

# Comparison of Serum Vitamin D Levels in Obese Subjects with and without Type 2 Diabetes Mellitus

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**Background:** Although observational studies have reported a correlation between vitamin D deficiency and type 2 diabetes mellitus (T2DM), epidemiological evidence on the risk of obese subjects suffering T2DM due to a vitamin D deficiency is limited. Therefore, we investigated the correlation between T2DM and serum vitamin D, lipids, blood pressure, insulin indexes in an obese population.

**Methods:** A total of 1440 participants including 450 healthy controls and 990 obese subjects, 470 without T2DM and 520 with T2DM. Serum vitamin D levels were measured, and the association between low levels and T2DM in obese subjects was examined using multinomial and linear regression analyses.

**Results:** Of the participants, 35% had deficient or insufficient vitamin D levels (ie, <20 ng/mL). Compared with healthy controls, obese subjects, particularly those with T2DM had lower vitamin D levels. Multinomial logistic regression analysis showed that obese subjects with T2DM had a gradually increasing risk for desirable ( $RO = 1.41$ , 95%  $CI$  1.06–1.93,  $P = 0.027$ ), insufficient ( $RO = 1.83$ , 95%  $CI$  1.27–2.84,  $P < 0.001$ ), or deficient ( $RO = 2.14$ , 95%  $CI$  1.15–3.75,  $P = 0.014$ ) vitamin D levels. In obese subjects with T2DM, vitamin D levels correlated inversely with the risk indicators for diabetes, such as the levels of HbA1c ( $\beta = -0.16$ ,  $P = 0.002$ ), fasting insulin (Fins;  $\beta = -0.31$ ,  $P = 0.008$ ), and HOMA-IR ( $\beta = -0.19$ ,  $P < 0.001$ ). In obese subjects without T2DM, vitamin D was associated negatively with the risk of having T2DM at five-year follow-up (relative risk = 0.93, 95%  $CI$  0.79–0.97,  $P = 0.037$ ).

**Conclusion:** This study demonstrates that low vitamin D levels correlate with the presence of T2DM in the obese population. This finding indicates that hypovitaminosis D may be a potential biological vulnerability factor for the development of T2DM in obese subjects.

**Keywords:** vitamins, T2DM, obesity, biomarker

## Introduction

Type 2 diabetes mellitus (T2DM) is a common metabolic disorder and its incidence is rising. It is well established that obesity is related to an increased risk of developing insulin resistance and subsequently T2DM.<sup>1</sup> In an obese population, the levels of non-esterified fatty acids, glycerol, hormones, and inflammatory cytokines derived from adipose tissue are increased significantly and promote the development of insulin resistance.<sup>2</sup> When insulin resistance is accompanied by functional beta-cell abnormalities this increases the risk of developing T2DM.<sup>2</sup> The etiology and pathophysiology of T2DM in obese subjects have not yet been fully understood, although recent studies have reported the underlying roles of some common biological factors that may influence the development of T2DM in the obese population.

For example, vitamin D is increasingly thought to be associated with insulin resistance, the metabolic syndrome, and obesity and it has been reported that hypovitaminosis D may contribute to T2DM in obese people.<sup>3</sup> Studies in humans have demonstrated the presence of vitamin D receptors (VDR) and 1 $\alpha$ -hydroxylase, an enzyme that catalyzes the synthesis of 1.25-dihydroxyvitamin D within adipose tissue.<sup>4</sup> Vitamin D also regulates blood glucose levels by controlling insulin secretion and sensitivity.<sup>5</sup> In addition, adipose tissue is a major storage site of vitamin D and also secretes

numerous adipocytokines involved in the inflammatory response, insulin resistance, obesity, and T2DM.<sup>6</sup> Notably, there is evidence that vitamin D regulates hepatic lipid and glucose metabolism and counteracts diet-stimulated insulin resistance in skeletal muscle.<sup>7,8</sup> Vitamin D also affects inflammatory cascades by inhibiting autoimmune pathways through VDR-mediated gene transcription, which in turn, is associated with insulin resistance.<sup>9</sup>

