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Association between serum vitamin D level and cardiovascular disease in Chinese patients with type 2 diabetes mellitus: a cross-sectional study

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The relationship between 25-hydroxyvitamin D (25(OH)D) status and cardiovascular disease (CVD) in the diabetes population still needs to be clarified. This study aimed to explore the association of 25(OH)D with CVD and cardiometabolic risk factors in Chinese population with type 2 diabetes mellitus (T2DM). This cross-sectional study was performed with 1378 hospitalized patients with T2DM. Participants were classified into three groups according to the serum 25(OH)D levels: vitamin D adequate, vitamin D insufficiency and vitamin D deficient. Multivariate logistic regression analysis, stratified analysis and interaction analysis were performed to determine the relationship between serum 25(OH)D levels and CVD outcome. After adjusting for confounders, serum 25(OH)D levels were significantly negatively associated with cardiovascular disease in type 2 diabetic patients [OR: 0.97 (0.94, 0.99), $p = 0.0131$]. Taking the vitamin D-sufficient group (≥ 20 ng/mL) as a reference, the vitamin D-deficiency group (< 12 ng/mL) was associated with a significantly higher risk of cardiovascular disease, with a 1.25-fold increased risk after adjusting for all potential confounders [OR: 2.25 (1.33, 3.79), $p = 0.0023$]. Stratification analysis showed that the association between vitamin D deficiency and increased risk of cardiovascular disease was particularly significant in women [OR: 4.32 (1.54, 12.12), $p = 0.0055$], older adults [OR: 4.14 (1.10, 15.56), $p = 0.0355$], normal-weight [OR: 4.09 (1.51, 11.10), $p = 0.0056$] and obese subjects [OR: 3.66 (1.03, 13.05), $p = 0.0453$]. Vitamin D deficiency was significantly associated with an increased risk of overweight/obesity [OR: 1.57 (1.10, 2.24), $p = 0.0134$], hypertension [OR: 1.81 (1.30, 2.51), $p = 0.0004$], hypertriglyceridemia [OR: 1.56 (1.12, 2.16), $p = 0.0078$] and reduced HDL-C [OR: 1.67 (1.19, 2.35), $p = 0.0033$]. Serum 25(OH)D levels were significantly negatively associated with CVD in T2DM patients and vitamin D deficiency was significantly associated with an increased risk of overweight/obesity, hypertension and dyslipidemia.

Keywords 25-hydroxyvitamin D, Cardiovascular disease, Type 2 diabetes mellitus, Cardiometabolic risks

The number of adults with diabetes is growing rapidly worldwide. In 2021, the International Diabetes Federation (IDF) reported that 537 million adults worldwide suffer from diabetes and this number is predicted to increase to 643 million by 2030[1]. The harm of diabetes primarily depends on its serious complications, particularly CVD. CVD is the leading cause of mortality and disability among people with T2DM, and approximately one in three adults with T2DM already have CVD[2]. Individuals with diabetes have two to fourfold increased risks of CVD and mortality compared with the normal population after adjustment for conventional risk factors[3–5]. Furthermore, CVD mortality accounts for approximately one-half of all deaths in diabetes[6]. Despite extensive

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epidemiological assessment of the growth of diabetes prevalence, the quantification of the disease burden of and variation in diabetes-related complications is lacking[7]. As China's population ages, the burden of death and disability caused by diabetes and its complicated CVD will continue to increase. Therefore, identifying modifiable cardiometabolic risk factors in individuals with diabetes is necessary for the prevention of diabetes-related cardiovascular complications[6].

Vitamin D is an essential fat-soluble vitamin that regulates calcium and phosphorus metabolism and maintains bone health. In addition, vitamin D plays an important role in the function of various organs and tissues, including the cardiovascular system[8]. One of the proposed mechanisms of action is renin-angiotensin-aldosterone (RAAS) activation. It was reported that the vitamin D receptor (VDR) knock-out mice have higher blood pressure and develop cardiac hypertrophy due to increased renin expression and subsequent activation of the RAAS[9]. Besides, Vitamin D has demonstrated a protective role in CVD by suppressing the inflammatory response, and reduces oxidative stress[10]. Accumulating epidemiologic studies have shown that serum 25(OH) D levels were associated with the incidence and progression of CVD[11–13]. These findings were largely based on general populations. Evidence regarding the relationships among vitamin D status and CVD events among individuals with diabetes is limited. Moreover, such a relationship must be clarified in this group of individuals, in whom vitamin D deficiency is particularly common. Furthermore, discrepancies in the studies on the relationship between serum vitamin D levels and CVD are observed because of various confounding factors. For example, one prospective study of 289 Danish patients with diabetes found that serum 25(OH)D deficiency was associated with an increased risk of all-cause and CVD mortality[14], and another study of 698 Swedish patients with diabetes showed a marginally inverse association of serum 25(OH)D with mortality in men, but not in women[15]. Furthermore, many linear Mendelian randomized analyses have found that serum vitamin D levels are not associated with CVD risks[16] and some studies also failed to demonstrate the beneficial effect of vitamin D supplementation on CVD outcomes[17–19]. We speculate that the contradictions may be related to gender, race, region, disease state and dietary habits[20,21]. Therefore, further studies are necessary to clarify whether serum levels of 25[OH]D are related to the CVD outcome in people with diabetes, particularly in the Chinese diabetic population. China was the country with the most diabetes in the world. From 1990 to 2024, the age-standardized incidence, prevalence and DALYs (Disability-adjusted life years) of overall diabetes in China are on the rise[1]. The public cognition level of diabetes in China is still at a relatively basic stage. Meanwhile, the age, race, region, eating habits and lifestyle influence the population vitamin D level a lot. At present, the relationship between vitamin D deficiency and CVD in the Chinese population is still unclear. Thus, understanding the relationship between vitamin D deficiency and cardiometabolic risk before the development of the disease is important to establish whether vitamin D supplementation can be used to prevent the development of CVD in patients with diabetes[3].

