Int J Clin Exp Med 2018;11(9):9911-9915
www.ijcem.com /ISSN:1940-5901/IJCEM0078530

Original Article

Relationship between serum 25-OH vitamin D level and nonalcoholic fatty liver disease in the elderly

Ruirui Hao[1,2], Zhen Zhao[1], Wei Wei[3], Hong You[2], Jidong Jia[2]

[1]Medical Healthcare Center, [2]Liver Research Center, [3]Clinical Epidemiology and Evidence-Based Medicine Center, Beijing Friendship Hospital, Capital Medical University, Beijing, China

Received April 25, 2018; Accepted June 28, 2018; Epub September 15, 2018; Published September 30, 2018

Abstract: Objective: To investigate the relationship between the 25-OH vitamin D level and nonalcoholic fatty liver disease (NAFLD) in elderly Chinese. Methods: A total of 663 patients aged between 65 to 101 years old, who received routine physical examination or were hospitalized in Beijing Friendship Hospital of Capital Medical University from January 2015 to March 2017, were retrospectively analyzed in this study. All the included patients were divided into the NAFLD group (36.5%, 242/663) and the non-NAFLD group (63.5%, 421/663) and underwent examinations including the body mass index (BMI), fasting blood glucose (FBG), HbA1C, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, aminotransferases (AST and ALT), uric acid, h-CRP, FT3, FT4, TSH and 25-OH vitamin D. All parameters were compared between the NAFLD and non-NAFLD group and the parameters with statistical difference were then analyzed by logistic regression analysis. Results: Compared with the non-NAFLD group, the NAFLD group had obviously higher FBG, triglycerides, HbA1C, ALT, and BMI, while evidently lower 25-OH vitamin D (all $P<0.05$) was observed. There was no significant difference between the two groups of patients in regard to male/female ratio, age, total cholesterol, HDL-cholesterol, LDL-cholesterol, AST, uric acid, hs-CRP, FT3, FT4, and TSH (all $P>0.05$). Logistic regression demonstrated the NAFLD was significant associated with high level FBG, triglycerides, HbA1C, BMI, and low level 25-OH vitamin D. Conclusion: Patients with NAFLD had reduced serum 25-OH vitamin D levels compared with subjects without NAFLD.

Keywords: Nonalcoholic fatty liver disease, elderly, 25-OH vitamin

Introduction

Nonalcoholic fatty liver disease (NAFLD) is a clinical-histological syndrome that refers to a spectrum of liver lesions ranging from steatosis to more complex patterns of necro-inflammation with various degree of fibrosis in the absence of alcohol intake [1, 2]. In some patients, NAFLD can deteriorate into cirrhosis and (or) hepatocellular carcinoma [3, 4]. Currently, NAFLD has become the most common etiology of chronic liver disease not only in the US and other developed countries, but also in developing countries like China, with the prevalence ranging from 9% to 37% [4-7]. NAFLD is especially common in children, teenagers, and young adults [8]. A previous study reported that the prevalence of NAFLD increased from younger to middle-aged individual and decreased at the age of 50 or 60. This phenomenon has been defined as an "inverted U-shaped curve" [8].

In recent years, vitamin D has emerged as an important factor in the development of NAFLD. In adult NAFLD patient, serum vitamin D level has been inversely associated with liver steatosis, necro-inflammation, and fibrosis [9]. Furthermore, vitamin D deficiency could exacerbate NAFLD by activating the Toll-like receptors by the way of endotoxin exposure; additionally, it could also cause insulin resistance, overexpression of hepatic resistin, and up-regulation of hepatic inflammatory genes [10, 11]. However, the relationship of level of 25-OH vitamin D and NAFLD has been rarely reported in the elderly. Therefore, the aim of this study was to investigate the relationship between the serum level of 25-OH vitamin D and NAFLD in elderly Chinese.