To date, epidemiological studies were performed to only explore the correlation between vitamin D and T2DM or obesity.<sup>10–13</sup> However, the effect of hypovitaminosis D on the obese subjects with T2DM has not been reported. Therefore, the current study assessed the relationship between vitamin D levels and T2DM in a large obese population taking key confounding factors into account. Moreover, our findings highlight that hypovitaminosis D may be a potential biological vulnerability factor for the development of T2DM in obese subjects. The main aim of the study was to compare the serum levels of vitamin D in healthy controls and obese subjects with or without T2DM. The study also examined whether serum vitamin D levels in subjects with T2DM were related to specific clinical characteristics. We hypothesized that serum vitamin D levels would be lower in the obese population with or without T2DM than that in healthy controls, and that low vitamin D levels in obese subjects with T2DM would correlate with less favorable clinical features and subsequent health outcomes.

## Materials and Methods

### Study Participants

From January 2019 to December 2023, a total of 990 obese subjects with ( $n = 520$ ) or without ( $n = 470$ ) T2DM were enrolled in the study. According to the 1998 criteria of the World Health Organization, the definition of obesity was adopted as  $BMI \geq 25 \text{ kg/m}^2$ . The study was approved by the local ethics committee, with informed, written consent provided by each participant. The subjects including 610 males and 380 females, aged 30–65 years (mean age  $51.0 \pm 11.4$  years) were enrolled from our hospital. In addition, 450 age- and sex- matched healthy individuals aged 29–62 years were recruited as controls (269 males and 181 females; mean age  $49.5 \pm 13.5$  years). T2DM was diagnosed based on the World Health Organization (WHO) criteria. Diabetes was diagnosed as a fasting plasma glucose level  $\geq 7.0 \text{ mmol/L}$  and 2-h post-load plasma glucose (2h PG) concentration  $\geq 11.1 \text{ mmol/L}$ . T2DM without ketosis and good  $\beta$ -cell reserve was defined by the results of the C-peptide assay (fasting  $\geq 0.6 \text{ pmol/mL}$ ; induced  $\geq 1.6 \text{ pmol/mL}$ ). To exclude the effect of drug therapy on the concentrations of serum markers, the participants with T2DM did not receive any drug therapy. Clinical data, including age, sex, education, exposure to sunlight in the previous 10 weeks, smoking status, alcohol use, physical activity, use of vitamin D supplements, body mass index (BMI), and blood pressure were collected from each individual. Participants in the control group with malignant tumors, renal or liver disorders, or other endocrinological disorders were excluded from the study. None of the control group were taking anti-hypertensive drugs, diabetes medications, estrogen supplements, or hypolipidemic drugs. The present study was approved by the ethics committee of Hubei Third People's Hospital Affiliated to Jiangnan University (No. 20180231).

### Biochemical Analysis

Blood samples were collected from the subjects after an overnight fast. The serum levels of total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were measured using a Siemens biochemical analyzer, while the levels of serum fasting insulin (Fins) were analyzed by an electrochemiluminescence immunoassay (Roche Elecsys Insulin Assay, Roche Diagnostics, Mannheim, Germany). The homeostatic model assessment of insulin resistance (HOMA-IR) was calculated according to fasting insulin level (Fins,  $\mu\text{mol/L}$ )  $\times$  fasting blood glucose (FPG,  $\text{mmol/L}$ ) / 22.5. Hemoglobin (HbA1c) levels were measured by high-performance chromatography. All the participants received computed tomography (CT) scanning at the L2-L3 and L4-L5 levels to assess the areas of abdominal visceral and subcutaneous fat. The mean visceral fat and the mean subcutaneous fat areas at the L2-L3 and L4-L5 levels were used in all the analyses.

