

The Association Between Vitamin D and Type 2 Diabetes Mellitus Complicated with Non-Alcoholic Fatty Liver Disease: An Observational Cross-Sectional Study

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Objective: To investigate the association between vitamin D deficiency and NAFLD risk in patients with type 2 diabetes mellitus (T2DM).

Methods: Overall, 434 patients with T2DM admitted to Hebei General Hospital from January 2019 to December 2019 were selected as the study subjects. According to abdominal ultrasound findings, patients were divided into the NAFLD group and the non-NAFLD group. Participants were divided into two study groups according to the 25-hydroxyvitamin D [25(OH)D] level. 25(OH)D deficiency was defined if 25(OH)D vitamin levels were <20 ng/mL. Chi-square test and one-way analysis of variance were used to compare groups. The relationship between 25(OH)D and NAFLD risk was analyzed using correlation and regression analyses. Furthermore, subgroup analyses were performed to verify the robustness of the results.

Results: The 25(OH)D level in patients with T2DM complicated by NAFLD was significantly lower than in patients with T2DM only. Vitamin D deficiency was highly prevalent among T2DM patients with NAFLD. This study suggested that vitamin D deficiency was an independent factor for developing NAFLD in patients with T2DM. T2DM patients with vitamin D deficiency had 2.045 times higher risk of developing NAFLD than those without vitamin D deficiency. Vitamin D deficiency was associated with high NAFLD preference in T2DM patients with BMI >23kg/m², but not those with BMI ≤23kg/m². The significant correlation between vitamin D deficiency and NAFLD was found in participants with BMI >23kg/m², age ≤65 years, without hypertension, TG <1.7mmol/l, HDL ≥1 mmol/l in men, ≥1.3 mmol/l in women, HBA1C ≤7%, or females.

Conclusion: This study suggests that T2DM people with BMI >23kg/m² were more susceptible to NAFLD by vitamin D deficiency and that it is necessary to maintain optimal serum vitamin D levels in this population.

Keywords: type 2 diabetes mellitus, non-alcoholic fatty liver disease, vitamin D

Introduction

Non-alcoholic fatty liver disease (NAFLD) was characterized by a spectrum of pathologies ranging from simple hepatocyte steatosis to non-alcoholic steatohepatitis (NASH). As the disease progresses, it can lead to liver cirrhosis and even the liver cancer.¹ In a recent meta-analysis of 86 studies, the global prevalence of NAFLD was estimated to be 25.24% in the general population, while several meta-analyses indicated that in type 2 diabetes mellitus (T2DM) patients the prevalence was double (54–59.67%).^{2–4} The prevalence of NAFLD has reached as high as 90%, particularly in T2DM patients with obesity.⁵ However, accumulating evidence indicated that the effects of NAFLD extend beyond the liver and are negatively associated with a range of chronic diseases, most notably cardiovascular disease (CVD), T2DM

and chronic kidney disease (CKD).⁶ However, there was no definitive treatment for NAFLD other than lifestyle intervention.⁷ Vitamin D was a lipid-soluble vitamin involved primarily in bone metabolism, calcium and phosphate homeostasis and skeletal development.⁸ 25-Hydroxyvitamin D [25(OH)D] was the active form of vitamin D.⁹ The evaluation of vitamin D status usually relied on detection of the serum 25(OH)D concentration.¹⁰ Several epidemiologic studies show that low serum levels of 25(OH)D were associated with adverse health outcomes, such as metabolic syndrome, diabetes, chronic liver disease, cancer, cardiovascular disease and all-cause mortality.^{11–16} Worldwide, vitamin D deficiency was one of the most important public health issues and its prevalence in general populations is approximately 36% in the United States, 61% in Canada, 92% in Northern Europe, 45–98% in Asia, 31% in Australia and 56% in New Zealand.¹⁷ A meta-analysis concluded that vitamin D deficiency was common in Asia based on data from 472 studies with 746,564 participants.¹⁸ Epidemiological evidence indicated that low 25(OH)D level was an independent risk factor for NAFLD.^{14,19} A recent meta-analysis indicated a significant association between low 25(OH)D level and NAFLD.²⁰ T2DM patients had multiple micro/macronutrient deficiencies, eg, magnesium deficiency.²¹ The risk of NAFLD was also linked with dietary components of the diet, eg, dietary insulinemic potential.²² NAFLD and T2DM interacted in a “cause or consequence” fashion such that the presence of one entity increases the predisposition and/or worsens the complications for the other disease.^{23–27} Based on the controversy over the relationship between vitamin D and NAFLD in patients with T2DM, so we aimed to explore the relationship between 25 (OH) D and NAFLD and to investigate whether there was any difference between different populations.

Methods

Patients and Study Design

The study was conducted following the Declaration of Helsinki and was approved by the Ethics Committee of Hebei General Hospital. Our study included 434 patients diagnosed with T2DM who were hospitalized in Hebei General Hospital of Shijiazhuang in China. All subjects had signed written informed consent. Studies were independently assessed by the two researchers and evaluated against inclusion and exclusion criteria by consensus.

