

Research Article

Suspected Nonalcoholic Fatty Liver Disease Is Not Associated with Vitamin D Status in Adolescents after Adjustment for Obesity

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This study investigated a potential independent association between hypovitaminosis D and suspected nonalcoholic fatty liver disease (NAFLD) in a nationally representative sample of the US adolescents. Data from 1630 subjects 12–19 years of age were examined using the National Health and Nutrition Examination Survey, 2001–2004. The vitamin D status of subjects was categorized into quartiles of serum 25-hydroxyvitamin D. Subjects with serum ALT > 30 U/L were classified as having suspected NAFLD. Data regarding age, sex, race, BMI, and poverty level were also analyzed in bivariate and multivariate analyses using SAS and SUDAAN software. Suspected NAFLD was identified in 12.1% of adolescents in the lowest quartile compared to 6.9% of adolescents in the second quartile, 8.0% in the third quartile, and 13.17% in the highest quartile of serum 25(OH)D concentrations ($P = .05$). In analyses utilizing vitamin D as a continuous variable, no independent association was found between Vitamin D levels and rates of elevated ALT levels. In multivariate analyses, higher risks for suspected NAFLD were observed in males and overweight adolescents; however, vitamin D status was not found to be independently associated with suspected NAFLD after adjusting for obesity.

1. Introduction

Vitamin D deficiency has been classically associated with rickets in childhood and osteomalacia in adults. However, the vitamin D receptor is ubiquitous, and the study of the physiologic roles of vitamin D has revealed health consequences of poor vitamin D status that extend beyond the skeletal system [1]. Vitamin D has been found to have a potential role in autoimmune and inflammatory processes, and there is a growing literature that suggests that low vitamin D status may contribute to the development of insulin resistance, hypertension, and the metabolic syndrome (MS) [2–7]. Evidence from randomized, placebo-controlled trials also suggests that vitamin D supplementation effectively reduces insulin resistance [8, 9].

Serum 25-hydroxyvitamin D₃, produced by the hydroxylation of vitamin D₃ (cholecalciferol) in the liver, reflects

body stores of vitamin D. Over the past two decades, serum 25(OH)D concentrations have markedly decreased in the general US population. Only 23% of children and adults were considered to be vitamin D sufficient (serum 25(OH)D ≥ 30 mg/L) according to national data from 2001 to 2004, as compared to 45% in 1988–1994 [10]. Additionally, over the past 3 decades, the prevalence of childhood obesity has increased, and with that has come a parallel increase in obesity-related sequelae such as non-alcoholic fatty liver disease (NAFLD) [11, 12]. NAFLD is the most common form of liver disease in the pediatric population, with a prevalence of 8.0% (as defined by ALT > 30 U/L) among 12–19-year olds [13]. NAFLD is also more common among those with greater adiposity and elevated fasting insulin levels.

With a rise in the number of overweight children and adolescents, it is important to consider the implications of poor vitamin D status on the development and progression

of obesity and its comorbidities. Given the increasing prevalence of hypovitaminosis D and the increasing prevalence of NAFLD, it is possible that there is an association between low-vitamin D status and NAFLD. To our knowledge, no previous study has examined the association between serum 25(OH)D concentrations and the presence of suspected NAFLD in a large, nationally representative sample of the US adolescent population. Previous smaller studies have investigated the relationship between vitamin D status and NAFLD in children and adults with conflicting results [14–16]. The purpose of this study was to utilize data from a national sample to investigate whether suspected NAFLD is independently associated with hypovitaminosis D in adolescents.

2. Methods

Data were examined regarding 1630 individuals aged 12–19 years who participated in the National Health and Nutrition Examination Survey (NHANES) from 2001 to 2004. NHANES is an ongoing series of cross-sectional surveys conducted by the National Center for Health Statistics of the Centers for Disease Control and Prevention. Data is collected from a nationally representative sample of the noninstitutionalized civilian population in the USA. During a home interview, participants provide information concerning family medical history, current medical conditions, medication use, and socioeconomic and demographic characteristics. Additional data are collected from participants who are randomly assigned to visit mobile examination centers. Participants undergo a physical examination and laboratory testing of blood and urine samples. Approximately 5000 individuals are surveyed annually, and about half are children and adolescents.

