The Association of Serum Vitamin D Deficiency and Metabolic Risk Factors in Chinese Adults with Prediabetes: A Cross-Sectional Study

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(Received November 28, 2018)

Summary The association of serum vitamin D deficiency and metabolic risk factors in Chinese adults with prediabetes (PreDM) has not been investigated. The present study aimed to investigate the association of serum vitamin D deficiency and metabolic risk factors in Chinese adults with PreDM. In this cross-sectional study, we stratified 412 PreDM patients into vitamin D sufficient, vitamin D insufficient and vitamin D deficient subgroups. The physical examination data was collected. Serum 25-hydroxyvitamin D_3 [25(OH)D_3] were measured by high performance liquid chromatography. The prevalence of vitamin D deficiency and insufficiency in PreDM patients were 30.58% and 26.70%, respectively. Compared with the vitamin D deficient group, the prevalence of metabolic syndrome, central obesity, hyperglycemia and hypertension were higher than those in the vitamin D insufficient or sufficient group ($p<0.05$). Moreover, the prevalence of dyslipidemia in the vitamin D deficient group was higher than those in the vitamin D sufficient group ($p<0.05$). We observed an inverse relationship between 25(OH)D_3 levels and waist circumference, triglyceride, and serum uric acid ($\beta=-0.315$; $\beta=-0.134$; $\beta=-0.239$), a positive relationship between 25(OH)D_3 levels and high-density lipoprotein cholesterol ($\beta=0.197$) after adjusting for age, sex and body mass index. Vitamin D deficiency is very common among PreDM patients in China and this deficiency is related to metabolic risk factors.

Key Words 25-hydroxyvitamin D_3, waist circumference, triglyceride, uric acid, high-density lipoprotein cholesterol

The prevalence of type 2 diabetes (T2DM) has increased significantly in recent decades in China (*1*). The most recent national survey in 2010 reported that the prevalence of diabetes was 11.6%, representing an estimated 113.9 million adults in China with diabetes (*2*). Two clinical constructs for identifying individuals at high risk of developing T2DM are prediabetes (PreDM) and metabolic syndrome (MS). MS is a cause of non-communicable diseases (NCDs), such as T2DM and cardiovascular disease (CVD) (*3*). The incidence of MS differs among nations or races according to the socio-cultural background and economic level, and it has been showing an increasing trend. A survey of the prevalence of MS of 98,042 Chinese aged 18 y and older utilizing the 2010–2012 China National Nutrition and Health Survey (CNNHS), revealed an incidence of 24.2% (*4*). According to the 2010 survey, the prevalence of PreDM was 50.1% in China (*2*), implying that approximately 500 million Chinese adults may have had PreDM. The incidence of T2DM from PreDM is about 10% (5.8–13.2%) per year (*5–8*). Therefore, the health management of subjects with PreDM is important for the effective management of NCDs.

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Vitamin D deficiency which is defined as a serum 25-hydroxyvitamin D_3 [25(OH)D_3] level of less than 20 ng/mL, has been termed a "worldwide public health issue" (*9*). In China, there have been some studies on vitamin D status in the metropolitan cities of China, such as Beijing (*10*, *11*), Shanghai (*12*) and Tianjin (*13*), and vitamin D deficiency/insufficiency, which was found to be highly prevalent. Tianjin is a municipality and the economic center in the Bohai rim region, which is located in the northern part of China, at a latitude of 39° N. The ultraviolet radiation is of a lower intensity than that in lower latitude areas. Moreover, the rapid industrialization of northern China has led to severe air pollution, with consequently decreased penetration of ultraviolet radiation from the sun (*14*). There was a high prevalence of vitamin D deficiency/insufficiency among urban and rural Han Chinese residents in Tianjin. There were 52.31% of participants who did not achieve the optimal serum vitamin D level, only 47.63% of participants achieved the optimal level (*13*).

Traditionally, vitamin D serves as an important factor for bone health and mineral metabolism (*15*). Recently, it has been reported that vitamin D might have additional metabolic effects on tissues other than bone and calcium metabolism (*16–18*). Some epidemiologic evidence have suggested that low serum 25(OH)D_3 levels

were also deemed to be related to the metabolic risk factors (*19*). Some US studies have reported that the importance of initial management in the prevention of MS as well as CVD in PreDM adults (*20*, *21*). And vitamin D might have a protective role in the underlying disorders of PreDM (*22*, *23*). To our knowledge, there have been several studies reported the positive relationship between vitamin D deficiency and MS and its components among adults with non-diabetic adults (*24*, *25*) or patients with diabetes (*26*). Although there was only one study has examined the association between serum vitamin D levels and metabolic risk factors among adults with PreDM in Korean (*27*), the result could not be directly applied to a Chinese population due to ethnic differences in vitamin D metabolism and its nutritional status (*28*). Thus, we aimed to explore the nature and strength of the relationship between serum vitamin D status and metabolic risk factors among Chinese adults with PreDM.

