12.2
CAP (dB/m)	332 ± 34.1	332 ± 34.0	337 ± 34.6
LSM (kPa)	7.63 ± 7.62	7.62 ± 7.65	7.73 ± 7.31
Serum vitamin D (nmol/L)	70.9 ± 30.0	71.0 ± 29.6	69.6 ± 34.2
Serum vitamin D levels			
Vitamin D insufficiency	430 (25.26)	389 (24.53)	41 (33.09)
Vitamin D sufficiency	909 (74.74)	823 (75.47)	86 (66.91)

[†]Continuous covariate data was presented as mean±SD and p value was calculated by weighted linear regression.
[‡]Classified covariate data was presented as unweighted frequency (weighted percentage) and p value was calculated by weighted.

Relationship between blood vitamin D levels and depression among NAFLD

As shown in Table 2, we constructed three additive models to evaluate the independent effects of blood vitamin D levels on the incidence of depression among NAFLD individuals. The logistic regression analysis revealed that increased blood vitamin D was independently associated with depression. Model 1 displayed that NAFLD individuals with sufficient vitamin D concentration in blood linked to a lower risk of depression than those with insufficient vitamin D concentration (OR=0.66, 95% CI: 0.48-0.90, p=0.012), suggesting that high blood vitamin D levels took a significant role in downregulating the occurrence of depression for NAFLD patients. Moreover, NAFLD patients with sufficient vitamin D levels were still at lower risk of depression compared to those with insufficient levels, even after adjusting for potentially confounding variables in Model 3 (OR=0.61, 95% CI: 0.37–0.99, p=0.048).

Subgroup analysis

Subgroup analysis by sex and BMI was performed, but no strong negative correlation was observed in either females (OR = 1.12, 95% CI: 0.52-2.42, p = 0.7) or in individuals who were not obese (OR=3.42, 95% CI: 0.47-24.9, p=0.2) (Table 3). Subgroup analysis by sex revealed that the inverse relationship between low vitamin D levels and depression was consistent among men (OR = 0.32, 95% CI: 0.13-0.81, p = 0.024) and the overall study population but was not observed among women. In the BMI-based subgroup analysis, vitamin D showed a significant inverse association with depression in obese individuals across all models (OR = 0.53, 95% CI: 0.33-0.86, p = 0.019). However, no significant negative associations were found among individuals who were not obese in any model.

DISCUSSION

This population-based investigation aimed to assess the independent effects of blood vitamin D levels on depression prevalence among American NAFLD individuals diagnosed via VCTE. This is the first study to identify a negative relationship between elevated serum vitamin D levels and depression prevalence in NAFLD patients, particularly among males and obese individuals.

As a major mental illness, depression is an important psychological comorbidity of NAFLD. A population-based study indicated that compared to individuals without NAFLD, the prevalence of depression was higher in patients with NAFLD (27.2%).[3] Kim et al. reported that depression was independently associated with NAFLD and significant fibrosis among adults in the United States.[24] Moreover, a large multicentre cohort of Japanese with NAFLD showed that steatosis, ballooning, and lobular inflammation were independently correlated with depression.[25] Currently, there are no licensed medications to improve or alleviate the pathological progression of NASH or advanced liver fibrosis. Therefore, lifestyle and dietary modifications are the cornerstone of disease management and are recommended as the first-line treatment. However, depressive disorders have been confirmed to contribute to poor adherence to dietary and physical ac-

Table 2. Relationship between blood vitamin D levels and depression among NAFLD

Serum vitamin D	OR	95% CI	*p*-value
Model 1†			
Vitamin D insufficiency	Reference		
Vitamin D sufficiency	0.66	0.48, 0.90	0.012*
Model 2‡			
Vitamin D insufficiency	Reference		
Vitamin D sufficiency	0.64	0.45, 0.92	0.019*
Model 3§			
Vitamin D insufficiency	Reference		
Vitamin D sufficiency	0.61	0.37, 0.99	0.048*

OR = Odds Ratio; CI = Confidence Interval
†Model 1: covariables were not adjusted.
‡Model 2: covariables were adjusted for age and sex.
§Model 3: covariables including age, race, sex, season of blood draw and BMI were further adjusted.
**p*-value<0.05 vs. the insufficient vitamin D concentration group

Table 3. Subgroup analysis for the relationship between blood vitamin D levels and depression among NAFLD†‡

