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

doi: 10.6133/apjcn.202408/PP.0005
Published online: August 2024

Running title: Vitamin D and Depression among NAFLD

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ABSTRACT

Background and Objectives: On the basis of the previous population-based observations linking serum vitamin D to depression in non-alcoholic fatty liver disease (NAFLD) phenotype, the precise correlation between serum vitamin D and depression among NAFLD individuals remains controversial and in dispute. 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) scores 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 decreased 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 obesity population (OR=0.53, 95% CI: 0.33-0.86, *p*=0.019). **Conclusions:** Increased serum vitamin D was negatively related with the prevalence of depression in males and obese subjects with NAFLD diagnosed by VCTE.

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

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is described as one chronic liver disorder with a characteristic of hepatic steatosis without excessive alcohol use and other causes of fatty liver.[1] Non-alcoholic fatty liver (NAFL), non-alcoholic steatohepatitis (NASH) and hepatic fibrosis are the subgroups of NAFLD which might result in adverse clinical, economic and patient-reported outcomes.

Depression has been viewed as one major psychological comorbidity of NAFLD with an estimated prevalence between 7% and 27% among individuals with NAFLD.[2, 3] Depression results in poor adherence to lifestyle and dietary habits modifications, which are the mainstay of NAFLD management and are recommended as the first line treatment.[4] More than half of depression cases are not correctly diagnosed in patients with NAFLD, and very few cases

receive adequate antidepressants. Therefore, the study to explore suitable and efficient treatment for depression among patients with NAFLD becomes very imminent.

There is mounting evidence of tremendous 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 conceded that the cutoff range of 25 (OH) D is between 30-60 ng/mL and with 'insufficiency' defined as <20ng/mL or 50nmol/L, even though an optimal critical value to define vitamin D deficiency or insufficiency has remained to be 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 occurrence and development of hepatic diseases.[9, 10] In the context of the depression, some animal investigations displayed that vitamin D was responsible for the treatment of depressive disorder, while several population-based findings on whether vitamin D possessed antidepressive effects didn't achieve a consensus.[11-17] Based on the previous observations, the precise correlation between serum vitamin D levels and depression among NAFLD individuals still remains controversial and in dispute. Thus, we conduct this study to evaluate the relationship between serum vitamin D [25 (OH) D] and depression among American participants with NAFLD defined by transient elastography of NHANES 2017–2018 cycle survey dataset.

MATERIALS AND METHODS

Depression score

Depression score is determined by the Patient Health Questionnaire-9 (PHQ-9). The PHQ-9 form is fulfilled during the face-to-face mobile exam centre interview and is designed to evaluate the frequency of depression symptoms during the past two weeks. Each entry of the questionnaire is 0 to 3 scores, thus the range of PHQ-9 scores are 0 to 27. In this investigation, PHQ-9 scores ≥ 10 are defined as depression based on previous studies, with a specificity and sensitivity of 88%.[18, 19]

Definition of NAFLD

Previously described methods including liver enzymogram and liver ultrasound examination to determine the adipohepatic degree and fibrosis of the liver were not reliable. NHANES 2017–2018 utilized VCTE to detect liver fat for the first time by reason of higher sensitivity (80%) and specificity (70%) presented via control attenuation parameter (CAP) score of ≥285 dB/m than liver enzymogram or liver ultrasound examination.[20,21]

Sample sources and study population

The NHANES is a population-based survey with the purpose of providing the representative samples of population living in American. The dataset from 2017 to 2018 was used to conduct this population-based analysis since this cycle was the only cycle with information on essential parameters including PHQ-9 scores, blood vitamin D levels and liver VTCE.