The details of the measurement and analysis of ALT concentrations and serum 25-hydroxyvitamin D in NHANES have been previously described [7, 12]. Serum 25(OH)D reflects the vitamin D obtained from sunlight exposure as well as from dietary intake [1]. The vitamin D status of subjects was categorized into quartiles of serum 25(OH) D in those analyses where vitamin D was treated as a categorical variable: I (≤ 19 ng/mL), II (19 ng/mL $>$ serum(OH)D ≤ 25 ng/mL), III (25 ng/mL $>$ serum(OH)D ≤ 31 ng/mL), and IV (>31 ng/mL). Other studies of the associations between hypovitaminosis D and cardiovascular disease risk factors have used similar but not identical values to assess vitamin D status; however, there is no consensus for defining hypovitaminosis D [6, 7, 13, 14]. Additionally, there is currently no consensus on optimal concentrations of 25(OH) D as measured in serum [1]. Adolescents with serum ALT ≥ 30 U/L were classified as having suspected NAFLD in analyses where vitamin D was treated as a categorical variable. While the most accurate diagnosis of NAFLD requires a biopsy, other observational studies also use elevated concentrations of serum alanine aminotransferase as a surrogate marker for NAFLD [12, 15–17].

Data regarding age, sex, race, BMI, waist circumference, and poverty level were also evaluated. Subjects with an age- and gender-adjusted BMI >5 th percentile and <85 th

percentile were classified as normal weight; those with a BMI ≥ 85 th but <95 th percentile were classified as overweight; those with a BMI ≥ 95 th percentile were classified as obese. Age- and gender-specific waist circumference was categorized as <90 th or >90 th percentile. Race/ethnicity was categorized as non-Hispanic white, non-Hispanic black, Mexican American, or “other” (including multiracial or other Hispanics).

The following exclusion criteria were applied to this sample: (1) positive for hepatitis B or hepatitis C, (2) pregnant, (3) adolescents who had not fasted for at least 6 hours, (4) type 1 diabetes (defined as adolescents who were taking insulin), (5) type 2 diabetes, (6) BMI <5 th percentile, (7) taking HMG-CoA reductase inhibitors or valproic acid, two common medications that may cause elevated ALT as a side effect, and (8) adolescents with serum iron concentrations >170 micrograms/dL. No information regarding the time of year in which the measurements of serum 25(OH)D or ALT were collected was available for analysis in this study. Alcohol consumption was also not recorded in the NHANES database for adolescents. None of the subjects in this study were taking vitamin D supplements.

3. Statistical Analyses

When the serum 25(OH)D of subjects was categorized into quartiles, the prevalence of suspected NAFLD in adolescents was identified only by serum ALT ≥ 30 . Bivariate and multivariate analyses using SAS (version 8.2) and SUDAAN (version 7.5) software were performed. In bivariate analyses both BMI and waist circumference status were included and independent *T*-tests were employed. Multivariate analyses, included age, sex, race, adiposity (as measured by BMI), and poverty status. All of the variables were included in the multivariate logistic regression analysis to determine independent associations with suspected NAFLD.

We repeated the analyses treating serum 25(OH)D as a continuous variable. The following multivariate models were employed: (1) age, gender, race/ethnicity, BMI, and poverty status, (2) age, gender, race/ethnicity, waist circumference, and poverty status, and (3) age, gender, race/ethnicity, and poverty status. For each of these models, we also used three different thresholds of ALT to define suspected NAFLD, including ALT ≥ 20 , ALT ≥ 30 , and ALT ≥ 40 . Finally, we conducted an additional bivariate analysis treating both 25(OH)D and ALT as continuous variables.

When serum 25(OH)D was treated as a continuous variable, the prevalence of suspected NAFLD in adolescents was identified using three different thresholds of ALT, including ALT ≥ 20 , ALT ≥ 30 , and ALT ≥ 40 . Bivariate and multivariate analyses were also conducted using SAS (Version 8.2) and SUDAAN (Version 7.5) software to adjust for age, sex, race, adiposity (as measured by BMI or waist circumference), and poverty status. All of the variables were included in multivariate logistic regression analyses to determine independent associations with NAFLD.

Furthermore, as a continuous variable, correlation of ALT with serum 25(OH)D was examined.

TABLE 1: Demographic and selected physical features and nonalcoholic fatty liver disease—NHANES 2001–2004: age 12–19*.