Vitamin D levels were obtained by calculating the sum of D2 and D3, and the concentrations of vitamin D2 and D3 were determined by liquid chromatography with tandem mass spectrometry (LC-MS/MS). In brief, serum (20  $\mu\text{L}$ ) and acetonitrile with stable isotope-labeled internal standard (200  $\mu\text{L}$ ) were transferred into a polypropylene conical

centrifuge tube, respectively. Then the tubes were mixed completely and centrifugated (12,000 g, 5 min at 4°C) for protein precipitation. Next, the tubes were moved to -20°C refrigerator for 20 min resulting in the separation of aqueous and organic phases. Finally, the upper organic phase (20 µL) was transferred into a 96-well plate and the diluent (acetonitrile/methanol, v/v=1:1) was added into each well for LC-MS/MS analysis. Participants in each group were divided into four groups based on their vitamin D levels, including deficient (< 10 ng/mL), insufficient (10 ~ 20 ng/mL), adequate (20 ~ 30 ng/mL), and desirable (> 30 ng/mL).

## Statistical Analysis

The data were expressed as percentages or mean ± s.d. as appropriate. Differences in baseline variables grouped according to T2DM status were analyzed using the Chi-square test or analysis of variance as appropriate. The adjusted mean levels of vitamin D across T2DM status in the two obese groups were compared by analysis of covariance. To identify significant differences, *post-hoc* tests between the groups were carried out using Tukey's test, with Cohen's d calculated as a measure of effect size. To observe possible differences due to confounding factors, sunlight hours, smoking habits, alcohol use, physical activity, BMI, HbA1c, TC, TG, LDL-C, Fins, HOMA-IR, subcutaneous fat, and visceral fat were entered into totally adjusted models. The odds ratio for desirable, adequate, and insufficient versus deficient vitamin D levels across the T2DM status groups were compared using multinomial logistic regression. To evaluate whether specific clinical variables were related to vitamin D levels, linear regression analysis was performed for each variable within the obese population with T2DM. Multivariate analysis was used to assess whether serum vitamin D levels were a predictor of T2DM in the obese population after a five-year follow-up period. All data were analyzed by SPSS 22.0 (SPSS Inc., Chicago, IL).

## Results

The clinical data of the healthy controls and the obese population are summarized in Table 1. The mean age of the participants was 50.5± 12.4 years with 61.0% being males. Obese participants without or with T2DM were exposed to

**Table 1** Clinical and Biochemical Characteristics of the Study Population

Variables	Controls (n=450)	Obese population		P
		Without T2DM(n=470)	With T2DM (n=520)	
Sociodemographic				
Age (mean ±s.d., years)	49.5±13.5	50.8±12.7	51.2±10.4	0.253
Sex (male, %)	59.8	62.4	60.9	0.207
Education (mean ±s.d., years)	12.8±4.1	13.9±3.5	13.0±3.8	0.351
Sunlight previous 10 weeks (h)(mean ±s.d.)	571.2±231.5	540.5±225.9	519.7±231.4	0.013
Lifestyle and health indicators				
Smoking status (n, %)				<0.001
Non smoker	171 (38.0)	119 (25.3)	143 (27.5)	
Former smoker	158 (35.1)	168 (35.7)	136 (26.2)	
Current smoker	121 (26.9)	183 (39.0)	241 (46.3)	
Drinking alcohol (%)				0.418
Everyday	13 (2.9)	6 (1.3)	2 (0.4)	
Sometime	286 (63.6)	308 (65.5)	351 (67.5)	
Ex-drinker	151 (33.5)	156 (33.2)	167 (32.1)	
Physical activity (MET-min per week)(mean ±s.d.)	3752.2±2856.3	3421.6±2746.8	3208.6±3011.4	0.011
Vitamin D supplement use (n, %)	43 (9.6)	51 (10.9)	49 (9.4)	0.617
Clinical indicators				
BMI (kg/m <sup>2</sup> )	21.5±3.6	26.6±3.9	27.8±3.7	0.004
SBP (mm Hg)	121.3±8.9	123.8±9.1	122.4±8.7	0.384
DBP (mm Hg)	72.5±5.9	71.4±5.3	73.8±6.1	0.518
HbA1c (%)	5.4±0.6	5.3±0.9	7.6±1.1	0.017

(Continued)