Inclusion Criteria

1) Age ≥ 18 years. 2) The clinical diagnosis of T2DM was established according to the following criteria: 1) Patients who were under treatment with either oral antidiabetic agents or insulin, and who gave a history of diabetes, also were considered to have T2DM. 2) T2DM conformed to 1999 WHO Diagnostic Criteria: typical symptoms of diabetes (such as polyphagia, polydipsia, polyuria and weight loss) and random blood glucose ≥ 11.1 mmol/l or fasting blood glucose (FPG) ≥ 7.0 mmol/l or glucose tolerance test two-hour blood glucose > 11.1 mmol/l. Patients without typical symptoms of diabetes should be rechecked another day. 3) Fatty liver was diagnosed by the findings of ultrasound performed by trained technicians. The participants with liver contrast and liver brightness among the four known criteria (hepatorenal echo contrast, liver brightness, deep attenuation, and vascular blurring) were diagnosed as having fatty liver.²⁸

Exclusion Criteria

1) Patients with type 1 diabetes mellitus, gestational diabetes and other particular types of diabetes were excluded. 2) Patients were excluded if they had a history of myocardial infarction, cerebral haemorrhage, severe dysfunction of liver and kidney, recent acute infection and stress within the last 3 months before enrollment. 3) Patients were excluded if they had taken calcium, vitamin D supplements or any drugs affecting vitamin D metabolism in the past 6 months. 4) Any participants currently using drugs that can increase NAFLD risk, such as amiodarone, corticosteroids, etc. 5) Patients were also excluded if they had a clear drinking history (≥ 30 grams/day in men and ≥ 20 grams/day in women). Subjects with positive for hepatitis B surface antigen (HBsAg) or anti-hepatitis C virus (HCV) antibody, autoimmune hepatitis, Wilson disease, primary biliary cirrhosis, primary sclerosing cholangitis, liver metabolic disorders, drug-induced hepatitis, hemochromatosis, malignancy, osteoporosis, thyroid disease or kidney disease were also excluded.

Data Collection

A questionnaire was utilized to collect basic information from T2DM patients, including age, sex, course of diabetes, history of hypertension, and medication history. Height (m) and weight (kg) were measured to calculate body mass index [BMI = weight (kg)/height (m²)]. Venous blood samples were drawn from all subjects after an overnight fast of 8 hours. Blood measurements included glycosylated haemoglobin (HbA1c), FPG, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ -glutamyl transferase (GGT), total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), very-low-density lipoprotein cholesterol (VLDL), 25(OH) D. The data and results will be entered into spreadsheets and cross-checked by two researchers. Serum 25(OH)D was determined by electrochemiluminescence immunoassays (ECLA) using Roche commercial kits (COBAS e 601, Roche, Germany).

Statistical Analysis

Statistical analyses were performed using SPSS software, version 25.0. Continuous variables were expressed as the mean \pm standard deviation (SD) if normally distributed and as medians and interquartile range (P25, P75) if not normally distributed. Independent group *t*-test was used for a continuous variable when the data conformed to normal distribution; otherwise, the Kruskal–Wallis test was applied. The enumeration data were expressed in percentage [n/(%)], and the Chi-square test tested the comparison between the groups. Descriptive statistics were calculated and compared between T2DM patients with and without NAFLD or vitamin D deficiency. The variables with a *p*-value level of less than 0.1 were entered into the multiple logistic regression model. Differences were considered statistically significant for *p* values <0.05. Taking $\alpha = 0.05$, $\beta = 0.10$, and bilateral testing, the PASS software (version 15.0) was used to calculate the sample size in this study.

Results

Comparison of Clinical Characteristics Between T2DM Patients with and without NAFLD

By comparing the clinical parameters of T2DM patients with NAFLD and those without NAFLD, there were no statistically differences in sex, the proportion of hypertension, the level of FPG and HbA1c between the two groups. Patients with NAFLD had a significantly shorter duration (*p*=0.049) and younger age (*p*=0.004) than patients without NAFLD. The levels of BMI (*p*<0.001), albumin (*p*=0.030), ALT (*p*<0.001), AST (*p*<0.001), GGT (*p*<0.001), TC (*p*=0.002), TG (*p*<0.001), LDL (*p*=0.004), VLDL (*p*<0.001) were higher among T2DM patients who had NAFLD compared to those without NAFLD. Patients with combined T2DM and NAFLD had decreased HDL levels compared with T2DM patients (Table 1).