We hypothesized that serum 25(OH)D levels were negatively associated with cardiovascular disease in the Chinese population with type 2 diabetes. In this study, we performed a retrospective analysis of the association of 25(OH)D with CVD and cardiometabolic risk factors in Chinese diabetics.

Methods

Study design

Initially, 2328 participants with T2DM aged over 18 were recruited from the First Affiliated Hospital of Zhengzhou University in China from January 2018 to December 2020. The exclusion criteria were as follows: metabolic syndrome (MetS) who cannot be diagnosed with T2DM, patients with acute diabetic complications such as ketoacidosis and hyperosmolar coma; tumor; acute infection; serious liver and kidney dysfunction; thyroid, parathyroid, and other endocrine gland-related diseases; autoimmune diseases; mental disease, and patients who are taking any medications known to affect vitamin D metabolism. In addition, we excluded participants who had missing laboratory results and questionnaire data. Finally, a total of 1378 patients with T2DM were enrolled (Fig. 1). The study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the ethics committee of First Affiliated Hospital of Zhengzhou University.

Data collection

From the medical records of the individuals selected we collected the relative data: the history of medical conditions, family history of disease, presence of comorbidities associated with TD2M, medication use and other lifestyle factors. Smoking status was categorized into never smoking, current smoker, and previous smoker. Current smoking was defined as having smoked at least 100 cigarettes in one's lifetime and is currently smoking cigarettes[22]. Alcohol intake was categorized into never drinking, current drinker and previous drinker. Alcohol drinking was defined as the consumption of alcohol ≥ 18 g during the past month[23]. In this study, anthropometric measurements were also collected in this study, such as weight, height, and blood pressure level. Weight and height were measured in accordance with the recommendations of the World Health Organization (WHO), with an accuracy to the nearest 0.1 kg and 0.1 cm, respectively, with the participants in light weight clothing without shoes. Body mass index (BMI) was calculated as follows: body weight (kg) divided by height square (m^2). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured using an automatic blood pressure meter after seating for at least 15 min and the average of the three measurements was recorded for calculate the mean BP. Cardiac function was assessed by echocardiography in all patients.

Laboratory measurements

All blood samples from patients who underwent overnight fasting were collected in the morning (around 6–7 a.m) so as to minimized the variation caused by specimen collection factors. An autobiochemical analyzer (Roche Diagnostic GmbH) was used to determine the serum concentrations of total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), fasting