	N (unweighted)	NAFLD (ALT \geq 30), %	P value
Age			.10
12–15 y	799	6.82	
16–19 y	831	9.88	
Gender			<.001
Male	853	13.70	
Female	777	2.66	
Race/ethnicity			.05
Non-Hispanic White	449	8.23	
Non-Hispanic Black	555	6.01	
Mexican American	515	11.63	
Other Hispanics	54	11.13	
Other Races	57	5.77	
BMI			.001
Normal weight	1035	3.25	
Overweight	284	9.03	
Obese	311	25.76	
Waist circumference above 90 percentile			.003
Yes	891	14.18	
No	739	3.14	
Poverty			.30
Yes	537	10.22	
No	1023	8.18	
25(OH)D quartile			.05
I (\leq 19 ng/mL)	686	12.31	
II (19 ng/mL < serum[OH]D \leq 25 ng/mL)	452	6.91	
III (25 ng/mL < serum[OH]D \leq 31 ng/mL)	297	6.81	
IV (\geq 31 ng/mL)	195	7.14	

* ALT and 25(OH)D values were available for 1630 individuals, and so each comparison has 1630 subjects, except as regards the analyses comparing poverty versus no-poverty status as information regarding income was missing for 70 individuals ** $P \leq .05$.

4. Results

4.1. 25(OH)D as a Categorical Variable. The overall prevalence of suspected NAFLD among adolescents was 8.39% (weighted percentage). Serum ALT \geq 30 U/L was most prevalent in subjects with the poorest 25(OH)D status. In the bivariate analyses, suspected NAFLD was identified in 12.31% of adolescents in the lowest quartile of serum 25(OH)D compared to 6.91% in the second quartile, 6.81% of adolescent in the third quartile, and 7.14% of adolescents in the fourth quartile ($P = .05$, Table 1). Additionally, male adolescents were more likely to have suspected NAFLD than females (males have a 13.70% of elevated ALT, while for females, it is only 2.66%; $P < .001$). Suspected NAFLD rates increased with higher BMI: for normal-weight adolescents, the prevalence of suspected NAFLD was 3.25, while for overweight adolescents, the prevalence was 9.03% and 25.76% for obese adolescents. The prevalence of suspected NAFLD varied by race/ethnicity with 11.63% for Mexican Americans and 6.01% for Non-Hispanic Blacks (Table 1).

Age and poverty status were not significantly associated with suspected NAFLD.

Additionally, BMI status was taken out of the multivariate analyses investigating the independent association between serum 25(OH)D and suspected NAFLD controlling for age, gender, race, and poverty status and it was found that individuals with the lowest quartile of 25(OH)D levels had significantly higher rates of suspected NAFLD compared to those in the fourth quartile (first quartile versus fourth quartile: OR: 2.44, 95% CI: 1.09–5.48). However, no significant association was found for those in the second versus those in the fourth quartile (OR = 0.82, 95% CI: 0.32–2.06) or those in the third versus those in the fourth quartile (OR = 0.83, 95% CI: 0.32–1.89).

Adjusted odds ratios (AOR) and 95% confidence intervals from multivariate analyses for the risk of suspected NAFLD are shown in Table 2. Gender and BMI were both significantly independently associated with suspected NAFLD ($P < .05$). Adolescent males were 6.25 times more likely than females to have suspected NAFLD (95%

TABLE 2: Factors associated with nonalcoholic fatty Liver disease (ALT \geq 30) in multivariable analyses—NHANES 2001–2004: age 12–19, $n = 1560^*$.

	Odds Ratio	Lower 95%	Upper 95%
Age			
12–15 y	1	1	1
16–19 y	1.61	0.92	2.82
Gender			
Female	1	1	1
Male*	6.25	3.59	10.92
Race/ethnicity			
Non-Hispanic White	1	1	1
Non-Hispanic Black	0.45	0.2	1.04
Mexican American	1.47	0.84	2.56
Other Hispanics	1.85	0.46	7.48
Other Races	0.88	0.27	2.86
BMI			
Normal weight	1	1	1
Overweight	2.63	1.14	6.03
Obese*	11.57	5.93	22.6
Poverty status			
No	1	1	1
Yes	1.54	0.92	2.57
25(OH)D quartile			
I (\leq 19 ng/mL)	1.15	0.92	2.57
II (19 ng/mL < serum[OH]D \leq 25 ng/mL)	0.48	0.51	2.55
III (25 ng/mL < serum[OH]D \leq 31 ng/mL)	0.69	0.48	1.18
IV (\geq 31 ng/mL)	1	1	1
Multivariate analyses without BMI**			
25(OH)D quartile			
I (\leq 19 ng/mL)*	2.44	1.09	5.48
II (19 ng/mL < serum[OH]D \leq 25 ng/mL)	0.82	0.32	2.06
III (25 ng/mL < serum[OH]D \leq 31 ng/mL)	0.83	0.32	1.89
IV (\geq 31 ng/mL)	1	1	1

$N = 1560$ because information was included in this model only for individuals with all of the relevant information regarding each variable.