Comparison of Clinical Characteristics in T2DM Patients with VDD and VDND Groups

Patients were divided into two groups according to their 25(OH)D levels: vitamin D-deficient group (VDD) (<20 ng/mL), and vitamin D non-deficient group (VDND) (>20 ng/mL), with 296, 138 patients in each group, respectively. In the VDD group, BMI (*p*=0.03), HbA1c (*p*=0.002), TG (*p*<0.001), VLDL (*p*=0.009) levels and female proportion (*p*<0.001) were significantly higher compared with the VDND group, while the levels of albumin were lower than T2DM patients in the VDND group. However, there was no significant difference in age, T2DM course, ALT, AST, GGT, TC, HDL, LDL, FPG and hypertension proportion between the VDD and VDND groups (Table 2).

Comparison of 25(OH)D Levels and Prevalence of NAFLD in T2DM Patients with Different Levels of BMI

Patients who underwent combined NAFLD still conferred a statistically significant lower level of 25(OH)D [15.89 (12.33, 19.94) vs 18.27 (14.05, 24.63), *p*<0.001] (Figure 1A) and a higher proportion of patients with vitamin

Table 1 Characteristics of Patients with and without NAFLD Included in This Study

	All Participants	Without NAFLD	With NAFLD	P value
n (%)	434	200	234	–
Age	58.74±12.92	60.79±11.99	56.98±13.45	0.004
Sex (F, %)	184 (42.4%)	85 (42.5%)	99(42.3%)	0.968
Hypertension (n, %)	217 (50%)	94 (47%)	123 (52.6%)	0.248
DM course (years)	9.87 (3, 15)	10.00 (3.00, 16.00)	8.00 (2.00, 15.00)	0.049
BMI (kg/m ²)	25.72±3.95	23.71±3.27	27.44±3.65	<0.001
Albumin (g/L)	40.18 (37.68, 42.93)	39.85 (37.60, 42.60)	40.80 (37.78, 43.20)	0.030
ALT (U/L)	24.42 (13.70, 28.50)	15.70 (12.53, 22.58)	21.20 (15.50, 34.45)	<0.001
AST (U/L)	22.50 (15.70, 24.10)	17.90 (14.63, 21.88)	20.00 (16.70, 26.80)	<0.001
GGT (U/L)	38.20 (17.15, 38.65)	20.60 (14.00, 29.63)	30.00 (19.60, 46.00)	<0.001
HbA1c (%)	8.97 (7.18, 10.50)	8.40 (6.90, 10.40)	8.80 (7.40, 10.50)	0.089
FPG (mmol/l)	8.87 (6.29, 11.15)	7.62 (6.12, 10.54)	8.38 (6.42, 11.54)	0.163
TC (mmol/L)	4.77 (3.88, 5.42)	4.45 (3.76, 5.18)	4.77 (4.01, 5.59)	0.002
TG (mmol/L)	2.05 (1.03, 2.33)	1.16 (0.87, 1.75)	1.86 (1.26, 2.71)	<0.001
HDL (mmol/L)	1.05 (0.84, 1.18)	1.04 (0.89, 1.24)	0.97 (0.83, 1.15)	0.002
LDL (mmol/L)	3.11 (2.46, 3.61)	2.90 (2.33, 3.48)	3.22 (2.59, 3.72)	0.004
VLDL (mmol/l)	0.51(0.35, 0.69)	0.43(0.28, 0.58)	0.57(0.40, 0.80)	<0.001
25(OH)D (mmol/l)	17.04 (12.99, 21.63)	18.27 (14.05, 24.63)	15.89 (12.33, 19.94)	<0.001
Vitamin D deficiency (%)	296 (68.2%)	118 (59%)	178 (76.1%)	<0.001

D deficiency (76.1% vs 59%, $P<0.001$) compared with T2DM patients without NAFLD (Table 1). NAFLD prevalence in T2DM patients with 25 (OH) D deficiency was higher than in those without 25 (OH) D deficiency, and the difference was statistically significant (60.1% vs 40.6%, $P<0.001$) (Figure 2A).

BMI was categorized as BMI $\leq 23\text{kg/m}^2$ and BMI $\geq 23\text{kg/m}^2$. We also carried out separate analyses for these two subgroups. In T2DM patients with BMI $>23\text{kg/m}^2$, the level of 25(OH)D was significantly lower in T2DM patients with NAFLD compared with those without NAFLD [15.80 (12.04, 19.73) vs 17.72 (13.36, 23.57), $P=0.002$] (Figure 1B). The NAFLD prevalence in patients with 25 (OH) D deficiency was higher than in those without 25 (OH) D deficiency, and the difference was statistically significant (68.4% vs 51%, $P=0.002$) in T2DM patients with BMI $>23\text{kg/m}^2$ (Figure 2B). However, no difference was observed in the levels of 25 (OH) D between NAFLD and non-NAFLD groups in T2DM patients with BMI $\leq 23\text{kg/m}^2$ (Figure 1C). There was no difference in the prevalence of NAFLD between VDND and VDD groups in T2DM patients with BMI $\leq 23\text{kg/m}^2$ (Figure 2C).