**Table 1** (Continued).

Variables	Controls (n=450)	Obese population		P
		Without T2DM(n=470)	With T2DM (n=520)	
TC (mmol/L)	4.19±0.52	4.23±0.58	5.71±0.62	0.028
TG (mmol/L)	1.35±0.47	1.52±0.51	2.43±0.74	0.039
HDL-C (mmol/L)	1.24±0.31	1.26±0.34	1.19±0.29	0.516
LDL-C (mmol/L)	2.03±0.57	2.21±0.54	3.24±0.59	0.041
Fins (mU/L)	8.6±2.3	9.7±2.9	12.9±3.8	<0.001
HOMA-IR	2.49±1.26	2.65±1.64	4.05±2.07	<0.001
Subcutaneous fat (cm <sup>2</sup> )	189±60.7	216±58.4	235±59.6	<0.001
Visceral fat (cm <sup>2</sup> )	45±21.5	75±25.3	95.7±31.6	<0.001
Vitamin D (ng/mL)	27.6±9.5	23.2±8.6	16.6±6.5	<0.001

**Notes:** assessment of insulin resistance. Continuous variables were shown as mean ±SD, categorical variables were shown as a number (%). Categorical variables were analyzed by the Chi-square test, and continuous variables were assessed using analysis of variance.

**Abbreviations:** BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, hemoglobin; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Fins, fasting insulin; HOMA-IR, homeostatic model.

less sunlight. Subjects with T2DM were more often smokers, carried out less physical activity, and had a higher BMI. In addition, the levels of HbA1c, TC, TG, LDL-C, Fins, HOMA-IR, subcutaneous fat, and visceral fat in obese individuals with T2DM were higher than that in obese subjects without T2DM and healthy controls. Only 9.93% of the participants used vitamin D supplements. These supplements were therefore not retained in the subsequent analysis due to their low prevalence and the lack of correlation with T2DM. The obese subjects with T2DM also had significantly lower levels of vitamin D. Interestingly, vitamin D levels were associated significantly with sunlight exposure ( $r = 0.38$ ,  $P < 0.001$ ), physical activity ( $r = 0.18$ ,  $P = 0.016$ ), BMI ( $r = -0.25$ ,  $P < 0.001$ ), and HOMA-IR BMI ( $r = -0.21$ ,  $P < 0.001$ ).

Table 2 shows the adjusted mean levels of vitamin D in the two obese groups. After adjustment for sunlight exposure, smoking habits, alcohol use, and physical activity, a visible ( $P < 0.001$ ) and progressively lower vitamin D level was found in healthy controls to obese subjects without T2DM to obese subjects with T2DM. Compared with controls, obviously lower vitamin D levels were found in obese subjects without T2DM ( $P = 0.006$ ) or with T2DM ( $P < 0.001$ ). Further adjustment for clinical indicators did not change these correlations ( $P = 0.002$ ), with differences between healthy controls and obese subjects without T2DM being decreased significantly ( $P = 0.054$ ), but remaining significant for obese participants with T2DM ( $P = 0.002$ ).

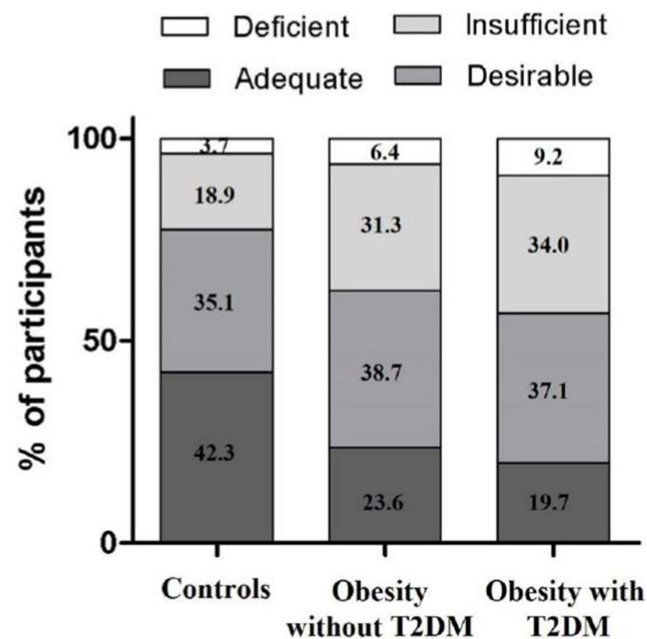
Of the participants, 28.4% had insufficient vitamin D levels (10 ~ 20 ng/mL) and 6.6% had deficient levels (< 10 ng/mL). The proportion of subjects with deficient vitamin D levels showed an increasing trend from the controls (3.7%) to the obese subjects without T2DM (6.4%) and to obese subjects with T2DM (9.2%) (Figure 1). Similarly, the proportion of subjects with adequate vitamin D levels showed a reducing trend from the controls (42.3%) to obese subjects without T2DM (23.6%) and to obese subjects with T2DM (19.7%).

