The Relationship between Vitamin D Status and Visceral Fat Accumulation in Males with Type 2 Diabetes

Bowei LIU, Dongmei FAN and Fuzai YIN*

Department of Endocrinology, The First Hospital of Qinhuangdao, No. 258 Wenhua Road,
Qinhuangdao, 066000, Hebei Province, China

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Summary Vitamin D deficiency may play an important role in obesity. The aim of the study was to explore the relationship between vitamin D status and visceral fat accumulation in males with type 2 diabetes. A cross-sectional study was conducted on 128 adult males with type 2 diabetes in Qinhuangdao. The nutritional status of vitamin D was assessed by circulating levels of 25(OH)D, vitamin D deficiency <30 nmol/L, vitamin D insufficiency 30–50 nmol/L and vitamin D sufficiency >50 nmol/L. Accumulation of visceral fat was defined as visceral fat area ≥ 100 cm². The prevalence of visceral fat accumulation was 35.9%. The prevalence of visceral fat accumulation was 14.6%, 45.1% and 50.0% in type 2 diabetes with vitamin D sufficiency, vitamin D insufficiency and vitamin D deficiency, respectively. In multiple logistic regression analysis, subjects with vitamin D insufficiency [OR=4.255, $p=0.012$] and vitamin D deficiency [OR=6.122, $p=0.022$] were more likely to have visceral fat accumulation compared with subjects with vitamin D sufficiency. Visceral fat accumulation linked to the cluster of cardiometabolic risk factor in males with type 2 diabetes. There was a significant correlation between vitamin D status and visceral fat accumulation in males with type 2 diabetes.

Key Words obesity, vitamin D deficiency, prevalence, cardiometabolic risk factor, diabetes

Type 2 diabetes is a serious threat to human health in China. Obesity plays an important role in the development and progression of type 2 diabetes. Obesity increased the risk of type 2 diabetes by aggravated insulin resistance (1, 2). Obesity also increased the risk of chronic complications of type 2 diabetes (3, 4). The fat distribution influences the outcomes of obesity. Excess visceral adipose are associated with vascular endothelial function, atherosclerosis and cardiovascular disease in type 2 diabetes (5–7).

Vitamin D deficiency is widespread around the world (8, 9). The classical role of vitamin D is about bone health. Vitamin D also has potential role in the prevention of nonskeletal disorders such as auto-immune disease, cancer, mental health problems and cardiovascular disease (10–13).

Vitamin D deficiency may play an important role in obesity. In a meta-analysis, vitamin D deficiency is associated with an increased level of body mass index (BMI) in both diabetic and non-diabetic subjects (14). Vitamin D deficiency was positively associated with both general and abdominal obesity (15). Abdominal visceral adipose tissue (VAT) are inversely associated with serum 25-hydroxyvitamin D [25(OH)D] concentrations in the general adult population from China, Germany and Denmark (16, 17). Hao et al. also found that 25(OH)D were inversely associated with visceral fat area (VFA) in Chinese males with normal glucose tolerance (18).

In type 2 diabetes, vitamin D deficiency is also associated with obesity (19, 20). However, obesity was evaluated by BMI, not VFA, in these studies. The aim of our study was to determine the relationship between vitamin D status and visceral fat accumulation in males with type 2 diabetes.

METHODS

Subjects. After obtaining informed consent from males with type 2 diabetes a cross-sectional study was conducted. All subjects were adult males with a diagnosis of type 2 diabetes (21). The exclusion criteria included the following: 1) subjects with type 1 diabetes, 2) subjects with clinical evidence of other endocrinopathy, 3) subjects were taking vitamin D, 4) subjects with renal dysfunction (estimate glomerular filtration rate (eGFR) less than $60 \text{ mL} \times \text{min}^{-1} \times 1.73 \text{ m}^{-2}$) or hepatic dysfunction (alanine aminotransferase (ALT) >100 U/L), 5) subjects with acute and chronic inflammation. This study was approved by the ethics committee of the First Hospital of Qinhuangdao (No. 2015C061). All subjects provided written informed consent before study initiation.