Spearman Correlation of 25(OH)D with Potential NAFLD Factors

Correlation analysis demonstrated that 25(OH)D level was positively correlated with albumin ($r=0.214$, $p<0.001$) and negatively correlated with BMI ($r=-0.138$, $p=0.004$), FPG ($r=-0.112$, $p=0.019$), HbA1c ($r=-0.190$, $p<0.001$), TG ($r=-0.231$, $p<0.001$), LDL ($r=-0.103$, $p=0.032$), VLDL ($r=-0.151$, $p=0.002$) in all study subjects. Figure 3 demonstrates the results of Spearman correlation analysis.

Table 2 Characteristics of Patients with and without Vitamin D Deficiency Included in This Study

	VDND	VDD	P value
n	138	296	–
Age	58.1756±12.91658	58.9965±12.94043	0.547
Sex (F, %)	39 (28.3%)	145 (49%)	<0.001
Hypertension (n, %)	60 (43.5%)	157 (53%)	0.064
NAFLD	56 (40.6%)	178 (60.1%)	<0.001
DM course (years)	7.5(3, 15)	9(3, 15)	0.834
BMI (kg/m ²)	25.345(22.865, 26.8975)	25.755(23.7025, 28.0975)	0.03
Albumin (g/L)	41.15(38.3, 43.8)	40.1(37.025, 42.6)	0.001
ALT (U/L)	19.85(13.925, 29.8)	18.4(13.7, 27.5)	0.66
AST (U/L)	19.1(15.7, 24.6)	19.2(15.7, 23.9)	0.988
GGT (U/L)	24.65(16.75, 37.6)	25.9(17.7, 38.7)	0.383
HbA1c (%)	8.2(6.875, 9.7)	8.9(7.4, 10.5)	0.002
FPG (mmol/l)	7.55(5.84, 10.62)	8.225(6.425, 11.18)	0.079
TC (mmol/L)	4.555(3.78, 5.2425)	4.665(3.8925, 5.505)	0.072
TG (mmol/L)	1.25(0.9175, 1.855)	1.655(1.0825, 2.4625)	<0.001
HDL-C (mmol/L)	1.01(0.88, 1.1825)	1(0.83, 1.1875)	0.345
LDL-C (mmol/L)	2.98(2.325, 3.4525)	3.09(2.47, 3.72)	0.071
VLDL (mmol/L)	0.46(0.3075, 0.61)	0.53(0.37, 0.72)	0.009

Multivariate Logistic Regression Analyses of NAFLD and Associated Factors

Multiple logistic regression analysis was employed to examine whether vitamin D deficiency was independently and significantly associated with the presence of NAFLD in T2DM patients. For all T2DM patients, vitamin D deficiency was

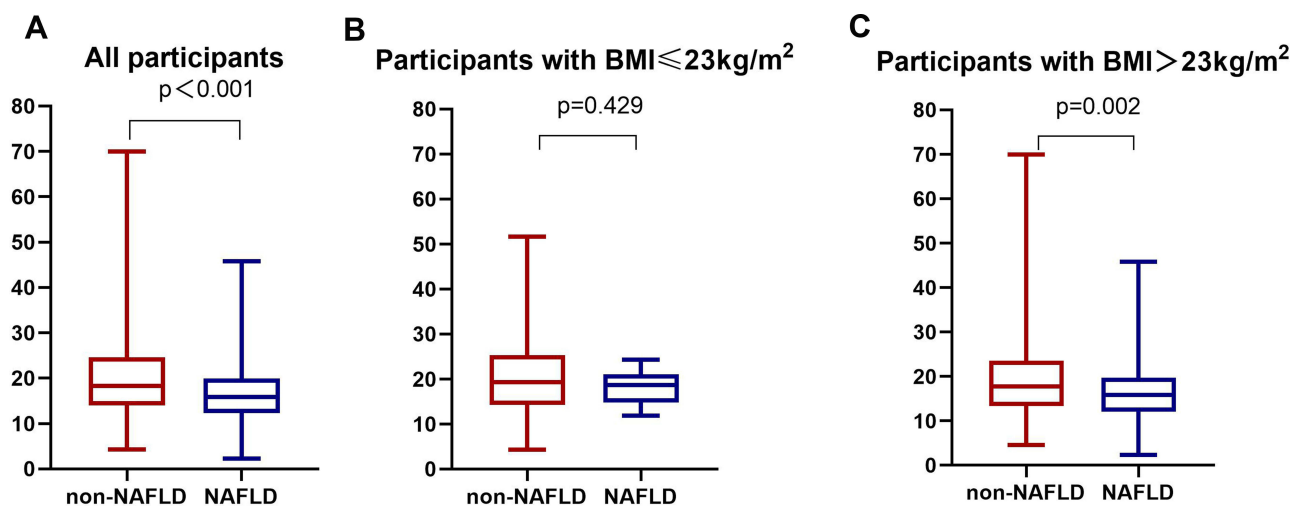


Figure 1 Comparison of 25(OH)D between the NAFLD group and the non-NAFLD group in participants with T2DM: (A) all participants; (B) participants with BMI >23kg/m²; (C) participants with BMI ≤23kg/m².