There were altogether 9254 participants enrolled in this investigation cycle. 3036 participants not receiving VCTE examination or 1379 participants lack of blood vitamin D levels and PHQ-9 data were omitted from this cross-sectional study. Eventually, 3498 participants remained after 1071 participants with excessive alcohol use, other causes of fatty liver or missing important parameters were excluded. Other causes of fatty liver were composed of viral hepatitis (Hepatitis B or Hepatitis C), autoimmune hepatitis and cancer of the liver. In addition, important parameters were composed of age, sex, race, glycosylated haemoglobin (HbA1c), moderate activity status, body mass index (BMI) and interesting blood biochemical values. Ultimately, 1339 NAFLD participants with CAP scores ≥285 dB/m composed the study population, among whom 127 were identified with 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 given by two 24-h dietary recall interviews. Participants with daily alcohol consumption ≥ 20 g/day for males or ≥10 g/day for females e were identified with heavy drinkers. Provided that a participant finished two 24-h recall and food intake frequency interviews, average alcohol intake was calculated based on the interviews data.[22] Otherwise, the alcohol intake was calculated according to the first 24-h recall and food intake frequency interview. Obesity degree was grouped into non-obesity (body mass index, BMI<30 kg/m^2) and obesity (BMI≥30 kg/m^2).[23] The serum concentration of 25-hydroxyvitamin D [25(OH)D] was determined by liquid chromatography. Those with

insufficient vitamin D were evaluated as serum concentration of vitamin D less than 20 ng/mL or 50 nmol/L and those with sufficient vitamin D were evaluated as serum concentration of vitamin D greater than or equal to 20 ng/mL (50 nmol/L) based on 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 by the student's t test and categorical variables were compared by the chi-squared test. In line with the guidelines offered by NHANES, every sample was endowed with corresponding weight.

Binary logical regression models were constructed to assess odds ratios (ORs) and weighted percentage (95% CI) related with serum concentration of vitamin D and depression. In model 1, any covariates were not adjusted for. In model 2, age and sex were adjusted for. In model 3, age, race, sex, season of blood draw and BMI were adjusted for. In addition, we performed subgroup analysis classified by two variables including sex (male/female) and obesity (yes/no).

RESULTS

Baseline characteristics

Table 1 displays the baseline characteristics of the overall sample. A total of 1339 individuals were diagnosed as NAFLD and were included in this investigation. 127 subjects were identified with depression, hence the occurring rate of depression among NAFLD individuals was 8.58% (weighted prevalence, the same below). In our population, mean age of the individuals was 51.54 ± 16.12 years. Among these NAFLD patients, 55.94% were men, 44.06% were women, 64.14% were non-Hispanic white, 12.61% were Mexican-American, 7.77% were non-Hispanic black, 5.61% were other Hispanic descent, 4.99% were non-Hispanic Asian. Compared to the NAFLD participants in non-depressed group, the depressed individuals were more likely to have diabetes mellitus and in higher degree of glycohemoglobin (HbA1c) as well as 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), but without significant change in serum vitamin D levels (p>0.05).

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. What's more, NAFLD patients with sufficient vitamin D levels were still more likely to have fewer depression risks than those with insufficient levels in Model 3 adjusted for potentially confounding variables (OR=0.61, 95% CI: 0.37–0.99, p=0.048).

Subgroup analysis

Subgroup analysis classified by sex and BMI was performed and a strong negative correlation was presented neither in females (OR=1.12, 95% CI: 0.52-2.42, p=0.7) nor in individuals who were not obese (OR=3.42, 95% CI: 0.47-24.9, p=0.2) (Table 3). Subgroup analysis stratified by sex displayed that the inverse linkage between unregulated blood vitamin D and depression among men (OR=0.32, 95% CI: 0.13-0.81, p=0.024) was consistent with that of those among the overall study population, but not among women. In the subgroup analysis established based on BMI, blood vitamin D presented an obvious inverse association with depression for obese individuals in the not adjusted model 1，partly adjusted model 2 and fully adjusted model 3 (OR=0.53, 95% CI: 0.33-0.86, p=0.019). However no significant negative associations were shown among individuals who were not obese in all models.