Measurements. Anthropometric measurements, including height, weight and waist circumference (WC) were obtained. WC was accurately measured at the level of midway between the lowest rib and the top of the iliac crest. Blood pressure was measured with a mercury sphygmomanometer while the subjects were seated after 10 min of rest. Sociodemographic variables were collected and included: age, duration of diabetes, family

*To whom correspondence should be addressed.
E-mail: yinfuzai62@163.com

Table 1. Characteristics of adult males with type 2 diabetes.

Variables	VFA<100 cm ² (n=82)	VFA≥100 cm ² (n=46)	<i>t</i> or χ^2	<i>p</i>
Age (y)	50.9±11.5	47.5±13.9	1.474	0.143
Duration of diabetes (y)	6.5±5.8	5.2±5.1	1.283	0.202
FHD [<i>n</i> (%)]	11 (13.4)	5 (10.9)	0.175	0.676
Hypertension [<i>n</i> (%)]	32 (39.0)	21 (45.7)	0.534	0.465
Smoking [<i>n</i> (%)]	41 (50.0)	26 (56.5)	0.502	0.478
Drinking [<i>n</i> (%)]	47 (57.3)	25 (54.3)	0.106	0.745
BMI (kg/m ²)	25.5±2.4	29.4±2.9	7.496	<0.001
WC (cm)	88.7±7.1	102.5±7.8	10.096	<0.001
SBP (mmHg)	125.3±12.6	124.1±9.0	0.607	0.545
DBP (mmHg)	81.8±7.9	82.0±6.7	0.188	0.851
FPG (mmol/L)	9.80±3.73	11.07±3.98	1.788	0.076
HbA1c (%)	8.5±1.9	8.9±1.9	1.083	0.281
TG (mmol/L)	2.13±1.71	3.53±4.01	2.255	0.028
HDL-C (mmol/L)	1.09±0.33	0.93±0.24	2.848	0.005
ALT (U/L)	26.4±16.5	30.1±18.6	1.138	0.257
Cr (μmol/L)	62.9±12.1	62.1±14.0	0.358	0.721
eGFR (mL×min ⁻¹ ×1.73 m ⁻²)	140.7±41.5	147.5±47.4	0.837	0.404
25(OH)D (nmol/L)	50.1±18.8	40.8±12.9	3.290	0.001

VFA: visceral fat area; FHD: family history of diabetes; BMI: body mass index; WC: waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; FPG: fasting plasma glucose; HbA1c: glycosylated hemoglobin A1c; TG: triglyceride; HDL-C: high-density lipoprotein cholesterol; ALT: alanine aminotransferase; Cr: creatinine; eGFR: estimate glomerular filtration rate; 25(OH)D: 25-hydroxyvitamin D.

history of diabetes (FHD, defined as mothers, fathers, offsprings or siblings with type 2 diabetes), hypertension (subjects with history of hypertension or systolic blood pressure (SBP) and/or diastolic blood pressure (DBP) ≥140/90 mmHg for three screenings), smoking and drinking status.

After a 10-h overnight fast, blood samples were collected from an antecubital vein into heparinised tubes. Fasting plasma glucose (FPG) concentration was measured using the glucose oxidase method, and serum lipid levels, as well as renal and hepatic function, were measured using enzymatic assays with an autoanalyzer (Hitachi, Tokyo, Japan). Glycosylated hemoglobin A1c (HbA1c) was measured by highperformance liquid chromatography (HPLC). Serum 25-hydroxyvitamin D [25(OH)D] was measured using enzyme linked immunosorbent assay (ELISA) kits produced by UK IDS Company. eGFR=175×creatinine (Cr, mg/dL)^{-1.234}×age (y)^{-0.179} (22).

Definition of metabolic syndrome. Metabolic syndrome (MetS) was defined using the definition of Chinese Diabetes Society. Participants had to meet any 3 or more of the following 5 factors: 1) abdominal obesity: WC ≥90 cm, 2) abnormal glucose metabolism: FPG ≥6.1 mmol/L or 2-h plasma glucose levels ≥7.8 mmol/L after a 75-g oral glucose tolerance test (OGTT) or have been diagnosed with diabetes, 3) elevated blood pressure: blood pressure ≥130/85 mmHg or have been diagnosed with hypertension, 4) high triglyceride (TG): TG ≥1.7 mmol/L, 5) low high density lipoprotein cholesterol (HDL-C): HDL-C <1.04 mmol/L (23).