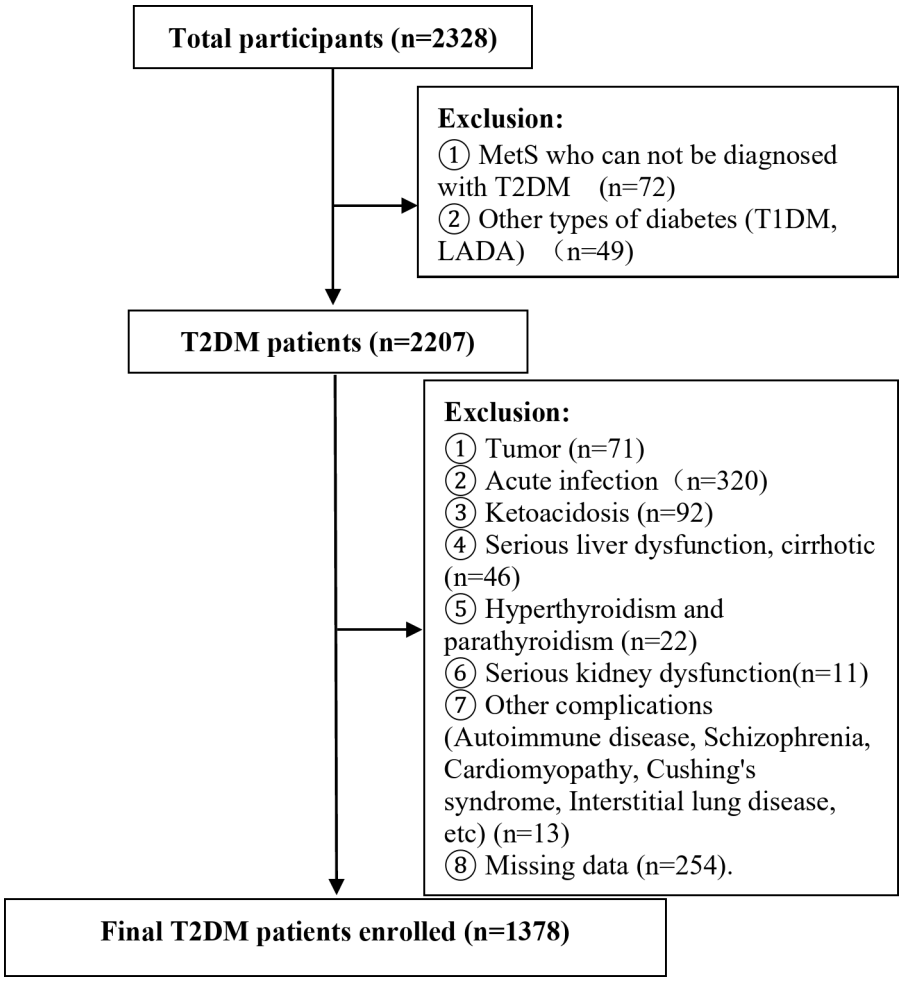

Fig. 1. Flow chart of study participant recruitment.

blood glucose (FBG), uric acid (UA), alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), creatinine (Cr), γ-glutamyl transferase (GGT), alkaline phosphatase (ALP), total protein (TP), albumin (ALB), total bilirubin (TBIL), direct bilirubin (DBIL), thyroid stimulating hormone (TSH), parathormone (PTH), total triiodothyronine (TT3), free tetraiodothyronine (FT4), fasting plasma insulin, C-peptide and C-reactive protein (CRP). 25(OH)D serum levels were detected by electrochemical method. Glycated hemoglobin (HbA1c) levels were quantified using high-performance liquid chromatography. Insulin resistance was estimated on the basis of the homeostasis model assessment of insulin resistance (HOMAIR) by using the following formula: fasting insulin (mU/L)×FBG (mmol/L)/22.5.

Determination of carotid intima-media thickness (IMT)

Carotid ultrasonography was performed using a color Doppler ultrasonic diagnostic instrument. IMT was defined as the mean of the maximum thickness in the right and left sides of the common carotid artery, and IMT is the distance between the lumen-intima interface and the media adventitia interface. Carotid artery plaque (CAP) was defined as either a focal structure that encroached into the arterial lumen by at least 50% of the surrounding IMT value or a thickness of > 1.5 mm. The presence of CAP was defined as ≥ 1 plaque in any of the carotid arteries.

Definition of diagnostic criteria

T2DM was defined as FBG ≥ 7.0 mmol/L, HbA1c ≥ 6.5%, or the use of any anti-diabetic medication or self-reported history of diabetes based on the American Diabetes Association, as well as exclude other types of diabetes (e.g., Type 1 diabetes, LADA)[24].

Sufficient, insufficient and deficient vitamin D statuses were defined as serum concentrations of 25(OH) D > 20.00 ng/mL, between 12.00 and 20.00 ng/mL, and < 12.00 ng/mL, respectively, according to the report released in 2010 by the Institute of Medicine[25].

CVD was defined as a positive medical history of a cardiovascular event, including myocardial infarction, angina pectoris, carotid artery diseases, heart failure, and cerebrovascular disease (e.g. cerebral infarction, cerebral hemorrhage, ischemic and hemorrhagic stroke). Overweight is defined as 24 ≤ BMI < 28 kg/m^2 and

obesity is defined as a BMI[26] of ≥ 28 kg/m^2. Hypertension was defined as SBP ≥ 130 mmHg and DBP ≥ 85 mmHg or treatment with anti-hypertensive medication[27]. Osteoporosis was divided into osteopenia and osteoporosis in accordance with the WHO diagnostic criteria[28].

For dyslipidemia, high (elevated) TC was defined as ≥ 5.20 mmol/L; high (elevated) TG was defined as > 1.70 mmol/L; high (elevated) LDL-C was defined as ≥ 3.40 mmol/L, and low (reduced) HDL-C was defined as < 1.29 mmol/L for women and < 1.04 mmol/L for men[27].

Statistical analysis

Continuous variables with a normal distribution are expressed as the mean [standard deviation (SD)] and those with a non-normal distribution are expressed as the median (IQR: Q1–Q3). In contrast, categorical variables were reported as numbers and percentages (%). Differences in continuous variables among the groups were tested using a one-way analysis of variance for normally distributed variables or a Kruskal-Wallis test for non-normally distributed variables. Differences in categorical variables were analyzed by using a Chi-square test.

Univariate and multivariate logistic regressions were used to estimate the association of serum levels of 25(OH)D with CVD or cardiometabolic risk factors in people with type 2 diabetes. Hosmer-Lemeshow test was used to evaluate the goodness of fit effect of the model. Sensitivity analysis was conducted, and multivariate adjusted models were used to assess confounding variables. Confounding factors were screened on the basis of the p value when introducing different indexes into the regression models, and indexes with p value less than 0.1 were taken as covariates. Trend analyses were also conducted by entering the median value of each category of vitamin D status levels as a continuous variable in the models[29]. In addition, stratified analyses and interaction analyses by gender (male and female), age (< 45 years, 45–60 years, ≥ 60 years) and BMI (< 24, 24–28, ≥ 28) were further conducted.