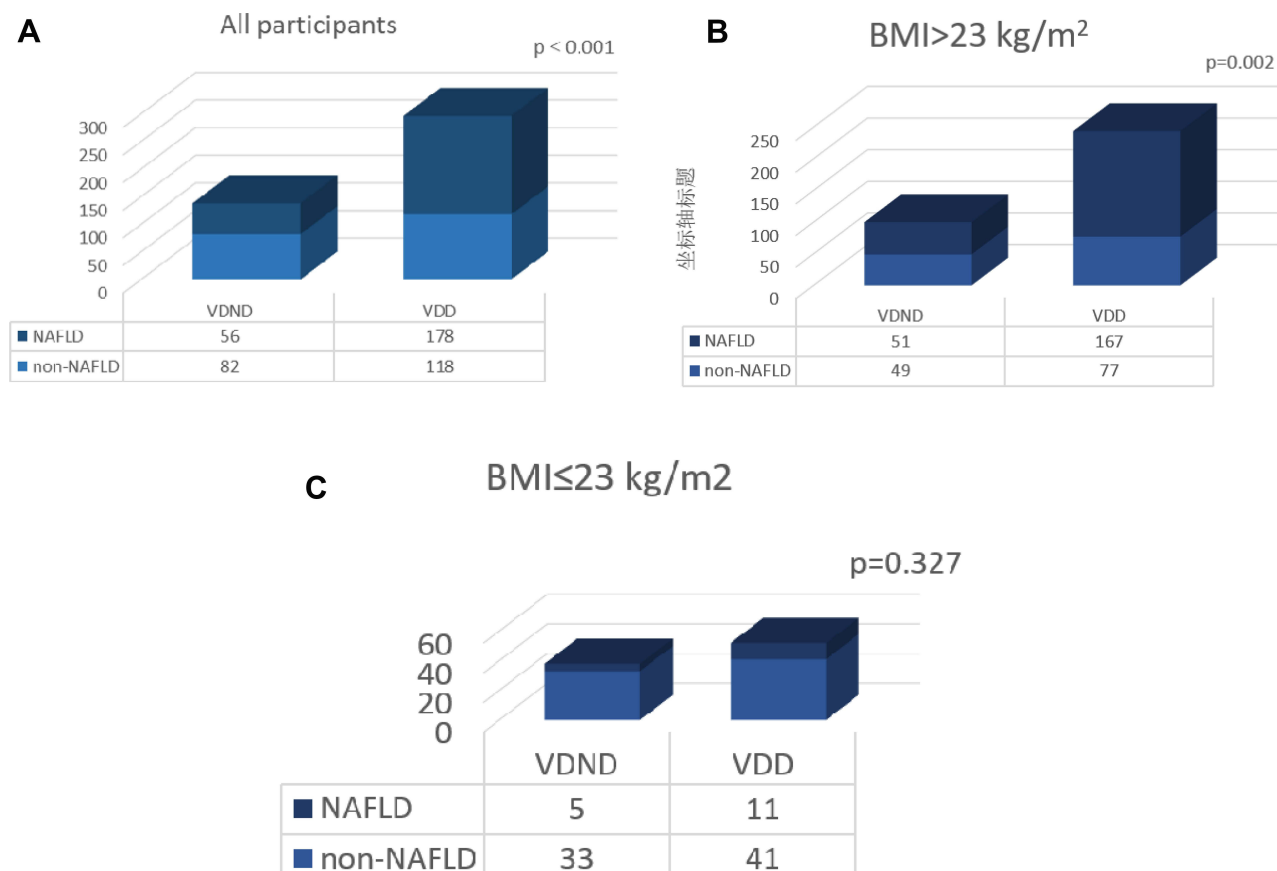


Figure 2 Comparison of the prevalence of NAFLD in T2DM patients with and without vitamin D deficiency: (A) all participants; (B) participants with BMI >23kg/m²; (C) participants with BMI ≤23kg/m².