Vitamin D status. The nutritional status of vitamin

D was assessed by circulating levels of 25(OH)D, vitamin D deficiency <30 nmol/L, vitamin D insufficiency 30–50 nmol/L and vitamin D sufficiency >50 nmol/L (24).

VFA estimation by bioelectrical impedance analysis (BIA). In this study, VFA was measured by the InBody S10 (Biospace Co, Ltd, Seoul, Korea) as an indicator of visceral fat accumulation. The measurements were performed with the subjects in sitting position. Measurements were taken using the 4-electrode 8-point touch electrode method by wiping the areas where the 8 electrodes would be attached (one each on thumb and middle fingers on both hands and one each on both ankles) with electrolyte tissue and connecting the holder electrode. Visceral fat accumulation was defined as VFA≥100 cm² (25).

Statistical analyses. All analyses were performed using the SPSS 11.5 statistical software (SPSS 11.5 for Windows; SPSS, Inc., Chicago, IL). Numerical variables were reported as mean±standard deviation. Comparisons were conducted between groups using the *t* test. Comparison of prevalence data was performed by χ^2 analysis. Multiple logistic regression models were used for modeling relationships between vitamin D status and visceral fat accumulation in males with type 2 diabetes. Computed tomography (CT) is golden methods for evaluating visceral adipose tissue. The correlation between visceral fat area measured by InBody S10 and by CT weakened in males with BMI ≥30 kg/m² (26). We excluded subjects with BMI ≥30 kg/m² and analyzed again. *p*<0.05 was considered statistically significant.

Table 2. Prevalence of metabolic syndrome in type 2 diabetes patients with different levels of visceral fat area.

Components	VFA<100 cm ² (n=82)	VFA≥100 cm ² (n=46)	χ^2	<i>p</i>
Abdominal obesity [n (%)]	41 (50.0)	44 (95.7)	27.531	<0.001
Elevated blood pressure [n (%)]	42 (51.2)	26 (56.5)	0.333	0.564
High TG [n (%)]	36 (43.9)	29 (63.0)	4.320	0.038
Low HDL-C [n (%)]	37 (45.1)	36 (78.3)	13.206	<0.001
Metabolic syndrome [n (%)]	47 (57.3)	44 (95.7)	21.073	<0.001

VFA: visceral fat area; TG: triglyceride; HDL-C: high-density lipoprotein cholesterol.

Table 3. Prevalence of visceral fat accumulation across vitamin D status.

Vitamin D status	<i>n</i> (%)	Model 1		Model 2	
		OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>
Sufficiency (n=41)	6 (14.6)	1		1	
Insufficiency (n=71)	32 (45.1)	4.786 (1.789–12.806)	0.002	4.255 (1.372–13.197)	0.012
Deficiency (n=16)	8 (50.0)	5.833 (1.577–21.572)	0.008	6.122 (1.298–28.881)	0.022

Model 1: univariate logistic regression analysis. Model 2: multiple logistic regression analysis, visceral fat accumulation was considered as the dependent variables in a multiple logistic regression analysis with age, duration of diabetes, FHD, smoking, drinking, HbA1c, ALT, eGFR, metabolic syndrome and vitamin D status as independent variables. OR: odds ratio; CI: confidence interval; FHD: family history of diabetes; HbA1c: glycosylated hemoglobin A1c; ALT: alanine aminotransferase; eGFR: estimate glomerular filtration rate.

Table 4. Prevalence of visceral fat accumulation across vitamin D status in subjects with BMI <30 kg/m².