Empower (R; www.empowerstats.com, X & Y Solutions Inc., Boston MA) and R (http://www.Rproject.org) were used for all statistical analyses[27,30]. Two-tailed p values less than 0.05 were considered statistically significant.

Results

Baseline characteristics of the study subjects

The present study population was composed of 1378 participants, with an average age of 50 years, and consisted of 946 males and 432 females. The median level of 25(OH)D for all subjects was 18.764 (13.20–22.15) ng/mL and we classified all patients into vitamin D adequate (≥ 20 ng/mL), vitamin D insufficiency (12–20 ng/mL) and vitamin D deficient groups (< 12 ng/mL) based on the serum 25(OH)D levels. The basic characteristics of the subjects were shown in Table 1. The sex composition, age, BMI, blood pressure, and alcohol consumption history were significantly different among the three groups ($p < 0.05$). There were no significant differences among the three groups in the duration of diabetes, the time of onset of diabetes, hypoglycemic treatment and the complications of diabetes ($p > 0.05$). Moreover, in terms of laboratory indicators, lipid metabolism (TG, HDL-C), blood glucose status (FBG, HbA1c, Insulin 120), renal function (BUN, Cr), liver function (AST, TP, ALB, TBIL, DBIL) and PTH were significantly different in various vitamin D statuses ($p < 0.05$).

The association between vitamin D status and cardiovascular disease in patients with T2DM

We then analyzed the association between cardiovascular disease and vitamin D status in diabetic patients by univariate and multivariate logistic regression analysis (Table 2). The association of vitamin D status with cardiovascular disease was measured by the odds ratio (OR). The Hosmer-Lemeshow goodness of fit tests was not significant for any of the logistic regression models (all $p > 0.05$), indicating that the goodness of fit of the models were good. In the analysis of the crude model (model 1), cardiovascular disease did not appear to be significantly associated with vitamin D levels before adjusting for confounders ($p > 0.05$). However, after adjusting for confounding factors by binary logistic regression, we found that 25(OH)D levels were significantly negatively associated with cardiovascular disease in type 2 diabetic patients [OR: 0.97 (0.94, 0.99), $p = 0.0131$]. Taking vitamin D-sufficient group (≥ 20 ng/mL) as reference, after adjusting for various confounding factors (model 2, model 3, model 4), the vitamin D-deficiency group (< 12 ng/mL) was still associated with a significantly higher risk of cardiovascular disease, with a 1.25-fold increased risk after adjusting for all potential confounders [OR: 2.25 (1.33, 3.79), $p = 0.0023$]. Further trend tests showed that the risk of cardiovascular disease in type 2 diabetes patients increased significantly with decreasing of vitamin D levels (p for trend = 0.0076).

We performed stratification analysis and interaction analysis to explore whether the association between vitamin D deficiency and a higher risk of cardiovascular disease was influenced by sex, age and BMI (Table 3). The results showed that after adjusting for relevant confounders, the association between vitamin D deficiency and an increased risk of cardiovascular disease was particularly significant in women [OR: 4.32 (1.54, 12.12), $p = 0.0055$], older adults (age > 60 years) [OR: 4.14 (1.10, 15.56), $p = 0.0355$], normal-weight (BMI < 24 kg/m^2) [OR: 4.09 (1.51, 11.10), $p = 0.0056$] and obese subjects (BMI ≥ 28 kg/m^2) [OR: 3.66 (1.03, 13.05), $p = 0.0453$]. Interaction analysis showed that sex, age and BMI did not significantly interfere with the association of vitamin D status and cardiovascular disease in type 2 diabetic patients. (all $p > 0.05$).

The relationship between vitamin D deficiency and cardiometabolic risk factors in diabetic patients

Finally, we analyzed the association of vitamin D levels with major cardiometabolic risk factors in diabetic patients. The results showed that vitamin D deficiency was strongly associated with a higher risk of cardiometabolic risk factors after adjusting for relevant confounders (Table 4). Compared with normal vitamin D levels, vitamin D deficiency was significantly associated with an increased risk of overweight/obesity [OR: 1.57 (1.10, 2.24), $p = 0.0134$], hypertension [OR: 1.81 (1.30, 2.51), $p = 0.0004$], hypertriglyceridemia [OR: 1.56 (1.12,