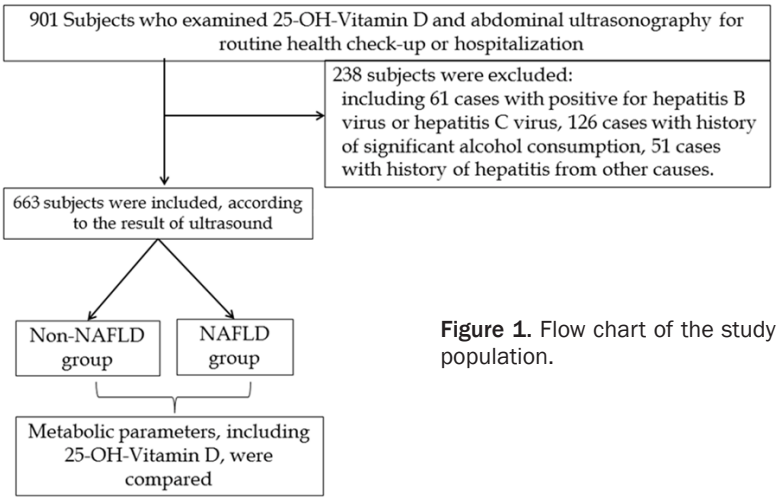

Figure 1. Flow chart of the study population.

Materials and methods

Ethics statement

This study was performed to investigate the association between NAFLD and the serum 25-OH vitamin D level in elderly Chinese and it was approved by the Ethics Committee of Beijing Friendship Hospital of Capital Medical University. As this was a retrospective study and all of the data were collected and analyzed anonymously, there was no need to obtain informed consent from patients.

Case selection

This retrospective study included 663 patients who performed Routine physical examination or hospitalization between January 2015 and March 2017 at the Medical Healthcare Center of Beijing Friendship Hospital, Capital Medical University. All the recruited subjects underwent comprehensive health examination and agreed to a simple interview for past medical history and lifestyle after the examination. According to the result of ultrasound, all these subjects were divided into two groups: the NAFLD group and non-NAFLD group.

Inclusion criteria: (1) age ≥65 years; (2) the serum 25-OH vitamin D level was examined; (3) had liver ultrasonography for diagnosis of fatty liver, which was based on the previously reported ultrasonographic criteria [12]; (4) for the NAFLD group, NAFLD was diagnosed based on the presence of fatty liver by ultrasonography without history of significant alcohol consumption (female <20 g/d, male <30 g/d).

Exclusion criteria: (1) age <65 yrs; (2) cirrhosis or autoimmune liver diseases; (3) positive for hepatitis B surface antigen or hepatitis C antibody; (4) current use of drugs known to influence 25 (OH) D3 metabolism, including glucocorticoids and calcium/vitamin D supplements; (5) severe disability, bone fracture, or psychiatric disorder; (6) current infectious condition; (7) the presence of a tumor and severe anemia; (8) history of hepatitis or cirrhosis of other causes, such as hemochromatosis, Wilson disease, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis or drug-induced liver injury; (9) incomplete clinical data [13, 14].

Information extraction and indicators

Basic information including sex, age, weight and height was collected and measured following standard guidelines. BMI was calculated by dividing the weight (kg) by the square of the height (m^2).

Fasting blood samples were collected to measure serum levels of fasting blood glucose (FBG), total cholesterol, low density lipoprotein-cholesterol (LDL-cholesterol), high density lipoprotein-cholesterol (HDL-cholesterol), triglycerides (TG), HbA1c, aspartate aminotransferase (AST), alanine aminotransferase (ALT), uric acid, high sensitivity C-reactive protein (hs-CRP), serum free Triiodothyronine (FT3), free Thyroxine (FT4), thyroid stimulating hormone (TSH), and 25-OH vitamin D.

Measurement of 25-OH vit D

All samples were collected in the time from the 1st September to the 30th April to minimize seasonal variation of 25-OH vitamin D levels. Blood samples for serum 25-OH vitamin D, and calcitriol levels were collected between 9 and 10 a.m. after a 12 hour fast to minimize interference from sunlight and dietary intake [15, 16]. The serum levels of 25-OH vit D was measured by using high-performance liquid chromatography/tandem mass spectrometry [17].

Table 1. Clinical Characteristics of participants

	NAFLD (n=242)	Non-NAFLD (n=421)	P
Male/Female ratio	161/81	269/152	0.494
Age (years)	79.98±8.33	80.45±7.86	0.467
FBG (mmol/L)	6.19±1.85	5.70±1.71	<0.001
Total cholesterol (mmol/L)	4.23±1.16	4.13±0.94	0.254*
HDL-cholesterol (mmol/L)	1.15±0.29	1.19±0.17	0.051*
LDL-cholesterol (mmol/L)	2.52±0.96	2.47±0.77	0.489*
TG (mmol/L)	1.51±0.73	1.11±0.58	<0.001*
HbA1c (%)	6.18±0.97	5.70±0.82	<0.001*
BMI (kg/m^2)	25.89±3.17	22.54±3.11	<0.001
AST (U/L)	20.43±9.23	20.29±13.68	0.875*
ALT (U/L)	19.03±13.09	15.37±12.23	<0.001
Uric acid (umol/L)	341.09±95.92	328.71±99.40	0.118
hs-CRP (mgl/L)	6.48±11.71	7.56±15.11	0.306*
FT3 (pmol/L)	4.09±0.77	3.98±0.88	0.094*
FT4 (pmol/L)	15.36±2.99	15.69±1.13	0.100*
TSH (uIU/mL)	2.75±2.27	2.71±2.37	0.832
25-OH Vitamin D (ng/mL)	11.55±7.66	15.09±9.27	<0.001*