Table 3 shows the odds ratios for deficient, insufficient, and desirable vitamin D levels analyzed by multinomial logistic regression in which adequate status (> 30 ng/mL) was set as the reference category. In the partially adjusted

**Table 2** Adjusted Means of Serum Vitamin D Levels Across the Obese Groups

	Controls	Obesity without T2DM		Obesity with T2DM	
	Mean (s.e.)	Mean (s.e.)	P <sup>a</sup>	Mean (s.e.)	P <sup>a</sup>
Model 1	27.2 (0.76)	23.0 (0.71)	0.006	15.9 (0.62)	<0.001
Model 2	26.5 (0.74)	23.4 (0.78)	0.054	16.4 (0.68)	0.002

**Notes:** Model 1, adjusted for sunlight exposure, smoking habits, alcohol use, physical activity. Model 2, adjusted further for BMI, HbA1c, TC, TG, LDL-C, Fins, HOMA-IR, subcutaneous fat, and visceral fat. <sup>a</sup>Post-hoc comparison (Tukey's test) with mean vitamin D levels of the controls.



**Figure 1** Clinical classification of serum vitamin D levels across the control and obese groups. Deficient, < 10 ng/mL; insufficient, 10 ~ 20 ng/mL; adequate, 20 ~ 30 ng/mL; desirable, > 30 ng/mL.

models, compared with controls, obese subjects with T2DM had a 1.44-fold ( $P = 0.025$ ), 2.02-fold ( $P < 0.001$ ), and 2.54-fold ( $P < 0.001$ ) increased risk for desirable, insufficient, and deficient vitamin D levels, respectively. In the fully adjusted models, compared with controls, obese subjects with T2DM had a 1.41-fold ( $P = 0.027$ ), 1.83-fold ( $P < 0.001$ ), and 2.14-fold ( $P = 0.014$ ) increased risk for desirable, insufficient, and deficient vitamin D levels, respectively. Compared with controls, obese subjects without T2DM had a 1.72-fold ( $P = 0.005$ ) increased risk for deficient vitamin D levels and a non-significant increased risk for insufficient or desirable levels.

Linear regression models were used to determine the correlation between the specific clinical indicators of T2DM and vitamin D levels in obese subjects with T2DM (Table 4). After partial adjustment, HbA1c ( $\beta = -0.24$ ,  $P < 0.001$ ), TC ( $\beta = -0.35$ ,  $P = 0.015$ ), LDL-C ( $\beta = 3.41$ ,  $P = 0.042$ ), Fins ( $\beta = -0.39$ ,  $P < 0.001$ ), and HOMA-IR ( $\beta = -0.24$ ,  $P < 0.001$ ) were negatively and significantly correlated with vitamin D levels. After full adjustment, HbA1c ( $\beta = -0.16$ ,  $P = 0.002$ ), TC ( $\beta = -0.28$ ,  $P = 0.047$ ), Fins ( $\beta = -0.31$ ,  $P = 0.008$ ), and HOMA-IR ( $\beta = -0.19$ ,  $P < 0.001$ ) were negatively and significantly correlated with vitamin D levels. No correlations were observed in the fully adjusted models for TG, LDL-C, subcutaneous fat, and visceral fat.