Characteristics	Vitamin D status			*P*-value
	Deficiency (< 12 ng/mL) *n* = 262	Insufficiency (12–20 ng/mL) *n* = 639	Sufficient(≥ 20 ng/mL) *n* = 477	
SEX, n (%)				< 0.001
Male	153 (58.40%)	447 (69.95%)	346 (72.54%)	
Female	109 (41.60%)	192 (30.05%)	131 (27.46%)	
Age, years	51.00 (40.00–59.00)	51.00 (43.00–57.50)	53.00 (45.00–59.00)	0.003
BMI, kg/m^2	26.00 (23.64–28.70)	25.69 (23.44–28.00)	25.00 (23.00–27.51)	0.004
SBP, mmHg	135.00 (126.75–146.25)	131.50 (124.00–142.75)	132.00 (122.00–142.00)	< 0.001
DBP, mmHg	84.00 (78.00–92.00)	82.50 (77.00–88.00)	83.00 (75.00–89.00)	0.009
Smoking status, n (%)				0.376
Never smoking	189 (72.14%)	441 (69.01%)	340 (71.28%)	
Current smoker	63 (24.05%)	171 (26.76%)	109 (22.85%)	
Previous smoker	10 (3.82%)	27 (4.23%)	28 (5.87%)	
Alcohol intake, n (%)				0.015
Never drinking	196 (74.81%)	414 (64.79%)	312 (65.41%)	
Current drinker	53 (20.23%)	201 (31.46%)	144 (30.19%)	
Previous drinker	13 (4.96%)	24 (3.76%)	21 (4.40%)	
History of diabetes				
New onset				0.248
No	203 (77.48%)	502 (78.56%)	391 (81.97%)	
Yes	59 (22.52%)	137 (21.44%)	86 (18.03%)	
Duration of T2DM (years)	5.00 (1.00–10.00)	5.00 (1.00–11.00)	6.00 (2.00–12.00)	0.136
Hypoglycemic therapy				0.101
No	141 (53.82%)	301 (47.10%)	219 (45.91%)	
Yes	121 (46.18%)	338 (52.90%)	258 (54.09%)	
Complication				
Fatty liver				0.658
No	81 (30.92%)	216 (33.80%)	162 (33.96%)	
Yes	181 (69.08%)	423 (66.20%)	315 (66.04%)	
Nephropathy				0.916
No	185 (70.61%)	447 (69.95%)	330 (69.18%)	
Yes	77 (29.39%)	192 (30.05%)	147 (30.82%)	
Thyroid nodule				0.791
No	131 (50.00%)	319 (49.92%)	229 (48.01%)	
Yes	131 (50.00%)	320 (50.08%)	248 (51.99%)	
Peripheral neuropathy				0.678
No	148 (56.49%)	341 (53.36%)	256 (53.67%)	
Yes	114 (43.51%)	298 (46.64%)	221 (46.33%)	
Vasculopathy				0.447
No	106 (40.46%)	235 (36.78%)	171 (35.85%)	
Yes	156 (59.54%)	404 (63.22%)	306 (64.15%)	
Osteoporosis				0.147
Normal	129 (50.39%)	291 (47.63%)	194 (41.54%)	
Osteopenia	101 (39.45%)	251 (41.08%)	220 (47.11%)	
Osteoporosis	26 (10.16%)	69 (11.29%)	53 (11.35%)	
Carotid atherosclerotic plaque				0.775
No	138 (54.55%)	332 (53.55%)	241 (51.94%)	
Yes	115 (45.45%)	288 (46.45%)	223 (48.06%)	
Cardiac function				0.668
Normal	92 (36.22%)	247 (39.46%)	180 (38.30%)	
Abnormal	162 (63.78%)	379 (60.54%)	290 (61.70%)	
Laboratory index				
TC, mmol/L	4.48 (3.75–5.09)	4.34 (3.70–5.18)	4.29 (3.53–4.99)	0.767
TG, mmol/L	1.71 (1.10–3.00)	1.74 (1.15–2.73)	1.48 (1.05–2.32)	< 0.001
HDL-C, mmol/L	0.97 (0.80–1.23)	1.01 (0.84–1.21)	1.07 (0.90–1.27)	< 0.001
LDL-C, mmol/L	2.58 (1.88–3.27)	2.54 (1.91–3.14)	2.46 (1.89–3.17)	0.181
Continued				

