Serum Vitamin D Level in Overweight Individuals and Its Correlation With the Incidence of Non-alcoholic Fatty Liver Disease

Yu-Lei QU[1#], Ying-Hao SONG[1#], Ru-Ru SUN[2], Ying-Jie MA[1], Yong ZHANG[3]
[#]*These authors contributed equally to this work*

[1]Department of Gastroenterology, People's Hospital of Henan University of Chinese Medicine, Henan University of Chinese Medicine, Zhengzhou, Henan Province, China, [2]Department of Emergency, The Second Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan Province, China, [3]Department of Gastroenterology, Zhengzhou Central Hospital Affiliated to Zhengzhou University, Zhengzhou University, Zhengzhou, Henan Province, China

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Summary

In this study, we investigated the serum vitamin D level in overweight individuals and its correlation with the incidence of nonalcoholic fatty liver disease (NAFLD). Between May 2020 and May 2021, the Department of Gastroenterology at the People's Hospital of Henan University of Traditional Chinese Medicine treated a total of 321 outpatients and inpatients with NAFLD, who were included in the NAFLD group, while 245 healthy age- and gender-matched individuals were included in the control group. All the data were collected for the relevant indices, including fasting plasma glucose, total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, alanine transaminase, and 25-hydroxy vitamin D (25[OH]D. The patients with NAFLD were divided into the normal BMI group, the overweight group, and the obese group, according to the body mass index, and the 25(OH)D levels were compared between the different groups. Spearman's correlation analysis was performed to analyze the correlation between the serum 25(OH)D level and NAFLD. Regarding the serum 25 (OH)D level, it was lower in the NAFLD group than in the control group ([18.36 + 1.41] μg/L vs [22.33 + 2.59] μg/L, t = −5.15, P<0.001), and was lower in the overweight group than in the normal group ([18.09 ± 5.81] μg/L vs [20.60 ± 4.16] μg/L, t = 0.26, P = 0.041). The serum 25(OH)D level was thus negatively correlated with the incidence of NAFLD in overweight individuals (r = 0.625, P<0.05). In conclusion, the level of 25(OH)D decreased in patients with NAFLD with increasing BMI (normal, overweight, obese).

Keywords

Nonalcoholic fatty liver disease • Vitamin D

Corresponding author

Yong Zhang, Department of Gastroenterology, Zhengzhou Central Hospital Affiliated to Zhengzhou University, Zhengzhou University, 16 Tongbai North Road, Zhongyuan District, Zhengzhou, 450000 Henan Province, China. Email: quyu0828@163.com

Introduction

In different regions of the world, nonalcoholic fatty liver disease (NAFLD) has varied epidemiological characteristics, and its incidence is usually related to obesity [1]. Obesity is a common complicating factor for 51.3 % of patients with NAFLD, and the prevalence of NAFLD in obese individuals increases to 60 % to 70 % [2]. Chinese individuals have extremely high overall obesity and abdominal obesity rates, at 7.5 % and 12.3 %, respectively [3]. In China, NAFLD has emerged as the most significant chronic liver disease [4]. However, the mechanisms by which obesity leads to NAFLD have not been fully elucidated. Obesity is characterized by increased adipose tissue mass, which leads to increased transportation of free fatty acids to the liver, potentially leading to lipid accumulation in the liver [5]. Traditional theories on the role of adipose tissue in energy storage have been radically altered by recent research [6]. In fact, adipose tissue is considered to be the primary and possibly largest endocrine organ capable of synthesizing and releasing a variety of hormones, cytokines, complements, growth factors, extracellular matrix