We further assessed whether serum vitamin D levels predicted the development of T2DM in 378 (80.4%) obese subjects without T2DM and available data during the five-year follow-up period (Table 5). After adjustment for all confounding factors, each s.d. increase in vitamin D levels was related to a 7% reduced risk ( $P = 0.037$ ) of having T2DM

**Table 3** Adjusted Correlation Between T2DM Status and Clinical Classification of Serum Vitamin D Levels

T2DM status	Adequate (n=403)	Desirable (n=533)			Insufficient (n=409)			Deficient (n=95)		
		OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
Model 1										
Controls	Reference category	1.00			1.00			1.00		
Obesity without T2DM		1.32	1.06–1.85	0.041	1.84	1.25–2.85	<0.001	1.74	0.97–2.87	0.057
Obesity with T2DM		1.44	1.09–1.98	0.025	2.02	1.41–3.02	<0.001	2.54	1.71–4.18	<0.001
Model 2										
Controls	Reference category	1.00			1.00			1.00		
Obesity without T2DM		1.29	0.99–1.76	0.086	1.50	0.91–2.63	0.105	1.72	1.14–2.55	0.005
Obesity with T2DM		1.41	1.06–1.93	0.027	1.83	1.27–2.84	<0.001	2.14	1.15–3.75	0.014

**Notes:** Model 1, adjusted for sunlight exposure, smoking habits, alcohol use, and physical activity. Model 2, adjusted further for BMI, HbA1c, TC, TG, LDL-C, Fins, HOMA-IR, subcutaneous fat, and visceral fat.

**Table 4** Adjusted Correlations Between T2DM Characteristics and Serum Vitamin D Levels in Obese Subjects with T2DM

Clinical characteristics	Model 1		Model 2	
	$\beta$ (s.e.)	P	$\beta$ (s.e.)	P
HbA1c	-0.24 (0.08)	<0.001	-0.16 (0.05)	0.002
TC	-0.35 (0.11)	0.015	-0.28 (0.09)	0.047
TG	-3.25 (2.14)	0.105	-3.01 (1.95)	0.246
LDL-C	-3.41 (1.85)	0.042	-3.24 (1.81)	0.096
Fins	-0.39 (0.11)	<0.001	-0.31 (0.09)	0.008
HOMA-IR	-0.24 (0.06)	<0.001	-0.19 (0.05)	<0.001
Subcutaneous fat	-4.65 (2.58)	0.158	-4.27 (2.42)	0.283
Visceral fat	-7.25 (3.26)	0.068	-7.04 (3.17)	0.109

**Notes:** Model 1, adjusted for sunlight exposure, smoking habits, alcohol consumption, and physical activity. Model 2, adjusted further for BMI, HbA1c, TC, TG, LDL-C, Fins, HOMA-IR, subcutaneous fat, and visceral fat.

**Table 5** Multivariate Analysis on Serum Vitamin D Level as a Predictor of T2DM in Subjects with Obesity During the Five-Year Follow-Up (n=378)

	Presence (yes/no) of T2DM after five years				Time with T2DM during the five-year follow-up							
	%	RR	95% CI	P	0–5 years			> 3.75 years (Highest quartile)				
					Estimate	s.e.	P	%	RR	95% CI	P	
Vitamin D per s.d. increase	42.4	0.93	(0.79–0.97)	0.037	-0.04	0.01	0.021	26.8	0.81	(0.58–0.96)	0.001	
Vitamin D status												
Adequate (n = 81)	38.9	Ref.			Ref.			21.5	Ref.			
Desirable (n = 152)	41.5	1.09	(0.91–1.42)	0.354	0.03	0.04	0.571	26.8	1.28	(0.84–1.85)	0.841	
Insufficient (n = 117)	43.9	1.15	(0.95–1.53)	0.183	0.08	0.04	0.032	30.5	1.59	(1.10–2.53)	0.035	
Deficient (n = 28)	53.8	1.39	(1.03–1.84)	0.028	0.05	0.03	0.094	28.9	1.84	(1.09–2.69)	0.013	

at follow-up (42.4% prevalence). Higher vitamin D levels also correlated with a lower time for having T2DM during the follow-up period ( $P = 0.021$ ) and a decreased tendency of having T2DM for > 3.75 years (highest quartile) during the follow-up period ( $P = 0.001$ ). Compared to subjects with adequate vitamin D levels, those with insufficient or deficient vitamin D levels had a 1.59 (95% CI, 1.10–2.53,  $P = 0.035$ ) and 1.84 (95% CI, 1.09–2.69,  $P = 0.013$ ) higher prevalence of having T2DM for > 3.75 years during the follow-up period.