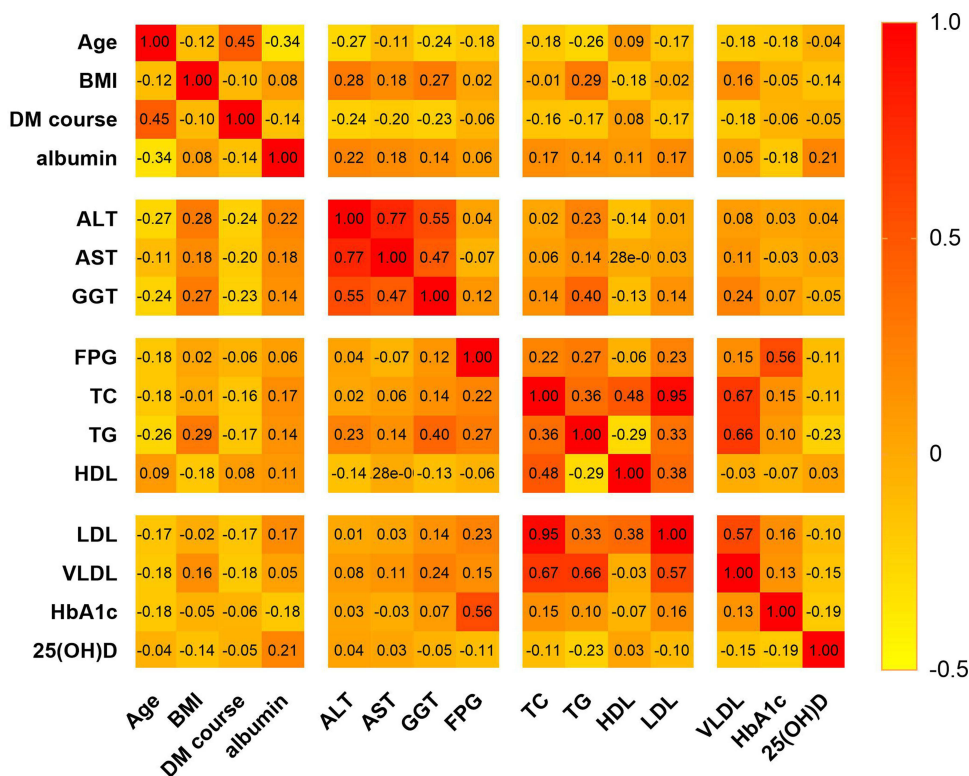


Figure 3 Spearman correlation analysis of 25(OH)D with potential risk factors for NAFLD.

Table 3 Logistic Regression Analysis of Vitamin D Deficiency for NAFLD in Patients with T2DM

	B	Std. Error	Wald	P	OR	95% CI (OR)
Model 1	0.843	0.262	10.4	0.001	2.324	(1.392, 3.88)
Model 2	0.863	0.269	10.269	0.001	2.369	(1.398, 4.016)
Model 3	0.715	0.286	6.246	0.012	2.045	(1.167, 3.583)

Notes: Model 1: adjusted for sex, age, BMI, hypertension; Model 2: adjusted for sex, age, BMI, hypertension, DM course, albumin, ALT, AST, GGT; Model 3: adjusted for sex, age, BMI, hypertension, DM course, albumin, ALT, AST, GGT, FPG, TC, TG, HDL, LDL, VLDL, HbA1c.

Table 4 Logistic Regression Analysis of Vitamin D Deficiency for NAFLD in T2DM Patients with BMI $\leq 23\text{kg/m}^2$

	B	Std. Error	Wald	P	OR	95% CI
Model 1	0.862	0.696	1.534	0.216	2.367	(0.605, 9.261)
Model 2	0.245	0.782	0.098	0.754	1.278	(0.276, 5.921)
Model 3	-0.21	1.03	0.042	0.838	0.811	(0.108, 6.097)

Notes: Model 1: adjusted for sex, age, BMI, hypertension; Model 2: adjusted for sex, age, BMI, hypertension, DM course, albumin, ALT, AST, GGT; Model 3: adjusted for sex, age, BMI, hypertension, DM course, albumin, ALT, AST, GGT, FPG, TC, TG, HDL, LDL, HbA1c.

significantly associated with a higher prevalence of NAFLD. Specifically, T2DM patients with vitamin D deficiency had a 2.045 (95% CI: 1.167, 3.583) times higher risk of developing NAFLD than those without vitamin D deficiency (Table 3).

Vitamin D deficiency was not associated with high NAFLD preference in T2DM patients with BMI $\leq 23\text{ kg/m}^2$, ($P = 0.216$ for model 1, $P = 0.754$ for model 2, and $P = 0.838$ for model 3) (Table 4). Vitamin D deficiency was associated with high NAFLD preference in T2DM patients with BMI $>23\text{kg/m}^2$, regardless of whether an unadjusted or adjusted model was used ($P = 0.004$ for model 1, $P = 0.003$ for model 2, and $P = 0.016$ for model 3) (Table 5).

Subgroup Analysis

To further investigate the impact of other risk factors on the correlation of vitamin D deficiency with NAFLD risk in T2DM patients with BMI $>23\text{ kg/m}^2$, subgroup analyses were carried according to sex, age, history of hypertension, TG, HDL and HbA1c. Table 6 has summarized the results of subgroup analysis results. The significant correlation between vitamin D deficiency and NAFLD was found in participants with age ≤ 65 years, without hypertension, TG $<1.7\text{mmol/l}$, HDL $\geq 1\text{ mmol/l}$ in men, $\geq 1.3\text{ mmol/l}$ in women, HbA1c $\leq 7\%$, or females.