MATERIALS AND METHODS

Population. A total of 1,115 subjects aged 20–70 y were performed routine health check-up in Health Education and Guidance Center of Heping District, Tianjin, China during November to December in 2015, were enrolled. Participants with fasting plasma glucose (FPG) concentration of 110–126 mg/dL (6.1–7.0 mmol/L) were classified as PreDM (*29*), those with a glucose concentration $<$110 mg/dL ($<$6.1 mmol/L) or $\geq$126 mg/dL (7.0 mmol/L) or self-reported current diabetes treatments were excluded. Subjects with incomplete data and vitamin D supplement were excluded. The final cross-sectional study population comprised 412 subjects.

The study protocol was approved by the Ethics Committee of Tianjin Medical University (TMUhMEC 20120110), and it was in compliance with the declaration of Helsinki. Written informed consent was obtained from all participates.

Data collection. Height was measured without shoes to the nearest 1 cm and weight measured in light clothing to the nearest 0.1 kg on a beam balance scale. Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters (kg/m^2). Waist circumference (WC) was measured with an inelastic tape to the nearest 0.1 cm at a midpoint between the lowest rib and the iliac crest. Two measurements of blood pressure were taken using a standardized mercury sphygmomanometer on the right arm, after a 15-min rest in a sitting position; the average of the two measurements was used as subject blood pressure. Venous blood samples were taken from all participants after an overnight fast (12 h at least) and the samples were stored at $-80^{\circ}C$ until assessment assayed performed. Serum total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were estimated by enzyme method with commerial assay kit from the Sichuan Marker Biotechnology Co., Ltd. (Chengdu, China). Serum uric acid (SUA), FPG and serum lipid profiles were determined by automatic biochemical analyzer (Hitachi-7180, Tokyo, Japan).

Information about demographic characteristics and lifestyle habits, including smoking, drinking and physical activity, were collected by trained interviewers. Current smokers were defined as those who smoked at least one cigarette per day and non-smokers were defined as those who were either former smokers or never smoked a cigarette in their lives. Those who stopped smoking for less than a year were classified as smokers. A participant was classified as "drinker" in case of having drunk beer or any other alcoholic beverage during the last year. Physical activity was recorded as a three level variable (light, moderate, and heavy), as recommended by the China Nutrition Society. The current time spent outdoors (h/d) and sunshine time (h/d) also documented the frequency and mean duration of daytime outdoor activity. Serum $25(OH)D_3$ levels were determined using high-performance liquid chromatography (HPLC).

Definition of terms. On the basis of the criteria of the American Diabetes Association, individuals with 110 mg/dL (6.1 mmol/L)$\leq$FPG$<$126 mg/dL (7.0 mmol/L) were classified as PreDM (*29*). Vitamin D status was defined as follows: A serum level of $25(OH)D_3$ $<$20 ng/mL was considered to be vitamin D deficiency, whereas a level 20–30 ng/mL was vitamin D insufficiency, and to maximize vitamin D's effect for health (vitamin D sufficiency), $25(OH)D_3$ should be $\geq$30 ng/mL (*30*).

The International Diabetes Federation (IDF) criteria (*31*) was used to define MS in the present study because this definition considers the ethnic difference for central obesity. According to the IDF criteria, participants were classified as having MS if they had central obesity (WC$\geq$90 cm for men and $\geq$80 cm for women) plus any other two abnormalities of those shown below: (1) Hypertension: systolic blood pressure (SBP)$\geq$130 mmHg, or diastolic blood pressure (DBP)$\geq$85 mmHg, or treatment of previously diagnosed hypertension; (2) Hypertriglyceridemia: TG$>$150 mg/dL or specific medical treatment for this lipid abnormality; (3) Low HDL-C: HDL-C$<$40 mg/dL for men or $<$50 mg/dL for women; (4) Hyperglycemia: FPG$\geq$100 mg/dL or treatment of previously diagnosed diabetes. Dyslipidemia was defined as having hypertriglyceridemia or low HDL-C.

Statistical analysis. Statistical analysis was performed with the SPSS 16.0 software (SPSS, Chicago). Means$\pm$SD were used as descriptive statistics for normally distributed variables. All quantitative variables were tested for normality distribution using the Kolmogorov–Smirnov test and continuous parameters with a non-normal distribution were logarithmically transformed before being used in the subsequent parametric procedures. For continuous variables, the analysis of variance (ANOVA) test with Bonferonni post hoc comparison was used for between-group comparisons of normally distributed. Comparative analyses of categorical variables were carried out using a Chi-square test. Multiple linear regression analysis was used to demonstrate a linear relationship between serum $25(OH)D_3$ levels and metabolic risk factors. The covariates for the adjusted β included age, sex and BMI. For all these anal-

Table 1. General characteristics of prediabetic patients by vitamin D status.