Characteristics	Vitamin D status			*P*-value
	Deficiency (< 12 ng/mL) *n* = 262	Insufficiency (12–20 ng/mL) *n* = 639	Sufficient(≥ 20 ng/mL) *n* = 477	
FBG, mmol/L	8.01 (6.41–10.71)	7.84 (6.31–10.30)	7.50 (5.99–9.69)	0.015
HbA1c, %	9.30 (7.70–10.71)	8.48 (7.40–10.15)	8.40 (7.00–9.90)	< 0.001
HOMA-IR	1.85 (0.72–3.30)	1.92 (0.92–3.52)	1.69 (0.90–3.26)	0.395
Insulin0, mU/L	4.41 (2.36–9.73)	5.60 (2.73–10.01)	5.44 (2.77–9.63)	0.336
Insulin120, mU/L	13.03 (6.49–26.27)	16.79 (8.36–31.80)	13.25 (5.71–23.75)	0.018
C peptide0, pmol/L	1.87 (1.12–2.79)	1.68 (1.07–2.50)	1.71 (1.13–2.36)	0.392
C peptide120, pmol/L	3.88 (2.77–5.88)	4.17 (2.87–6.21)	4.26 (2.91–5.62)	0.709
CRP, mg/L	1.13 (0.61–3.00)	1.13 (0.54–2.94)	1.08 (0.50–2.25)	0.060
TT3, pmol/L	4.73 (4.23–5.23)	4.75 (4.32–5.20)	4.77 (4.37–5.21)	0.374
FT4, pmol/L	11.48 (10.21–12.54)	11.40 (10.34–12.57)	11.19 (10.03–12.43)	0.486
TSH, mIU/L	2.09 (1.35–3.11)	1.91 (1.30–2.83)	1.87 (1.31–2.88)	0.675
PTH, pg/mL	37.16 (28.82–49.03)	33.97 (26.58–42.07)	29.27 (22.87–36.95)	< 0.001
BUN, mmol/L	5.40 (4.34–6.45)	5.30 (4.50–6.21)	5.62 (4.69–6.70)	0.001
Cr, μmol/L	60.00 (51.00–71.00)	64.00 (54.00–73.00)	67.00 (56.00–76.00)	0.005
UA, μmol/L	280.00 (225.00–350.00)	291.00 (244.00–349.00)	293.00 (240.50–348.00)	0.697
ALT, U/L	19.00 (13.00–31.00)	20.00 (14.00–28.50)	20.00 (15.00–28.00)	0.200
AST, U/L	17.00 (14.00–22.00)	18.00 (14.00–23.00)	19.00 (15.00–24.00)	0.018
GGT, U/L	25.00 (16.75–40.00)	24.00 (16.00–38.00)	23.00 (15.00–37.50)	0.879
ALP, U/L	73.00 (61.00–85.00)	70.00 (58.00–84.00)	70.00 (59.00–84.00)	0.455
TP, g/L	65.80 (62.40–70.20)	68.00 (64.30–72.20)	69.20 (65.77–72.82)	< 0.001
ALB, g/L	41.80 (39.70–44.80)	43.60 (41.10–46.20)	44.10 (42.00–46.90)	0.009
TBIL, μmol/L	8.12 (5.98–11.31)	9.92 (7.30–12.94)	10.11 (7.50–13.86)	0.043
DBIL, μmol/L	3.54 (2.66–4.71)	4.07 (3.08–5.30)	4.30 (3.20–5.61)	< 0.001

Table 1. Basic characteristics of the participants. Data are presented as the Mean (SD) or Median (IQR: Q1–Q3) for continuous variables and percentage for categorical variables. *The One-way ANOVA or Kruskal Wallis rank sum test or χ^2 test were used for comparisons between subgroups. *BMI* body mass index, *SBP* systolic blood pressure; DBP, diastolic blood pressure, *T2DM* type 2 diabetes mellitus, *TC* total cholesterol, *TG* triglyceride, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *FBG* fasting blood glucose, *HbA1c* glycosylated hemoglobin c, *HOMA-IR* homeostasis model assessment of insulin resistance, *CRP* C-reactive protein, *TT3* total triiodothyronine, *FT4* free thyroxine, *TSH* thyroid stimulating hormone, *PTH* parathyroid hormone, *BUN* blood urea nitrogen, *Cr* creatinine, *UA* uric acid, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *GGT* gamma-glutamyl transpeptidase, *ALP* alkaline phosphatase, *TP* total protein, *ALB* albumin, *TBIL* total bilirubin, *DBIL* direct bilirubin.

CVD	Model 1		Model 2		Model 3		Model 4	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
25(OH)D	1.00 (0.99, 1.01)	0.9622	0.99 (0.98, 1.01)	0.2761	0.99 (0.98, 1.01)	0.2995	0.97 (0.94, 0.99)	0.0131
25(OH)D categorical								
≥20	1.0		1.0		1.0		1.0	
12–20	0.98 (0.73, 1.32)	0.9001	1.23 (0.89, 1.70)	0.2166	1.20 (0.86, 1.67)	0.2829	1.08 (0.70, 1.65)	0.7298
< 12	1.37 (0.96, 1.96)	0.0840	1.88 (1.25, 2.81)	0.0023	1.87 (1.24, 2.81)	0.0028	2.25 (1.33, 3.79)	0.0023
P for trend	0.98 (0.96, 1.01)	0.1536	0.96 (0.93, 0.99)	0.0042	0.96 (0.94, 0.99)	0.0054	0.95 (0.92, 0.99)	0.0076

Table 2. Multivariate analysis of the association of CVD with 25(OH)D status. Model 1 was unadjusted; Model 2 was unadjusted for sex, age, BMI, SBP, DBP, Smoking status, Alcohol intake; Model 3 was unadjusted for Model 2 plus new onset, duration of T2DM, hypoglycemic therapy and Osteoporosis; Model 4 was unadjusted for Model 3 plus TC, TG, HDL-C, LDL-C, FBG, HbA1c, C-peptide 0, C-peptide 120, BUN, Cr, ALT, ALB, TBIL, PTH. Hosmer-Lemeshow goodness of fit tests was not significant for any of the logistic regression models (all $p > 0.05$). *OR* odds ratio, *CI* confidence interval.