Discussion

The results of this study revealed that the 25(OH)D level in patients with T2DM complicated by NAFLD was significantly lower than that in patients with T2DM only. It was consistent with the result of Xiu et al.²⁹ Recently, it was shown that bariatric surgery could also influence vitamin D levels in obese patients.³⁰ No patients in this study underwent bariatric surgery. A meta-analysis of 10 RCTs (randomized controlled trials) showed that Sodium-Glucose Transporter 2 (SGLT2) inhibitors could remarkably reduce hepatic enzymes and hepatic fat.³¹ Another meta-analysis

Table 5 Logistic Regression Analysis of Vitamin D Deficiency for NAFLD in T2DM Patients with BMI $>23\text{kg/m}^2$

	B	Std. Error	Wald	P	OR	95% CI (OR)
Model 1	0.809	0.282	8.215	0.004	2.246	(1.292, 3.906)
Model 2	0.849	0.29	8.595	0.003	2.338	(1.325, 4.126)
Model 3	0.747	0.312	5.753	0.016	2.111	(1.146, 3.888)

Notes: Model 1: adjusted for sex, age, BMI, hypertension; Model 2: adjusted for sex, age, BMI, hypertension, DM course, albumin, ALT, AST, GGT; Model 3: adjusted for sex, age, BMI, hypertension, DM course, albumin, ALT, AST, GGT, FPG, TC, TG, HDL, LDL, VLDL, HbA1c.

Table 6 Effect of Vitamin D Deficiency on NAFLD Risk Stratified by Subgroups

Characteristics	No. of Participants	OR(95% CI)	P-value
Age (years)			
≤65	306	2.374(1.144, 4.923)	0.02
>65	128	1.184(0.267, 5.248)	0.824
Sex			
Males	250	1.345(0.633, 2.857)	0.44
Females	184	6.641(1.571, 28.072)	0.01
Hypertension			
No	217	3.275(1.225, 8.759)	0.018
Yes	217	1.561(0.661, 3.687)	0.31
HBA1C (%)			
≤9	246	1.986(0.899, 4.385)	0.09
>9	188	2.007(0.587, 6.86)	0.587
TG (mmol/l)			
≥1.7	187	0.673(0.183, 2.477)	0.551
<1.7	247	2.813(1.297, 6.101)	0.009
HDL (mmol/l)			
≥1 in men, ≥1.3 in women	149	4.947(1.204, 20.315)	0.027
<1 in men, <1.3 in women	285	2.04(0.905, 4.598)	0.085

found that pioglitazone could significantly improve the histological performance of the liver and insulin sensitivity.³² Moreover, this study demonstrated that none of the T2DM patients used SGLT2 inhibitors or pioglitazone.

Our results indicated that vitamin D deficiency was highly prevalent among T2DM patients with NAFLD. It was demonstrated that the relation between vitamin D deficiency and NAFLD was bidirectional. On the one hand, vitamin D (either synthesized in the skin – cholecalciferol – or obtained from dietary – ergocalciferol) was metabolized within the liver to 25(OH) D and within the kidneys to the biologically active (1,25- dihydroxy vitamin D).³³ On the other hand, insulin resistance was at the root of both T2DM and NAFLD, and vitamin D may significantly impact insulin sensibilization through its anti-inflammatory effects and its role in regulating insulin secretion.³⁴

Because obesity was a confounding factor,³⁵ we measured BMI, a surrogate measure of obesity, and it had also mainly been demonstrated.³⁶ Several recent studies recommend that BMI may be best maintained within 23kg/m².^{37–41} Therefore, we performed multiple regression analysis in all T2DM subjects and T2DM patients with BMI>23kg/m² and BMI ≤23kg/m², respectively. We observed that vitamin D deficiency was an independent risk factor for NAFLD in T2DM patients, especially in those with BMI >23kg/m².

The explanation for why obese and lean individuals have inconsistent correlations between vitamin D and NAFLD remains unclear, although several possibilities exist.⁴² First, obesity could be a contributing factor to low vitamin D levels. Second, patients with vitamin D deficiency have higher serum levels of proinflammatory cytokines, which promote NAFLD development. Third, under vitamin D deficiency conditions, the flow of free fatty acids (FFAs) in the blood increases, and fat deposition into hepatocytes is accelerated, contributing to the progress of NAFLD.