Vitamin D status	<i>n</i> (%)	Model 1		Model 2	
		OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>
Sufficiency (n=41)	6 (14.6)	1		1	
Insufficiency (n=53)	16 (30.2)	2.523 (0.886–7.179)	0.083	3.292 (0.902–12.021)	0.071
Deficiency (n=13)	5 (38.5)	3.646 (0.887–14.988)	0.073	8.301 (1.195–57.643)	0.032

Model 1: univariate logistic regression analysis. Model 2: multiple logistic regression analysis, visceral fat accumulation was considered as the dependent variables in a multiple logistic regression analysis with age, duration of diabetes, FHD, smoking, drinking, HbA1c, ALT, eGFR, metabolic syndrome and vitamin D status as independent variables. BMI: body mass index; OR: odds ratio; CI: confidence interval; FHD: family history of diabetes; HbA1c: glycosylated hemoglobin A1c; ALT: alanine aminotransferase; eGFR: estimate glomerular filtration rate.

RESULTS

This study enrolled 128 males with type 2 diabetes, age 49.7 ± 12.5 y, duration of diabetes 6.0 ± 5.6 y. Among these subjects, 46 males (35.9%) were characterized by the accumulation of visceral fat. The age, history of diabetes, FHD, smoking and drinking were similar between patients with VFA<100 cm² and VFA≥100 cm² ($p>0.05$). The levels of BMI, WC and TG were all significantly higher in patients with VFA≥100 cm² than in patients with VFA<100 cm² ($p<0.05$). The levels of HDL-C and 25(OH)D were all significantly lower in patients with VFA≥100 cm² than in patients with VFA<100 cm² ($p<0.05$). The SBP, DBP, FPG and HbA1c were similar between patients with VFA<100 cm² and VFA≥100 cm² ($p>0.05$) (Table 1).

Except elevated blood pressure, the prevalences of

abdominal obesity, high TG, low HDL-C and MetS were all significantly higher in patients with VFA≥100 cm² than in patients with VFA<100 cm² ($p<0.05$) (Table 2).

Among these subjects, 55.4% were characterized by the vitamin D insufficiency and 12.5% were characterized by the vitamin D deficiency. Multivariate-adjusted odds ratios (ORs) [and 95% confidence intervals (CIs)] for visceral fat accumulation across different vitamin D status are shown in Table 3. The prevalence of visceral fat accumulation was 14.6%, 45.1% and 50.0% in type 2 diabetes with vitamin D sufficiency, vitamin D insufficiency and vitamin D deficiency, respectively. When visceral fat accumulation was considered as the dependent variables in a multiple logistic regression analysis with age, duration of diabetes, FHD, smoking, drinking, HbA1c, ALT, eGFR, metabolic syndrome and vitamin D

status as independent variables, subjects with vitamin D insufficiency [OR=4.255, $p=0.012$] and vitamin D deficiency [OR=6.122, $p=0.022$] were more likely to have visceral fat accumulation compared with subjects with vitamin D sufficiency. After subjects with BMI ≥ 30 kg/m² were excluded, subjects with vitamin D insufficiency [OR=2.523, $p=0.083$] and vitamin D deficiency [OR=3.646, $p=0.073$] were still more likely to have visceral fat accumulation compared with subjects with vitamin D sufficiency (Table 4). This difference was not statistically significant.

DISCUSSION

More than a third of males with type 2 diabetes have visceral fat accumulation. MetS were very common in type 2 diabetes (27). However, the prevalence of MetS increased further, nearly 100%, in males with visceral fat accumulation. When males present with these conditions together, the chances for MetS is greater than type 2 diabetes presenting alone.

In the Framingham Heart Study, the prevalence of MetS increased linearly across increasing VAT quartiles in males with normal-weight, overweight and obesity (28). In Chinese population, visceral fat was also a risk factor for MetS in males (29). Males with visceral fat obesity have higher risk of MetS even though with normal WC (30). Cohort study found that increased visceral fat promote the occurrence of metabolic abnormalities, especially abnormal lipid metabolism (31, 32). Consistent with previous research, dyslipidemia was worse in type 2 diabetes males co-exist with visceral fat accumulation.

The pattern of fat deposition exists gender differences. Males are more likely to deposit in the visceral fat (33). Visceral fat is mainly composed of mesenteric and omental fat and retroperitoneal adipose tissue (34). Mesenteric and omental fat are drained to the portal vein. Pro-inflammatory factors and free fatty acids from these depots are drained directly to the liver and eventually lead to hepatic insulin resistance and metabolic abnormalities (35). Epidemiologic studies also confirmed that VAT remains more strongly associated with MetS compared with subcutaneous adipose tissue (28, 36).