Characteristic	No. of participants	25(OH)D status [OR (95% CI), *p* value]			*p* for interaction
		Sufficient	Insufficiency	Deficiency	
Sex					0.5383
Male	946	1.0	0.84 (0.50, 1.43) 0.5320	1.69 (0.84, 3.40) 0.1408	
Female	432	1.0	2.08 (0.83, 5.21) 0.1188	4.32 (1.54, 12.12) 0.0055	
Age (years)					0.1224
≤45	415	1.0	0.30 (0.08, 1.17) 0.0825	1.90 (0.45, 8.12) 0.3856	
45–60	683	1.0	1.22 (0.66, 2.24) 0.5251	1.96 (0.90, 4.27) 0.0908	
>60	280	1.0	1.29 (0.45, 3.64) 0.6356	4.14 (1.10, 15.56) 0.0355	
BMI (kg/m^2)					0.3537
<24	417	1.0	1.20 (0.52, 2.77) 0.6781	4.09 (1.51, 11.10) 0.0056	
24–28	581	1.0	0.76 (0.38, 1.53) 0.4434	1.47 (0.61, 3.54) 0.3888	
≥28	348	1.0	2.49 (0.85, 7.26) 0.0950	3.66 (1.03, 13.05) 0.0453	

Table 3. Stratified analyses and interaction tests of the association between 25(OH)D status and cardiovascular disease in T2DM subjects. The effect size of association was quantified by OR and 95% CI. Adjusted for sex, age, BMI, SBP, DBP, Smoking status, Alcohol intake, new onset, duration of T2DM, hypoglycemic therapy, Osteoporosis, TC, TG, HDL-C, LDL-C, FBG, HbA1c, C-peptide 0, C-peptide 120, BUN, Cr, ALT, ALB, TBIL and PTH except the subgroup variable. *CI* confidence interval.

Cardiometabolic risk factors	Vitamin D status				
	Continuous	Sufficient (≥20 ng/mL)	Insufficiency (12–20 ng/mL)	Deficiency (<12 ng/mL)	*P* for trend
Overweight/obesity	1.00 (0.99, 1.01) 0.5397	1.0	1.30 (0.99, 1.71) 0.0585	1.57 (1.10, 2.24) 0.0134	0.0085
Hypertension	1.00 (0.99, 1.01) 0.5163	1.0	1.04 (0.81, 1.33) 0.7676	1.81 (1.30, 2.51) 0.0004	0.0026
Elevated TG	1.00 (0.99, 1.01) 0.5299	1.0	1.52 (1.18, 1.96) 0.0012	1.56 (1.12, 2.16) 0.0078	0.0015
Elevated TC	0.99 (0.98, 1.01) 0.3105	1.0	1.26 (0.93, 1.70) 0.1404	1.04 (0.70, 1.55) 0.8322	0.5466
Elevated LDL-C	0.99 (0.98, 1.01) 0.4924	1.0	1.13 (0.82, 1.56) 0.4525	1.05 (0.70, 1.59) 0.8142	0.6831
Reduced HDL-C	0.99 (0.98, 1.00) 0.0846	1.0	1.39 (1.07, 1.80) 0.0135	1.67 (1.19, 2.35) 0.0033	0.0014

Table 4. Multiple logistic regression for the association of cardiometabolic risks factors with vitamin D status. Multivariate model was adjusted for sex, age, BMI, SBP, DBP, Smoking status, Alcohol intake, new onset, duration of T2DM, hypoglycemic therapy, Osteoporosis.

2.16), $p=0.0078$] and reduced HDL-C [OR: 1.67 (1.19, 2.35), $p=0.0033$]. However, no significant association was observed between vitamin D deficiency and hypercholesterolemia and higher LDL-C (all $p>0.05$).

Discussion

In this cross-sectional study of Chinese adults with type 2 diabetes, we found that the serum 25(OH)D levels was significantly and negatively associated with CVD. The association was independent of traditional risk factors, including sex, age, BMI, lifestyle, and other confounding factors. Furthermore, vitamin D deficiency was strongly associated with a high risk of cardiometabolic risk factors, including overweight/obesity, hypertension, and dyslipidemia.

Vitamin D deficiency and insufficiency are common in people with diabetes. The average 25(OH)D concentration in the present study was 18.764 (13.20–22.15) ng/mL, which was lower than Chinese general population (22.4 ng/mL)[31]. Consistent with other studies, we found there are sex, age, BMI, blood pressure, and alcohol consumption history differences in various vitamin D statuses. Numerous epidemiological studies have explored the association among vitamin D status, CVD and mortality between older individuals and the general population, which support the association between higher serum 25 (OH)D levels and a lower risk of CVD morbidity and mortality[32–35]. Among patients with diabetes, who had a high prevalence of vitamin D deficiency and a high risk of CVD[7], evidence is limited and inconclusive. Several large prospective cohort studies found that higher serum 25(OH)D levels were associated with reduced risk of cardiovascular outcomes among participants with diabetes[6,21] Consistent with previous studies, we observed that 25(OH)D levels were significantly and negatively associated with CVD in patients with type 2 diabetic after adjusting for confounding factors. Further trend tests showed that the risk of CVD in patients with type 2 diabetes increased significantly with the decrease of vitamin D levels. Our findings indicate the importance of monitoring vitamin D status in the population with diabetes. Several potential mechanisms could explain the observed relationships between serum 25(OH)D levels and high risk of CVD. Vitamin D has anti-inflammatory and anti-mitotic actions that stabilize the endothelium, one of the key explanations for its cardiovascular-protective effects[36,37]. Furthermore, a previous study indicated that vitamin D is a negative regulator of the renin-angiotensin-aldosterone system (RAAS) in vivo[38].