It was recognised that a strong association between a low level of 25(OH)D and NAFLD existed in patients with T2DM.⁴³ Another study conducted in Korea has also reported similar results indicating a negative association between

25(OH)D and NAFLD after adjustment for potential confounders.⁴⁴ Recently, Nelson et al⁴⁵ reported that 25(OH)D deficiency was commonly associated with the increased risk of NAFLD diagnosed by liver biopsy. In a meta-analysis by Eliades et al,²⁰ 25(OH)D level was lower in patients diagnosed with NAFLD. In addition, several studies have demonstrated that vitamin D status was associated with dyslipidemia, inflammation, insulin resistance, oxidative stress and obesity.^{11,46–49} Vitamin D levels can be modulated by consuming other drugs/supplements, eg, omega-3 fatty acids.⁵⁰ Thus, there have been recommendations that taking vitamin supplements may potentially contribute to NAFLD treatment. However, the results are inconsistent. Findings by Talaei et al⁵¹ suggested that a 2-month course of vitamin D supplementation improved insulin resistance in patients with T2DM. A study by Papapostoli et al⁵² had demonstrated that vitamin D supplementation reduced the severity of hepatic steatosis in patients with NAFLD. The results of Barchetta et al⁷ revealed that hepatic steatosis was not able to improve after 24 weeks of supplementation of vitamin D. As pointed out by Heaney,⁵³ a central bias behind the inconsistent results from trials on the effects of vitamin D supplementation may be represented by the well-known physiology of nutrients, which do not show the dose–response relation observed for most drugs. Results from a recent meta-analysis that included 16 RCTs indicated that Vitamin D supplementation could be considered an effective strategy in managing patients with NAFLD.⁵⁴ Patients with NAFLD were also prone to develop liver fibrosis and even liver cancer if they were associated with vitamin D deficiency.^{55,56}

Vitamin D deficiency may play a role in the pathogenesis of NAFLD by decreasing the expression of the glucose transporter, reducing hepatic glucose output, and stimulating intrahepatic lipid synthesis.⁵⁷ Thus, a low serum vitamin D level was potentially prone to intrahepatic lipid accumulation, leading to NAFLD. The first “two hits” theory of NAFLD pathogenesis mainly involved insulin resistance and excessive free fatty acids in the circulation.⁵⁸ Vitamin D decreased insulin resistance induced by free fatty acids in peripheral tissues and hepatocytes.⁵⁹ In addition, Thais et al’s study⁶⁰ also showed insulin resistance could be improved in vitamin D-supplemented animals. Moreover, they proved vitamin D deficiency had a particularly adverse impact on metabolism, hepatic steatosis, and changes caused by hepatic stellate cell activation (liver fibrosis, β -oxidation, lipogenesis, and liver inflammation). Animals appeared to improve all these data after vitamin D supplementation.

Oxidative stress was considered the second hit of the “two hits” theory of NAFLD pathogenesis. Some studies have demonstrated higher oxidative stress biomarkers in people with a low 25(OH)D level. Intake of vitamin D also decreased oxidative stress.^{61,62} Indeed, Eftekhari et al⁶³ found that the intake of calcitriol (1,25(OH)2D3) significantly reduced TC, LDL, TG, and malondialdehyde levels in patients with T2DM. They concluded that 1, 25(OH)2D3 could reduce oxidative stress and improve lipid profiles. Nakano et al⁶⁴ recently found that sunlight therapy ameliorated hepatocyte inflammation and fibrosis by regulating lipid transfer/metabolic. Inflammation could also lead to the development and progression of NAFLD.⁶⁵ Vitamin D was also known to exhibit anti-inflammatory effects on macrophages.⁶⁶ The study also demonstrated that vitamin D deficiency was associated with impaired T lymphocyte immune function and increased inflammation through elevated levels of proinflammatory cytokines.⁶⁷ A potentially novel insight was provided into the interactions of the liver and intestine in the progression and pathogenesis of NAFLD.⁶⁸ Vitamin D deficiency facilitated non-alcoholic steatohepatitis progression by impaired enterohepatic circulation in animal models.⁶⁹ Hamed et al showed that the NAFLD patients with T2DM were characterized by different gut compositions,⁷⁰ which supported the role of gut microbiota in the pathogenesis of T2DM and NAFLD. The findings from this study suggest intake of vitamin D should be emphasized in order to prevent NAFLD in obese T2DM populations.

The present study had a few limitations. Firstly, a causal relationship cannot be established due to the cross-sectional study design. Further studies are required to evaluate the causative relationships between 25(OH)D and NAFLD, the effect of vitamin D supplementation on NAFLD, and patients with T2DM. Secondly, the diagnosis of NAFLD was based on ultrasonography and the exclusion of other known causes of liver disease but was not confirmed by liver biopsy. Third, the BMI classification criteria applied in this study are limited to Asian people, so our findings may not be generalizable to other ethnic populations.

Conclusion

This study suggests that T2DM people with BMI $>23\text{kg/m}^2$ were more susceptible to NAFLD by vitamin D deficiency and that it is necessary to maintain optimal serum vitamin D levels in this population.

Data Sharing Statement

The original data can be available by email request at any time (Yuling Xing:xingy195@163.com).

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Disclosure

The authors declare that they have no conflicts of interest.

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