proteins, and vasoactive substances, resulting in a variety of pro-inflammatory and potentially harmful effects [7]. Vitamin D is mainly stored in adipocytes, and according to many studies, adipose tissue may be a direct target of vitamin D and play an important role in regulating the pathophysiology of adipose tissue [8, 9]. In our previous study, we discovered that vitamin D has a variety of roles in NAFLD, including inflammatory regulation, immune regulation, cell proliferation, differentiation, and apoptosis [10]. When liver function is impaired, decreased 25-hydroxylase activity and decreased activation of vitamin D metabolism may contribute to vitamin D deficiency [11, 12]. The decrease in serum vitamin D level affects the ability of the liver to eliminate lipids, resulting in increased adipokines and inflammatory mediators, enhanced insulin resistance, hepatocyte apoptosis, and activated inflammatory pathways [13,14]. NAFLD and vitamin D insufficiency interact in a causative manner. In a previous study, it was discovered that obesity is associated with decreased serum 25(OH)D concentration [15], and a meta-analytic assessment was also discovered that NAFLD is associated with obesity [16]. Therefore, we sought to investigate whether serum 25(OH)D concentration is lower in patients with NAFLD who were overweight than in normal controls.

Study materials and methods

Study participants

The NAFLD group (18 to 65 years) consisted of a total of 321 inpatients and outpatients with NAFLD admitted to the Department of Gastroenterology and the Fatty Liver Clinic of the People's Hospital of Henan University of Traditional Chinese Medicine from May 2020 to May 2021, and the control group consisted of 245 healthy age- and gender-matched individuals. The *Guidelines for the Diagnosis and Treatment of Nonalcoholic Fatty Liver Disease (2018 Revision)* were used as the clinical diagnostic criteria to make the diagnosis of NAFLD [17]. The exclusion criteria included i) individuals with a history of heavy long-term drinking (alcohol equivalent to ≥ 40 g/d for men and ≥ 20 g/d for women); ii) individuals with recent drug usage affecting vitamin D levels; iii) individuals with other specific liver diseases that could lead to fatty liver, such as alcoholic liver disease (ALD), chronic viral hepatitis, autoimmune liver disease, or hepatolenticular degeneration; and iv) individuals with serious clinical diseases, such as chronic heart, brain, kidney, or lung disease.

Clinical data collection

Data pertaining to the medical history, gender, age, height, weight, and blood pressure of all participants were routinely collected. The body mass index (BMI) values were then calculated and the patients with NAFLD were accordingly classified into subgroups as follows: the normal group (BMI: 18.5–23.9 kg/m^2), the overweight group (BMI ≥ 24 kg/m^2), and the obese group (BMI ≥ 30 kg/m^2) based on the relevant guidelines (Obesity Group 2011). Fasting plasma glucose (FPG), total cholesterol (TC), triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and alanine transaminase (ALT) were then measured using an automatic biochemical analyzer (Olympus Company, AU400), while the serum 25(OH)D levels were measured using a Triple Quad TM 4500 mass spectrometer (USA) *via* liquid chromatography-tandem mass spectrometry.

Ethics review

The Medical Ethics Committee of the People's Hospital of Henan University of Traditional Chinese Medicine approved this study as it complied with all the applicable rules and regulations on medical ethics (Approval No. 20220144). The Chinese Clinical Trial Registry issued the trial registration number ChiCTR-1900021534 (www.Chictr.org).

Statistical methods

Complete data were analyzed using the SPSS20.0 software, and the enumeration data were subjected to a chi-squared test. The measured data conforming to a normal distribution are expressed as mean ± standard deviation. The differences between the groups were evaluated by a Student's t-test (for 2 groups) or ANOVA (for more than 2 groups) followed by an LSD post hoc test. The rank-sum test was applied to the measured data that did not follow a normal distribution, and the results are reported in terms of the median (*M; P25, P75)*. A *P*-value of less than 0.05 indicated that the difference was statistically significant. Spearman's correlation analysis was also performed.