Note: NAFLD: nonalcoholic fatty liver disease; FBG: fasting blood glucose; HDL-cholesterol, high-density lipoprotein-cholesterol; LDL-cholesterol, low density lipoprotein-cholesterol; TG, triglycerides; BMI: body mass index; AST: aspartate aminotransferase; ALT: alanine aminotransferase; hs-CRP, high sensitivity C-reactive protein; FT3, serum free Triiodothyronine; FT4, free Thyroxine; TSH, thyroid stimulating hormone; *unpaired t test with Welch's correction.

Table 2. Assignment description of multiple logistic regression analysis

Factors	Assignment	Description
FBG (mmol/L)	X1	< mean - SD, X1=0; mean - SD ~ mean + SD, X1=1; > mean + SD, X1=2
TG (mmol/L)	X2	
HbA1c (%)	X3	
BMI (kg/m^2)	X4	
ALT (U/L)	X5	
25-OH Vitamin D (ng/mL)	X6	

Note: FBG: fasting blood glucose; TG, triglycerides; BMI: body mass index; ALT: alanine aminotransferase.

Statistical analysis

Analyses were performed with SPSS 20.0 (StataCorp LP, College Station, TX) and MedCalc 11.4 (MedCalc, Mariakerke, Belgium) [18]. Measurement variables are presented as a mean with standard deviation and the comparison between groups was adopted independent sample t test for the data with homoscedasticity; for data with heteroscedasticity, unpaired t test with Welch's correction was applied. Categorical variables were expressed as frequencies or percentages and the analysis was adopted Chi-square test. Variables showed significant difference between the two groups were analyzed with multiple logistic regression analysis to determine the independent correlated variables for NAFLD. A two-tailed *P* value of <0.05 was considered to indicate statistical significance.

Results

Case selection result

After applying the inclusion and exclusion criteria, 663 subjects between 65 to 101 years were initially included in this study. Of the 663 subjects, 242 subjects were diagnosed as NAFLD, while 421 subjects were diagnosed as non-NAFLD as shown in **Figure 1**.

Baseline characteristics

The baseline characteristic in subjects with and without NAFLD are listed in **Table 1**. The results showed that individuals with NAFLD had significantly higher FBG, TG, HbA1C, BMI and ALT, while obviously lower 25-OH vitamin D compared with those without NAFLD (all P<0.05).

Relationship between 25-OH vitamin D and NAFLD

Multiple logistic regression analysis showed that NAFLD was independently correlated with low serum level of 25-OH vitamin D and high level of FBG, TG, HbA1C, and BMI (**Tables 2**, **3**).

Discussion

The prevalence of decreased 25-OH vitamin D levels is relatively high as reported by Holick et al. [19]. The prevalence of hypo-25-OH vitamin D in the elderly would be even higher due to inadequate food intake, decreased outdoor activity and exposure to sunlight, as well as

Table 3. Multiple logistic regression analysis result of these parameters

Variables in the Equation								
	β	S.E.	Wald	df	Sig.	Exp (β)	95% C.I. for Exp (β)	
							Lower	Upper
HbA1C	0.567	0.126	20.057	1	0.000	1.762	1.375	2.258
BMI	0.325	0.036	81.76	1	0.000	1.384	1.290	1.484
FBG	-0.167	0.067	6.173	1	0.013	0.846	0.741	0.965
TG	0.828	0.162	26.105	1	0.000	2.290	1.666	3.146
ALT	0.015	0.008	3.257	1	0.071	1.015	0.999	1.032
Vit D	-0.081	0.014	32.531	1	0.000	0.922	0.897	0.948
Constant term (β_0)	-8.526	1.512	31.803	1	0.000	0.000		

Note: FBG: fasting blood glucose; TG, triglycerides; BMI: body mass index; ALT: alanine aminotransferase.

impairment of kidney and hepatic functions [20]. The 25-OH vitamin D level is related with many factors, such as environmental factors (including season, local climate, latitude), modifiable life habits (including sun-exposure, clothing), and unchangeable parameters (including skin pigmentation, skin thickness) [20]. Therefore, in the present study, to eliminate (or at least to minimize) the influence of geographical and seasonal variation of 25-OH vitamin D levels, all subjects were recruited from Beijing and all blood samples were collected in the time from the 1st September to 30th December of each year. We believe this important strength made our study results more reliable.