DISCUSSION

This population-based investigation was designed to evaluate the independent effects of blood vitamin D levels on the prevalence of depression among American NAFLD individuals diagnosed via VCTE. This is the first investigation to point out that elevated serum vitamin D was negatively related with the prevalence of depression among NAFLD individuals, especially in 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] There are currently no licensed medicines improving or alleviating the pathological progression of NASH or advanced liver fibrosis, so that lifestyle and dietary habits modifications are the mainstay 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 activity modifications.[26] In comparison to non-depressed individuals, depressed patients were three times more likely to suffer from disobedience with recommendations for medical treatment of chronic diseases.[27] Therefore, it is urgent to find appropriate approaches to control depression in patients with NAFLD.

Experiments in cellular and animal models corroborated that blood vitamin D would be candidates for immunoregulation for hepatic steatosis. It was well accepted that vitamin D could eliminate the severity of NAFLD by inhibiting the production and production of proinflammatory factors such as interleukins (IL), tumour necrosis factor-α (TNF-α) as well as tissue inhibitor of metalloproteinase-1 (TIMP-1). Over the past decades, researchers were becoming more interested in the linkage between vitamin D and pathogenetic mechanisms of depression. Accumulating evidence from animal models have indicated that vitamin D could regulate neuronal survival and differentiation through increasing the levels of neurotrophins in the brain, such as nerve growth factor (NGF), brain-derived neurotrophin factor (BDNF) and neurotrophin (NT)-3. Restoring the expression of BDNF was responsible for the treatment of depression. NT-3 and NGF might be beneficial for the proliferation and the survival of neural progenitor cells, therefore affecting depression directly or indirectly.[11-13] Inconsistent with the results from animal tests, population-based findings on whether vitamin D possessed antidepressive effects didn't achieve a general consensus.[14, 15] Pan et al. showed no correlation between depressive symptoms and vitamin D in Chinese.[28] Ganji et al. reported that decreased serum vitamin D levels were related to a nonsignificant but increased risk of depression in adult US population.[29] However, Hoogendijk et al. indicated that low 25(OH)D presented a significant association with depression in elderly residents from the Netherlands.[15] Similarly, our study indicated that high levels of vitamin D were shown to be correlated with a decreased risk of depression among NAFLD subjects. Not comprehensively considering different concomitant diseases and sociodemographic factors, such as gender, races, BMI,

family affluence, education levels, diet patterns, drinking and smoking may explain inconsistent results of these observational investigations.

This cross-sectional investigation assessed the relationship between blood vitamin D levels and depression among NAFLD males, but failed to present among females, in line with some recent studies having reported that serum 25(OH)D levels were irrelevant to depression among females.[30] This gender difference was most likely due to the protective effects of a sex hormone-oestrogen against depression.[31] As a result, the power of blood vitamin D on depression was diluted among NAFLD females. Additionally, obesity and depression have been proven a significant correlation as well. According to the recent study, reasonable weight losing were able to decrease depression value and ameliorate depressive status 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 cut-off BMI for obesity weren't in consistency, and more researches and discussions were warranted for confirmation.

Here, several limitations of this investigation should be highlighted. First, it is of difficulties to make cause-effect conclusions in our investigation owning to the cross-sectional nature of the survey design with the imprecise causal direction. Second, the positive cases in our investigation were relatively fewer, so there might be potential unstable results which were needed to strengthen in further studies. In addition, a change from NAFLD to metabolic dysfunction-associated fatty liver disease (MAFLD) has been brought forward, suggesting that further studies will have to ascertain the precise correlation between serum vitamin D and depression among both MAFLD/NAFLD.

Conclusion

The inverse association between blood vitamin D levels and depression among individuals with NAFLD identified by VCTE is obvious, especially among men and those who are obese. The information data provides some new insights on the prevention and control of depression among NAFLD patients.

CONFLICT OF INTEREST AND FUNDING DISCLOSURE

The authors declare no competing interests.