*Independently associated with NAFLD at $P \geq .05$.

**Separate multivariate analysis between 25(OH)D and ALT \geq 30 controlling for age, gender, race, and poverty status.

CI 3.59–10.92). Obese adolescents were 11.57 times more likely to have suspected NAFLD (95% CI 5.93–22.60) when compared to normal-weight adolescents. In contrast, serum 25(OH)D was not independently associated with suspected NAFLD in the multivariate model.

4.2. 25(OH)D as a Continuous Variable. In bivariate analyses treating vitamin D as a continuous variable, a lower mean value of serum 25(OH)D was observed in subjects with ALT \geq 30 as compared to those with an ALT < 30. Mean vitamin D was lower still among those with an ALT \geq 40 when compared to those with ALT < 40. In contrast, there was no difference in mean vitamin D level when individuals with ALT levels below 20 were compared to those with ALT levels \geq 20 (Table 3). When both ALT and vitamin D status were used as continuous, we found that with one unit

TABLE 3: Relationship between various ALT levels and 25(OH)D assessed as a continuous variable, NHANES 2001–2004: age 12–19, bivariate analyses ($n = 1630$).

	N (unweighted)	25(OH)D mean (SE)	P-value
ALT < 20	1118	25.09 (0.77)	.1943
ALT > 20	512	25.94 (1.07)	
ALT < 30	1487	25.58 (0.80)	.0268
ALT > 30	143	23.01 (1.39)	
ALT < 40	1564	25.50 (0.81)	.0286
ALT > 40	66	22.13 (1.65)	

of vitamin D increasing, there is likely 0.059 unit of ALT decreasing ($P = .045$).

In bivariate analyses, waist circumference >90th percentile was significantly associated ($P < .001$) with suspected NAFLD at all thresholds (ALT ≥ 20 , 30 and 40) not shown.

Analyses were conducted to investigate potential interactions between obesity and serum 25(OH)D and their relationship ALT ≥ 30 . It was found that only obese adolescents, irrespective of vitamin D status, were at increased risk for elevated ALT (data not shown).

Also not shown in tables are the following results treating vitamin D as a continuous variable in the multivariate models described in the Methods section. Vitamin D was not independently associated with suspected NAFLD in the multivariate analyses that included either BMI or waist circumference. When the multivariate models did not include either BMI or waist circumference variables, serum 25(OH)D levels were, however, significantly associated with suspected NAFLD as defined by ALT ≥ 30 (OR: 0.96; 95% CI: 0.92–0.99) and ALT ≥ 40 (OR: 0.93; 95% CI: 0.88–0.99).

5. Discussion

The findings of this study demonstrate that while serum 25(OH)D was inversely associated with ALT, this association was abolished by adjusting for obesity as a confounding factor. Thus, these findings do not indicate an independent association between vitamin D status and suspected NAFLD, as suggested by ALT level. This is true when vitamin D status was assessed both categorically and as a continuous variable. In contrast, increased BMI was consistently associated with increased rates of ALT elevation.

It is well known that adolescents with obesity and its comorbidities are at increased risk for developing NAFLD [13] and that increased BMI is a significant independent predictor of hypovitaminosis D [17]. Low concentrations of serum 25(OH)D found in overweight and obese adolescents may reflect an inadequate diet or a more sedentary lifestyle with less time spent outdoors, resulting in less sunlight exposure [10, 17, 18]. It also is possible that lower serum 25(OH)D levels in heavier individuals reflect the sequestration of vitamin D in adipose tissue [19].

Other predictors of hypovitaminosis D in adolescents may include ethnicity, season, latitude, and milk and juice consumption [17, 20].

In the statistical models treating serum 25(OH)D as a categorical variable, obesity and male gender were found to be independently associated with suspected NAFLD; lower levels of 25(OH)D were not found to be independently associated with NAFLD after adjusting for confounding variables including age, sex, race, BMI, and poverty level. These results were confirmed by treating 25(OH)D as a continuous variable and assessing for three different levels of ALT, that is, ≥ 20 , ≥ 30 , and ≥ 40 U/L, as potential measures of NAFLD. The method of measuring adiposity (BMI or waist circumference >90th percentile) did not affect the results of these multivariate analyses. Hypovitaminosis D was, however, independently associated with suspected NAFLD in the only multivariate model that did not include either BMI or waist circumference. Considering that adiposity is

well documented as contributing to the risk of developing NAFLD, these results suggest that it is obesity, rather than vitamin D status, that is in fact independently associated with NAFLD.