## Discussion

This study in a large cohort including obese subjects and healthy controls showed that after adjusting for many possible confounding factors, low serum levels of vitamin D correlated with obesity in T2DM subjects and also the development of the disorder in the obese population. Clinically insufficient and deficient levels of vitamin D were more likely to be found in obese individuals. Furthermore, in the obese population low serum vitamin D levels were associated with an increased risk for developing T2DM over a five-year follow-up period.

It has been reported recently that a major cause for the development of insulin resistance is an insufficient level of vitamin D.<sup>3</sup> Some clinical studies have shown that vitamin D supplementation ameliorates major metabolic parameters associated with insulin resistance, such as LDL-C, TC, HbA1c, TG, and HOMA-IR.<sup>14,15</sup> Barzegardi et al also reported a significant reduction in the serum levels of TG, LDL-C, and TC in patients with diabetic nephropathy following vitamin D supplementation.<sup>16</sup> In addition, the status of insulin-resistant obesity has been shown to be related closely to low circulating levels of vitamin D.<sup>17</sup> Some studies have also confirmed that vitamin D modulates fatty acid composition



in subcutaneous adipose tissue by directly regulating the expression of Elovl3.<sup>18</sup> Collectively, these investigations confirm that vitamin D ameliorates the metabolic abnormalities of diabetes. Moreover, our study also showed that vitamin D levels were negatively and significantly correlated with HbA1c, TC, Fins, and HOMA-IR after full adjustment for all other confounders.

However, some clinical studies have reported that vitamin D levels have no effect on insulin resistance and other abnormalities such as oxidative stress and inflammation. For example, several studies in patients with T2DM have shown that vitamin D supplementation has no effect on hs-CRP levels, oxidative stress markers, LDL, HDL, or HbA1c.<sup>19,20</sup> However, these clinical studies had a small sample size and did not fully take confounding factors into account. Notably, our results provided strong confirmative evidence to the findings of these previous studies and were based mainly on a small sample size and vitamin D supplementation and analyzed the association between vitamin D and T2DM in obese subjects using direct measurement of serum vitamin D levels. Significantly, low serum levels of vitamin D were found in the obese population. Nevertheless, no definite conclusions regarding this correlation can be inferred from the current results. Hypovitaminosis D may also be a consequence of obesity, due to the fact obesity is known to affect health-associated lifestyle, including physical activity and diet, both of which have been reported to correlate with serum vitamin D levels.<sup>21,22</sup> However, our findings should promote further longitudinal and experimental studies to clarify the presence of consistent time-sequenced correlations and explain the link between the causality of T2DM and vitamin D levels. Clarifying the role of vitamin D in the signaling pathways involved in the development of T2DM in the obese population may have important implications. Although hypovitaminosis D is common,<sup>23</sup> underlying modified determinants of vitamin D status, including dietary habits, use of dietary supplements, or sun exposure provide new strategies to prevent T2DM in obese individuals.<sup>24</sup>

The current study had some limitations. The research design was mainly cross-sectional and therefore no inference on the directionality of the association between T2DM and vitamin D levels can be made. In addition, the dietary intake of vitamin D was not taken into account due to the unavailability of nutritional data. The study also had some strengths, such as a large sample size, a gold-standard method to measure vitamin D, and full adjustment for potential confounding factors in the statistical analyses.

## Conclusion

In summary, our findings show that low vitamin D levels correlate with the presence of T2DM in an obese population. This suggests that hypovitaminosis D may represent a potential biological vulnerability for T2DM in the obese population. Our data allow us to confirm that normalization of vitamin D levels may become a potential future strategy to prevent T2DM and its complications in obese subjects.

## Ethical Statement

Our study complies with the Declaration of Helsinki.

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## Disclosure

The authors declare that they have no conflicts of interest for this work.

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