A recent systematic review showed that 25-OH vitamin D level more than 25 ng/mL were associated with a 43% lower risk of type 2 diabetes compared with those less than 14 ng/mL [21]. Furthermore, George PS also reported that 25-OH vitamin D supplementation significantly improved insulin resistance when compared with placebo, while insulin resistance was an important pathogenic factor of NAFLD and is involved in the occurrence and development of NAFLD [22-24]. Another study showed that liver expression of 25-OH vitamin D receptor is inversely related with histological spectrum of NAFLD, independently from other metabolic parameters, such as BMI, insulin resistance, or adiponectin [13]. Furthermore, studies showed that serum level of 25-OH vitamin D was associated with age and treatment of 25-OH vitamin D deficiency may prevent fibrosis in chronic liver disease including NAFLD, suggesting that vitamin D deficiency play a role in development of NAFLD in the elderly [25-27]. Therefore, vitamin supplementation in the elderly may prevent both skeletal and non-skeletal adverse consequences of vitamin D deficiency including NAFLD. In our study of elderly patients, we demonstrate that serum levels of 25-OH vitamin D in NAFLD patients are lower than that in patients without NAFLD. Furthermore, 25-OH vitamin D level was independently associated with the presence of NAFLD, indicating that the 25-OH vitamin D may influence the development of NAFLD, consistent with previous reports.

There are also some limitations in the present study. First, we could not obtain the data regarding the patient's diet habit, sun exposure, and other life behaviors, which may potentially affect the vitamin D status. Second, this was a single center study, which will increase the risk of bias. Therefore, we will improve experimental scheme and validate the results by prospective multicenter cohort studies.

Conclusion

Elderly patients with NAFLD had reduced serum 25-OH vitamin D levels compared with patients without NAFLD. 25-OH vitamin D was independently associated with NAFLD.

Disclosure of conflict of interest

None.

Address correspondence to: Jidong Jia, Liver Research Center, Beijing Friendship Hospital, Capital Medical University, No. 95 Yong'an Road, Xicheng District, Beijing 100050, China. Tel: +86-010-63137642; Fax: +86-010-63137642; E-mail: jiamd@263.net

References

[1] Wesolowski SR, Kasmi KC, Jonscher KR, Friedman JE. Developmental origins of NAFLD: a