There is currently a paucity of studies investigating the relationship between vitamin D status and NAFLD in adolescents. The findings reported here are consistent with another study by Ashraf et al. [14]. Those authors found no significant differences in ALT or aspartate aminotransferase (AST) when comparing adolescents with or without adequate concentrations of serum 25(OH)D. Adequate serum 25(OH)D was defined as a concentration greater than 15 ng/ml. However, the study by Ashraf et al. was limited to 51 African American female adolescents who were obese. The current study includes a larger, nationally representative sample of adolescents that more accurately reflect the USA population. In contrast, a study by Targher et al. found, for the first time, that adults with biopsy-proven NAFLD had higher rates of hypovitaminosis D than matched control subjects [15]. Targher et al. observed an inverse relationship between serum 25(OH)D and biopsy-determined diagnoses of NAFLD, independent of insulin sensitivity and the metabolic syndrome. However, that study involved a small sample of only 60 adults and these results may not be applicable to adolescents because adults may accumulate a number of other insults to the liver over their lifespans. In the pediatric population, another small study also identified lower concentrations of serum 25(OH)D in children with biopsy-proven nonalcoholic liver disease [16]. It also is possible that 25-hydroxylation of vitamin D may be reduced when there is preexisting liver damage, rather than that low vitamin D levels lead to liver disease.

Racial and ethnic differences in rates of NAFLD have been documented for some time in the USA [13, 21, 22]. Elevated ALT concentrations are more common in Hispanic adolescents [23, 24]. In contrast, non-Hispanic Black adolescents have a lower prevalence of NAFLD. During 1999–2004, rates of elevated ALT concentrations (>30 U/L) were 11.5% among Mexican American adolescents, 6.0% among Black adolescents, and 7.4% among white adolescents [13]. The mechanisms underlying these differences are not known, although Non-Hispanic Black adolescents have less intraperitoneal fat and less lower extremity fat compared to whites and Hispanics, and intraperitoneal fat has been identified as a potential risk for liver damage at a young age [13, 25].

5.1. Limitations. These data come from cross-sectional analyses and thus have substantial limitations for drawing causal inferences.

A definitive diagnosis of NAFLD requires a liver biopsy which is not feasible in large-scale epidemiological studies [11]. ALT is a widely accepted biomarker for liver fat accumulation; however, it is neither as specific nor as sensitive as biopsy. There is no consensus regarding a standard threshold for elevated ALT, although previous values used in the literature range from 20 to 40 U/L [13, 26]. Future studies may explore the correlation of vitamin D and liver

pathology using ultrasonography, as it is a valuable non-invasive method of screening for liver disease [27, 28].

It also is well recognized that season exerts major influences on cutaneous vitamin D₃ production [29]. Photosynthesis of vitamin D is higher with more exposure to UVB sunlight. Of note, a recent study of adults found higher levels of most liver function tests in the winter, suggesting that seasonal variation be taken into consideration when establishing either reference intervals or cut-off values, especially regarding aminotransferases [30].

Also, no data were available regarding alcohol consumption in this sample. Future studies of adolescent NAFLD should consider utilizing alcohol consumption as an exclusion criterion. Oral contraceptives use has been associated with higher serum 25(OH)D and also may be deserving of investigation in future studies [31].

6. Conclusions

This study, like others before it, indicates that overweight and obese adolescents are much more likely than normal-weight adolescents to have elevated serum ALT, a surrogate biomarker for NAFLD. It is unclear whether poor vitamin D status contributes directly to the risk of developing NAFLD, or if this association is overwhelmingly confounded by obesity. This study examined the relationship between hypovitaminosis D and suspected NAFLD and did not find that low-vitamin D status is an independent predictor of NAFLD.

It is important for clinicians to identify and treat children with obesity and its comorbidities as early as possible [32]. In a prospective study, Forouhi et al. demonstrated that low-vitamin D status is a predictor of future hyperglycemia and insulin resistance [33]. Previous work has also found that insulin sensitivity improves after vitamin D supplementation [8, 9]. Therefore, further research is needed to determine if vitamin D supplementation might be effective in preventing or treating NAFLD in obese adolescents.

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