In addition, the significant relationships between vitamin D deficiency and increased risk of CVD was observed in women, older adults, and obese patients with diabetes. In general, vitamin D deficiency status is common among women, people with obesity, and older people. Cross-sectional studies showed that obesity is consistently characterized by lower 25(OH)D serum levels and a higher prevalence of vitamin D insufficiency and deficiency[39]. Individuals with obesity tend to expose their skin less to sunlight because of less physical activity outdoors, which could explain the high prevalence of hypovitaminosis D[40]. Another study shows an inverse correlation between the level of 25(OH)D and severity of coronary atherosclerosis in women and men over 70 years old[41]. Moreover, a negative interference of age with the concentrations of 25(OH)D is observed because the aged skin produces less vitamin D than the skin of younger people[42]. Vitamin D deficiency is especially common among elderly people, who often have less sun exposure (because of reduced outdoor activity) and limited capacity of the skin to produce vitamin D metabolites. Gender remarkably affects vitamin D status. Women are generally more prone to low 25(OH)D concentrations than men (possibly because of a positive correlation of 25(OH)D with testosterone levels). A study showed that lower 25(OH)D levels observed in females, as compared with males, play a more relevant role in conditioning the severity of coronary artery disease[20]. Our results of stratified and interaction analysis further confirm the reliable association between vitamin D deficiency and CVD.

Studies have shown that low vitamin D levels were associated with cardiometabolic risk markers such as hypertension[43], atherogenic lipid profile[44] and obesity[45]. Our study showed that vitamin D deficiency was strongly associated with a higher risk of cardiometabolic risk factors after adjusting for relevant confounders, which is consistent with some of the studies. Compared with normal vitamin D levels, vitamin D deficiency was remarkably associated with an increased risk of overweight/obesity, hypertension, hypertriglyceridemia, and reduced HDL-C. There is no consensus in the literature regarding the independent effects of 25(OH)D and obesity on cardiometabolic parameters. A study showed that vitamin D status is favorably associated with the cardiovascular risk factors in adults with obesity[46]. However, other study found no statistical significance in the association between 25(OH)D and body fat percentage[47]. Palacios observed a negative correlation between 25(OH)D and the percentage of body fat, but not a statistically significant correlation between 25(OH)D and BMI[48]. Notably, many confounding factors seem to influence these relationships. After adjusting for relevant confounders such as sex, age, BMI, SBP, DBP, smoking status, alcohol intake, new onset, duration of T2DM, hypoglycemic therapy, and osteoporosis, our study confirmed that a low serum 25(OH)D level was markedly associated with increased risk of overweight/obesity.

Hypertension is a serious risk factor for CVD. Our study confirmed that vitamin D deficiency was remarkably associated with an increased risk of hypertension. This result was consistent with previous studies[49–51]. The present study also showed that vitamin D deficiency was markedly associated with an increased risk of hypertriglyceridemia and reduced HDL-C. In addition, no significant association was observed between vitamin D deficiency and hypercholesterolemia, which is different from other studies. Farshad reported that vitamin D deficiency may be a risk factor for hypercholesterolemia, but not for hypertriglyceridemia (low HDL-c)[46]. The authors excluded patients with obesity resulting from endocrine disorders, which may explain the different results observed between their study and our study.

The strength of our study was that abundant information was available on basic characteristics, lifestyle habits, disease statues, medication and other covariates, which may enhance the validity of the conclusions through adjustment for a lot of potential confounding factors in this study. However, several limitations were worthy of consideration when interpreting our findings. First, as an observational study, this study did not conduct random sampling and causality cannot be determined. The participants of the study were Chinese patients with T2DM in a single center. Therefore, the present results might not be representative of the general T2DM population. Moreover, although many potential confounding factors were adjusted for analyses, we cannot exclude the role of residual confounding factors resulting from errors in the measurement of covariates and other important factors that may influence vitamin D levels (e.g. seasonal information on vitamin D, diet, vitamin D supplement information, physical activity, etc.) that were not assessed in the cohort.

Conclusion

In conclusion, our study suggested that serum 25(OH)D levels were significantly negatively associated with with CVD in Chinese type 2 diabetic patients. Vitamin D deficiency was significantly associated with a increased risk of overweight/obesity, hypertension, hypertriglyceridemia and reduced HDL-C. In the future, prospective multicenter follow-up cohort studies are worthy of implementation, and confounding factors not included in this study are fully considered, so as to further clarify the causal association between vitamin D levels and cardiovascular disease in diabetic population and the potential benefits of vitamin D supplementation for diabetic patients.

Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Author contributions
LT, YW and HT designed and revised the study; YW, WL, DX, RC and NZ conducted the research; HT, HZ and WL analyzed the data; HT and NZ wrote the manuscript. All authors read and approved the final manuscript.

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Declarations

Ethics approval and consent to participate
This study was approved by the Institutional Review Board of the First Affiliated Hospital of Zhengzhou University. Written informed consent to participate was obtained from all participants.

Competing interests
The authors declare no competing interests.

Additional information
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