Results

Comparison of general data and the 25-hydroxy vitamin D levels between the two main groups

A total of 321 patients with NAFLD were enrolled, comprising of 140 males and 181 females, with an average age of (55.59 ± 8.48) years, while 245 healthy

individuals were included in the control group, comprising of 99 males and 146 females, with an average age of (56.80 ± 8.38) years. All the participants were local residents. The results indicated that the 25(OH)D level in the NAFLD group was lower than that in the control group ([19.18 ± 4.62] μg/L vs [21.16 ± 2.59] μg/L, t = 6.01, P<0.001). There were no significant differences in other indictors between the two groups, other than BMI, FPG, and ALT (P<0.05) (Table 1).

Comparison of general data and the 25-hydroxy vitamin D levels between the normal body mass index, overweight, and obese groups

According to the Chinese Expert Consensus on the Prevention and Treatment of Adult Obesity [18], individuals with a BMI of 18.5–23.9 kg/m^2 were categorized in the normal group, those with a BMI of 24-28 kg/m^2 were categorized in the overweight group, and those a BMI > 28 kg/m^{2}were categorized in the obese group. The results indicated that the 25(OH)D level was lower in the overweight group and obese group than in the normal group (P<0.05). The comparisons of other indicators among the three groups are shown in Table 2.

We combined the categories of overweight and obese individuals to conduct the subgroup analysis as there was just one healthy individual with obesity. Patients in the overweight and obese group with NAFLD (n = 276) had much lower 25(OH)D level than healthy individuals (n = 78) ([18.93 ± 4.38] μg/L vs [21.00 ± 2.49] μg/L, t = 4.00, P< 0.001). But in the normal group, patients with NAFLD (n = 45) had similar 25(OH)D level to healthy individuals (n = 167) ([20.73 ± 5.69] μg/L vs [21.23 ± 2.64] μg/L, t = 0.84, P = 0.404).

Table 1. Comparison of General Data and 25(OH)D Level between the NAFLD Group and the Control Group

	Control group (n=245)	NAFLD group (n=321)	Statistical value	*P*
Age (years)	56.80±8.38	55.59±8.48	t=1.70	0.090
Gender (Male %)	40.41	43.61	X^2=0.59	0.444
BMI(kg/m^2)	23.33±1.62	26.51±2.81	t=-5.78	<0.001
FPG(mmol/L)	5.03±0.70	6.51±1.77	t=-12.40	<0.001
TC(mmol/L)	4.50±1.38	4.41±1.35	t=0.81	0.416
TG(mmol/L)	2.51±0.40	2.07±1.04	t=1.21	0.229
HDL-C(mmol/L)	1.43±0.42	1.39±0.43	t=-1.91	0.276
LDL-C(mmol/L)	2.82±0.76	2.90±0.99	t=-1.01	0.311
ALT (U/L)	26.00 (18.00, 32.00)	30.00 (23.00, 69.00)	Z=-6.70	<0.001
25(OH)D (μg/L)	21.16±2.59	19.18±4.62	t=6.01	<0.001

Table 2. Comparison of General Data and 25(OH)D Level between the Normal BMI Group, the Overweight Group and the Obese Group

	Normal BMI Group (n=212)	Overweight Group (n=277)	Obese Group (n=77)	Statistical value	*P*
Age (years)	57.13±7.72	55.79±8.41	54.51±10.15*	F=3.15	0.044
Gender (Male %)	32.55	46.21	54.55	X^2=14.73	0.001
FPG (mmol/L)	5.38±1.37	6.10±1.66*	6.38±1.55*	F=18.13	<0.001
TC (mmol/L)	4.64±1.40	4.37±1.30*	4.20±1.43*	F=3.99	0.019
TG (mmol/L)	2.10±0.07	2.46±0.36	2.00±0.11	F=0.64	0.527
HDL-C (mmol/L)	1.43±0.45	1.42±0.44	1.30±0.32*$^{\#}$	F=2.91	0.055
LDL-C (mmol/L)	2.87±0.86	2.83±0.97	2.97±0.72	F=0.79	0.453
ALT (U/L)	26.00(19.00, 34.00)	29.00(21.00, 47.00)*	33.00(24.00, 62.00)*	X^2= 19.44	<0.001
25(OH)D (μg/L)	21.12±3.50	19.58±4.04*	18.67±4.37*	F=14.85	<0.001