Our study was funded by General project of Jiangsu Provincial Health Commission (H2023044), 'Qinglan Project' of Jiangsu University, General Project of "Philosophy and Social Science Research" Funded by Colleges and Universities in Jiangsu Province (2024SJYB0588) and Project of "Natural Science Research" Funded by Colleges and Universities in Jiangsu Province (22KJB330005).

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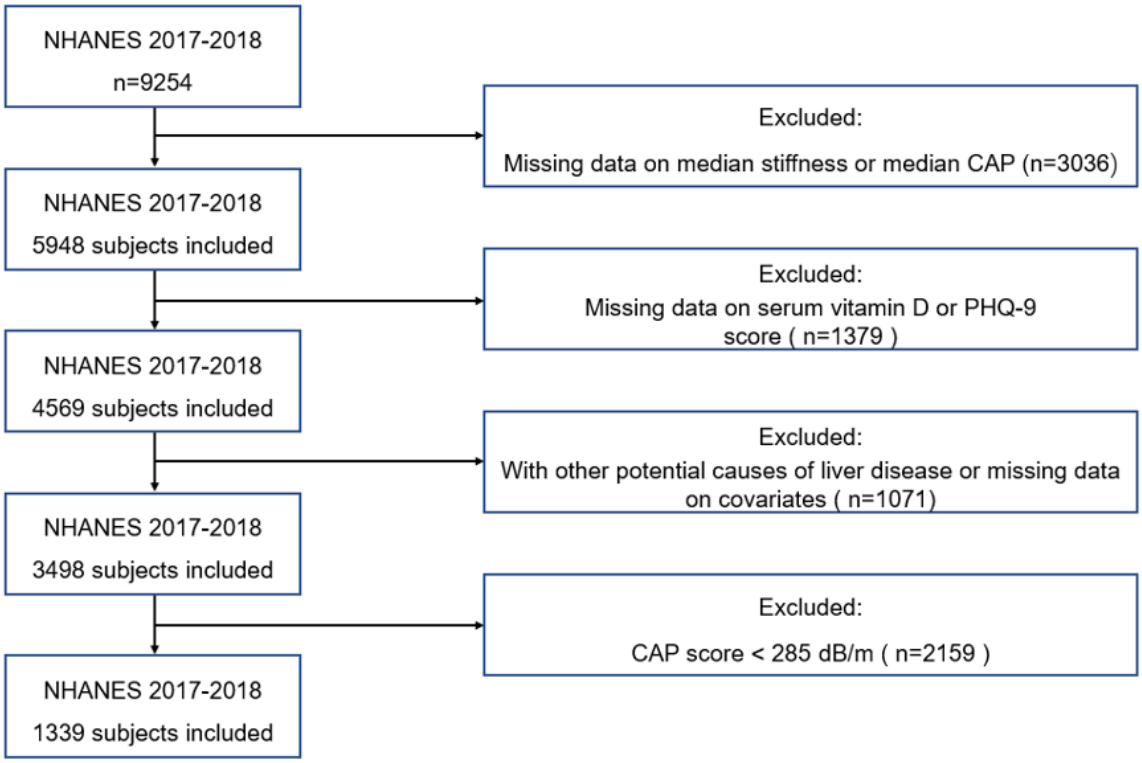

Figure 1. Flowchart of the sample selection in the 2017–2018 NHANES.

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)	51.54 ± 16.12	51.53 ± 16.13	51.71 ± 16.07
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)	34.69 ± 7.36	34.49 ± 7.36	36.82 ± 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)	22.41 ± 10.38	22.36 ± 10.20	22.95 ± 12.21
CAP (dB/m)	332.27 ± 34.09	331.86 ± 34.02	336.62 ± 34.60
LSM (kPa)	7.63 ± 7.62	7.62 ± 7.65	7.73 ± 7.31
Serum vitamin D (nmol/L)	70.87 ± 29.98	70.98 ± 29.56	69.63 ± 34.21
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 .

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