Vitamin D status is strongly associated with visceral adiposity in nondiabetic individuals (37). In our study, we found that vitamin D insufficiency and deficiency was also correlated with visceral fat accumulation in males with type 2 diabetes. The mechanism of vitamin D on fat metabolism is not very clear. In vitro experiments, 1,25-dihydroxyvitamin D3 restrains adipogenesis through suppressing the expression of CCAAT-enhancer-binding protein, peroxisome proliferator-activated receptor-gamma, involved in adipocyte differentiation (38). Preadipocytes have important role in the homeostasis of adipose tissue. Recent research found that 1,25-dihydroxyvitamin D3 modulate vitamin D receptor expression and cell cycle in preadipocytes (39).

The results of vitamin D supplementation on visceral fat accumulation were disagreement. In 2017, a sys-

tematic review evaluated the effect of vitamin D supplementation on non-skeletal disorders. Vitamin D supplementation had no significant effect on markers of adiposity. In this study, adiposity was evaluated by BMI and weight (40). Several clinical trials verified that vitamin D with or without calcium supplementation contributes to a beneficial reduction of VAT (41–43). But another clinical trial found that vitamin D treatment have no effects on VAT (44). In type 2 diabetes, Shab-Bidar et al. found that daily intake of vitamin D3-fortified doogh for 12 wk improved the visceral fat accumulation (45). Vitamin D supplementation may be an effective means for preventing visceral fat accumulation and metabolic disorder in type 2 diabetes. The effect of vitamin D supplementation should be proved in type 2 diabetes by further study.

However, there are limitations to our study. First, the causality between visceral fat accumulation and vitamin D deficiency is debatable. In visceraally obese males, adipose tissue loss can increase the levels of 25(OH)D after 1-y lifestyle intervention (46). Vitamin D is a fat soluble hormone and is stored in adipose tissue. Volumetric dilution can partly explain the low vitamin D status of obesity (47). The decreased expression of the 25-hydroxylase in liver and subcutaneous adipose tissue could be another reason (48, 49). Because of the cross-sectional design of this study, we could not identify the causal relationship between visceral fat accumulation and vitamin D deficiency. Second, VAT were measured by bioelectrical impedance analysis in our study. Magnetic resonance imaging (MRI) and computed tomography (CT) are golden methods for evaluating visceral adipose tissue (50). The correlation between VFA measured by CT and measured by BIA did not display consistently on all studies. Some of them showed good correlations between VFA measured by CT and measured by BIA (51, 52). However, the correlation weakened with an advancing degree of obesity. The correlation coefficient reached 0.994 in males with BMI < 30 kg/m² and declined to 0.736 in males with BMI ≥ 30 kg/m² (26). In our study, 21 males (16.4%) have BMI ≥ 30 kg/m². This might partly influence the outcome of our study. So we excluded subjects with BMI ≥ 30 kg/m² and analyzed again. Vitamin D insufficiency and vitamin D deficiency were still more likely to have visceral fat accumulation. But this difference was not statistically significant. This may be due to the decreased sample size. Third, insulin resistance is a potential confounding factor with visceral fat accumulation. Homeostasis model assessment of insulin resistance (HOMA-IR) is a major assessment of insulin resistance. However, insulin levels were not measured in our study. As we know, metabolic syndrome reflect the status of insulin resistance. In model 2, the relationship between vitamin D status and visceral fat accumulation has not changed after adjusted MetS.

CONCLUSION

In summary, visceral fat accumulation linked to the cluster of cardiometabolic risk factor in males with type

2 diabetes. There was a significant correlation between vitamin D deficiency and visceral fat accumulation. Further work will be necessary to confirm whether vitamin D supplementation can prevent visceral fat accumulation or lose weight can improve vitamin D status in type 2 diabetes.

Authorship

Research conception and design: FZY; experiments: DMF; statistical analysis of the data: BWL; writing of the manuscript: BWL.

Disclosure of state of COI

All authors declare that they have no conflict of interest.

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Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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