Note: *P<0.05 vs. Normal BMI group; #P<0.05 vs. Overweight group

Table 3a. Comparison of General Data and 25(OH)D Level between the males and females

	Males (n=239)	Females (n=327)	Statistical value	*P*
Age (years)	54.73±8.58	57.12±8.22	*t*=-3.37	<0.001
FPG (mmol/L)	6.06±1.62	5.73±1.55	*t*=2.45	0.015
TC (mmol/L)	4.01±1.36	4.76±1.27	*t*=-6.72	<0.001
TG (mmol/L)	2.06±0.88	2.11±1.19	*t*=-0.57	0.567
HDL-C (mmol/L)	1.36±0.43	1.45±0.42	*t*=-2.52	0.012
LDL-C (mmol/L)	2.65±0.82	3.02±0.93	*t*=-5.85	0.293
ALT (U/L)	28.00(21.00, 36.00)	28.00(21.00, 40.00)	*Z*=-0.11	0.916
25(OH)D (μg/L)	19.68±4.26	20.29±3.77	*t*=-1.80	0.072

Table 3b. Results of gender-based subgroup analysis of 25(OH)D

		NAFLD group			
25(OH)D (μg/L)	**Control group Male:Female = 99:146**	**NAFLD with normal BMI group Male:Female = 4:41**	**NAFLD with overweight group Male:Female = 95:105**	**NAFLD with obesity group Male:Female = 41:35**	**Overall Male:Female = 140:181**
Males	21.39±2.71	19.40±1.05	19.12±4.57	19.51±4.52	19.18±4.48
Females	20.94±2.40	19.68±5.96	20.13±4.14	19.88±2.43	19.95±4.34
t value	1.37	-0.07	-1.63	-0.450	-1.56
P value	0.173	0.950	0.100	0.660	0.120

Comparison of general data and the 25-hydroxy vitamin D levels between males and females

Males in the study cohort, were younger (P<0.001), had higher FDG levels (P = 0.015), lower TC levels (P< 0.001), and lower levels of HDL-C l (P = 0.012) than females. However, the 25(OH)D levels between males and females were not significantly different ([19.68 ± 4.26) μg/L vs [20.29 ± 3.77] μg/L, t = -1.80, P = 0.072) (Table 3a).

In the NAFLD group, male and female patients had similar 25 (OH) D levels ([18.68 ± 4.46) μg/L vs [19.56 ± 4.64] μg/L, t = -1.70, P = 0.091). Similarly, in the control group, males did not show a higher 25 (OH) D level than females ([21.39±2.71) μg/L vs [20.99±2.50] μg/L, t = 1.16, P = 0.247). Thus, the above results indicated that gender did not significantly affect 25 (OH) D levels (Table 3b).

Comparison of general data and the 25-hydroxy vitamin D levels between patients with normal BMI and NAFLD, and overweight and obese patients with NAFLD

Patients with NAFLD, with a BMI of 18.5-23.9 kg/m^2 were categorized in the normal group, and those with a BMI of 24–28 kg/m^2 were categorized in the overweight group. Patients with a BMI more than 28 kg/m^2 were categorized in the obese group. The results indicated that the 25 (OH) D levels were lower in the overweight and the obese group than in the normal group (P<0.05). The 25 (OH) D level in the overweight group was not significantly different from that in the obese group. There were no significant differences in other indicators among the three groups, except in terms of gender and TC (P<0.05) (Table 4).

Correlation between the 25-hydroxy vitamin D level and the observation indices in the overweight and obese individuals

The results of the Spearman's correlation analysis indicated that the serum 25(OH) D level was negatively correlated with FPG, TC, and the incidence of NAFLD in the overweight and obese individuals (r = −0.772, −0.658, −0.625, respectively, P<0.05).