womb with a clue. Nat Rev Gastroenterol Hepatol 2017; 14: 81-96.
[2] Bedossa P. Histological assessment of NAFLD. Dig Dis Sci 2016; 61: 1348-55.
[3] Murillo AG, Dimarco DM, Fernandez ML. The potential of non-provitamin a carotenoids for the prevention and treatment of non-alcoholic fatty liver disease. Biology (Basel) 2016; 5.
[4] Pereira K, Salsamendi J, Casillas J. The global nonalcoholic fatty liver disease epidemic: what a radiologist needs to know. J Clin Imaging Sci 2015; 5: 32.
[5] Ekstedt M, Nasr P, Kechagias S. Natural history of NAFLD/NASH. Curr Hepatol Rep 2017; 16: 391-397.
[6] Liu XL, Pan Q, Zhang RN, Shen F, Yan SY, Sun C, Xu ZJ, Chen YW, Fan JG. Disease-specific miR-34a as diagnostic marker of non-alcoholic steatohepatitis in a Chinese population. World J Gastroenterol 2016; 22: 9844-52.
[7] Yan J, Xie W, Ou WN, Zhao H, Wang SY, Wang JH, Wang Q, Yang YY, Feng X, Cheng J. Epidemiological survey and risk factor analysis of fatty liver disease of adult residents, Beijing, China. J Gastroenterol Hepatol 2013; 28: 1654-9.
[8] Bertolotti M, Lonardo A, Mussi C, Baldelli E, Pellegrini E, Ballestri S, Romagnoli D, Loria P. Nonalcoholic fatty liver disease and aging: epidemiology to management. World J Gastroenterol 2014; 20: 14185-204.
[9] Targher G, Bertolini L, Scala L, Cigolini M, Zenari L, Falezza G, Arcaro G. Associations between serum 25-hydroxyvitamin D3 concentrations and liver histology in patients with non-alcoholic fatty liver disease. Nutr Metab Cardiovasc Dis 2007; 17: 517-24.
[10] Nobili V, Giorgio V, Liccardo D, Bedogni G, Morino G, Alisi A, Cianfarani S. Vitamin D levels and liver histological alterations in children with nonalcoholic fatty liver disease. Eur J Endocrinol 2014; 170: 547-53.
[11] Ha Y, Hwang SG, Rim KS. The association between vitamin D insufficiency and nonalcoholic fatty liver disease: a population-based study. Nutrients 2017; 9.
[12] Marunchyn NA, Dynnyk OB, Kovalerenko LS. Using the principle of multiparametric ultrasound for the diagnosis of nonalcoholic fatty liver disease in patients with type 2 diabetes mellitus. Mezhdunarodnyi Endokrinologicheskii Zhurnal 2017; 13: 171-176.
[13] Seo JA, Eun CR, Cho H, Lee SK, Yoo HJ, Kim SG, Choi KM, Baik SH, Choi DS, Yim HJ, Shin C, Kim NH. Low vitamin D status is associated with nonalcoholic fatty liver disease independent of visceral obesity in Korean adults. PLoS One 2013; 8: e75197.
[14] Bril F, Maximos M, Portillo-Sanchez P, Biernacki D, Lomonaco R, Subbarayan S, Correa M, Lo M, Suman A, Cusi K. Relationship of vitamin D with insulin resistance and disease severity in non-alcoholic steatohepatitis. J Hepatol 2015; 62: 405-11.
[15] Jang W, Park J, Kim JS, Youn J, Oh E, Kwon KY, Jo KD, Lee MK, Kim HT. Vitamin D deficiency in Parkinson's disease patients with orthostatic hypotension. Acta Neurol Scand 2015; 132: 242-50.
[16] Holick MF. Vitamin D status: measurement, interpretation, and clinical application. Ann Epidemiol 2009; 19: 73-8.
[17] van den Ouweland JM, Vogeser M, Bacher S. Vitamin D and metabolites measurement by tandem mass spectrometry. Rev Endocr Metab Disord 2013; 14: 159-84.
[18] Barchetta I, Angelico F, Del Ben M, Baroni MG, Pozzilli P, Morini S, Cavallo MG. Strong association between non alcoholic fatty liver disease (NAFLD) and low 25(OH) vitamin D levels in an adult population with normal serum liver enzymes. BMC Med 2011; 9: 85.
[19] Holick MF. Vitamin D deficiency. N Engl J Med 2007; 357: 266-81.
[20] Annweiler C, Beauchet O. Vitamin d in older adults: the need to specify standard values with respect to cognition. Front Aging Neurosci 2014; 6: 72.
[21] Mitri J, Muraru MD, Pittas AG. Vitamin D and type 2 diabetes: a systematic review. Eur J Clin Nutr 2011; 65: 1005-15.
[22] George PS, Pearson ER, Witham MD. Effect of vitamin D supplementation on glycaemic control and insulin resistance: a systematic review and meta-analysis. Diabet Med 2012; 29: e142-50.
[23] Du X. Effect and mechanism of histone modification on NAFLD of FASN gene promoter region under insulin action. Chongqing Medical University 2017.
[24] Fan KL, Zhang HJ, Zheng A. Relationship between nonalcoholic fatty liver fibrosis score and insulin resistance. Acta Academiae Medicinae Xuzhou 2016; 36: 673-675.
[25] Chen MM, Jiang X, Du YP. Investigation of factors impacting serum levels of 25-hydroxyvitamin D in the elderly living in Shanghai community. Chinese Journal of Geriatrics 2016; 35: 1005-1010.
[26] Potter JJ, Liu X, Koteish A, Mezey E. 1,25-dihydroxyvitamin D3 and its nuclear receptor repress human alpha1 (I) collagen expression and type I collagen formation. Liver Int 2013; 33: 677-86.
[27] Eliades M, Spyrou E, Agrawal N, Lazo M, Brancati FL, Potter JJ, Koteish AA, Clark JM, Guallar E, Hernaez R. Meta-analysis: vitamin D and non-alcoholic fatty liver disease. Aliment Pharmacol Ther 2013; 38: 246-54.