Serum vitamin D	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 2 OR (95% CI)
Stratified by sex			
Male	0.44 (0.22, 0.85)*	0.39 (0.20, 0.74)*	0.32 (0.13, 0.81)*
Female	1.00 (0.55, 1.85)	1.05 (0.59, 1.87)	1.12 (0.52, 2.42)
Stratified by BMI			
Non-obese	2.99 (0.51, 17.5)	2.37 (0.41, 13.6)	3.42 (0.47, 24.9)
Obese	0.63 (0.43, 0.92)*	0.61 (0.41, 0.92)*	0.53 (0.33, 0.86)*

OR = Odds Ratio; CI = Confidence Interval
†Weighted logical regression models were adopted for subgroup analysis.
‡The models were not adjusted for the stratification variable itself.
**p*-value<0.05 vs. the insufficient vitamin D concentration group

tivity modifications.[26] Compared to non-depressed individuals, depressed patients were three times more likely to non-compliance with medical treatment recommendations for chronic diseases.[27] Therefore, it is urgent to identify effective approaches to manage depression in NAFLD patients.

Experiments in cellular and animal models have confirmed that blood vitamin D could be a candidate for immunoregulation in hepatic steatosis. It is well accepted that vitamin D can reduce the severity of NAFLD by inhibiting the production of proinflammatory factors, such as interleukins (IL), tumor necrosis factor-α (TNF-α), and tissue inhibitor of metalloproteinase-1 (TIMP-1). Over the past decades, researchers have become increasingly interested in the link between vitamin D and the pathogenesis of depression. Accumulating evidence from animal models suggests that vitamin D can regulate neuronal survival and differentiation by increasing levels of neurotrophins in the brain, such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and neurotrophin-3 (NT-3). Restoring BDNF expression has been shown to help treat depression, while NT-3 and NGF may benefit the proliferation and survival of neural progenitor cells, thus affecting depression either directly or indirectly.[11-13] In contrast to animal studies, population-based findings on whether vitamin D has antidepressant effects have not reached a consensus.[14, 15] Pan et al. found no correlation between depressive symptoms and vitamin D levels in the Chinese population.[28] Ganji et al. reported that lower serum vitamin D levels were associated with a non-significant but increased risk of depression in the adult U.S. population.[29] However, Hoogendijk et al. found a significant association between low 25(OH)D levels and depression in elderly residents from the Netherlands.[15] Similarly, our study found that higher levels of vitamin D were correlated with a decreased risk of depression among NAFLD subjects. The inconsistent results of these observational studies may be due to insufficient consideration of various concomitant diseases and sociodemographic factors, such as gender, race, BMI, family affluence, education levels, diet, alcohol consumption, and smoking.

This cross-sectional investigation assessed the relationship between blood vitamin D levels and depression among NAFLD males but did not include females. Recent studies have similarly reported that serum 25(OH)D levels are unrelated to depression in females.[30] This gender difference is likely due to the protective effects of the sex hormone estrogen against depression.[31] As a result, the impact of blood vitamin D on depression was less pronounced among NAFLD females. Additionally, obesity and depression are significantly correlated. Recent studies have shown that effective weight loss can reduce depression scores and improve depressive symptoms in obese individuals.[32] Similarly, the subgroup analysis stratified by BMI in this investigation also showed a statistically significant association among the obese participants. All the results revealed the importance of blood vitamin D on decreasing the risks of suffering from depression in NAFLD, particularly in obese individuals. However, the optimal cutoff for BMI to define obesity is inconsistent, and further research and discussion are needed for clarification.

Several limitations of this investigation should be highlighted. First, due to the cross-sectional nature of the survey design, establishing causal relationships is difficult, and the direction of causality remains uncertain. Second, the relatively small number of positive cases may lead to unstable results that need to be confirmed in future studies. Additionally, the recent shift from NAFLD to metabolic dysfunction-associated fatty liver disease (MAFLD) suggests that further research is needed to clarify the precise relationship between serum vitamin D levels and depression in both MAFLD and NAFLD.

Conclusion

The inverse association between blood vitamin D levels and depression in NAFLD patients identified by VCTE is clear, particularly among men and those who are obese. This data offers new insights into the prevention and management of depression in NAFLD patients.

CONFLICT OF INTEREST AND FUNDING DISCLOSURE

The authors declare no competing interests.

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