Table 4. Comparison of General Data and 25(OH)D Level among NAFLD patients with different BMI

	NAFLD patients with normal BMI (n=45)	NAFLD patients with overweight (n=200)	NAFLD patients with obese (n=76)	Statistical value	*P*
Age (years)	57.20±6.59	55.70±8.13	54.36±10.13	F=1.64	0.196
Gender (Male %)	6.67	48.00	54.95	X^2=29.84	<0.001
FPG (mmol/L)	6.68±2.23	6.51±1.73	6.40±1.55	F=0.35	0.704
TC (mmol/L)	5.31±1.10	4.29±1.29*	4.19±1.44*	F=12.81	<0.001
TG (mmol/L)	2.16±0.17	2.09±0.07	1.99±0.11	F=0.42	0.659
HDL-C(mmol/L)	1.41±0.44	1.42±0.47	1.31±0.31	F=1.91	0.149
LDL-C(mmol/L)	3.15±1.08	2.81±1.06	2.97±0.73	F=2.56	0.080
ALT (U/L)	30.00 (25.00, 75.00)	30.00 (22.00, 73.00)	33.00 (24.75, 62.00)	X^2=1.48	0.478
25(OH)D (μg/L)	20.73±5.69	19.04±4.38*	18.63±4.38*	F=3.23	0.041

Note: *P<0.05 vs. NAFLD patients with normal BMI

Discussion

According to the findings of this study, the NAFLD group exhibited a lower serum 25(OH) D level compared to the normal control group. Additionally, higher BMI, FPG, and ALT levels were observed in the NAFLD group, consistent with our previous study [10]. Furthermore, it was also discovered in this study that individuals with obesity had a lower serum 25(OH)D level than those with normal weight. Specifically, limited to patients with NAFLD, those who are obese had a lower serum 25(OH) D level compared to their normal-weight counterparts. Moreover, there was a negative correlation between serum 25 (OH) D levels and FPG, NAFLD incidence, and TC among obese individuals. These findings suggest that obesity influences vitamin D status in patients with NAFLD, and that serum 25 (OH) D levels is associated with the occurrence of NAFLD in obese individuals.

Hepatic steatosis manifests when the balance between free fatty acid synthesis and transport exceeds the oxidizing or exporting capacity of the liver [19]. Vitamin D is mainly stored in adipocytes. Adipose tissue may be a direct target site of vitamin D, and the dysfunction of visceral adipose tissue is considered to be the primary cause of NAFLD [20]. Although the mechanism by which vitamin D affects the liver in patients with NAFLD has not been clearly elucidated, some relevant articles have reported as follows: Seo [21] and Parikh [22] also discovered that the serum vitamin D level is affected by body composition, while elevated body fat mass is an independent predictor of vitamin D deficiency, i.e., the serum 25(OH)D level can decrease by about 1.3 nmol/l for every 1 kg/m^2 increase in BMI [15]. Decreased 25-hydroxylase activity and metabolic activation during liver failure may occur in patients with NAFLD-associated vitamin D deficiency [9]. Decreased serum vitamin D levels can impair lipid clearance by the liver, and increase adipokines and inflammatory mediators, while worsening insulin resistance and affecting hepatocyte apoptosis [23]. An activated inflammatory pathway exists between NAFLD and vitamin D deficiency [24].

This study also has the following limitations. First, there was a broad age range in the selected patients, and NAFLD worsens with age, which may cause confounding variables to affect the results. Second, only propensity matching was carried out in this study without subgroup analysis. Even the healthy participants in this study had 25(OH) D levels that qualify in the category of minimal vitamin D due to inherent limitations in this retrospective study. Therefore, the findings of this study need to be further validated in prospective cohort studies.

In conclusion, the level of 25(OH)D decreased in patients with NAFLD with increasing BMI (normal, overweight, obese), so NAFLD patients with overweight and obese should take measures to reduce their BMI. In addition, vitamin D supplementation may be considered to be given in patients with NAFLD with overweight and obese.

Conflict of Interest

There is no conflict of interest.

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