Characteristics	Vitamin D status				*p* value
	Total	Vitamin D deficiency (<20 ng/mL)	Vitamin D insufficiency (20 to<30 ng/mL)	Vitamin D sufficiency (≥30 ng/mL)	
Number of subjects	412	126	110	176	
Male (%)	96 (23.30)	41 (32.54)	19 (17.27)	36 (20.45)	0.016
Age (y)	48.49±11.47	49.75±10.47	48.73±10.87	47.43±12.44	0.215
Smoking (%)					0.301
Never	376 (91.26)	113 (89.68)	98 (89.09)	165 (93.75)	
Current	36 (8.74)	13 (10.32)	12 (10.91)	11 (6.25)	
Drinking alcohol (%)					0.998
Daily	10 (2.43)	2 (1.59)	6 (5.45)	2 (1.14)	
Occasionally	172 (41.75)	55 (43.65)	39 (35.45)	78 (44.31)	
Never	230 (55.82)	69 (54.76)	65 (59.10)	96 (54.55)	
Physical activity (%)					0.336
Heavy	5 (1.21)	2 (1.59)	1 (0.91)	2 (1.14)	
Middle	82 (19.90)	20 (15.87)	28 (25.45)	34 (19.32)	
Light	325 (78.89)	104 (82.54)	81 (73.64)	140 (79.54)	
Daytime outdoor activity (%)					0.242
Never	121 (29.37)	34 (26.98)	29 (26.36)	58 (32.95)	
<1 h/d	85 (20.63)	30 (23.81)	22 (20.00)	33 (18.75)	
1–3 h/d	188 (45.63)	54 (42.86)	54 (49.09)	80 (45.45)	
>3 h/d	18 (4.37)	8 (6.35)	5 (4.55)	5 (2.85)	
Sunshine time (%)					0.625
<1 h/d	262 (63.59)	81 (64.29)	70 (63.64)	111 (63.07)	
1–2 h/d	133 (32.28)	40 (31.74)	38 (34.54)	55 (31.25)	
>2 h/d	17 (4.13)	5 (3.97)	2 (1.82)	10 (5.68)	

Values are presented as mean±SD or *n* (%).

ysis a p value<0.05 based on two-sided test was considered statistically significant.

RESULTS

General characteristics of prediabetic patients by vitamin D status

The characteristics of participants are summarized in Table 1. Overall, 96 men and 316 women were included in the analysis. The prevalence of a deficiency (<20 ng/mL) or insufficiency (20–30 ng/mL) of vitamin D was 30.58% and 26.70%, respectively. The proportion of subjects who had a serum 25(OH)D_3 level≥30 ng/mL was 42.72%. Generally, women with vitamin D deficiency or insufficiency were higher than the men (p<0.05). There were no significant differences for age, drinking, smoking, physical activity, daytime outdoor activity and sunshine time among three groups (p>0.05). The subject whose sunshine times less than 1 h per day was 63.59%.

Metabolic characteristics of prediabetic patients by vitamin D status

The metabolic characteristics by serum 25(OH)D_3 level are shown in Table 2. The BMI and WC in the vitamin D insufficient and deficient group were higher than those of the vitamin D sufficient group (p<0.05). The SBP, DBP, TG, LDL-C, SUA and creatinine in the vitamin D deficient group were higher than those in the vitamin D sufficient group (p<0.05). The HDL-C in the vitamin D deficient group was lower than those in the vitamin D sufficient group (p<0.05). However, there were no differences in TC and urea nitrogen among these three groups (p>0.05).

Comparison of prevalence of metabolic risk factors in prediabetic patients by vitamin D status

As shown in Table 3, the total prevalence of MS was 13.83%. Compared with the vitamin D deficient group, the prevalence of MS, hyperglycemia and hypertension were higher than those in the vitamin D insufficient group or sufficient group (p<0.05). The prevalence of central obesity in the vitamin D deficient group were higher than those in the vitamin D insufficient and vitamin D sufficient group, and the prevalence of central obesity in the vitamin D insufficient group was also higher than those in the vitamin D sufficient group (p<0.05). Moreover, the prevalence of dyslipidemia in the vitamin D deficient group was higher than those in the vitamin D sufficient group (p<0.05).

Linear regression analysis between serum 25(OH)D_3 levels and MS risk factors

The association between serum 25(OH)D_3 levels and MS risk factors was assessed using linear regression analysis (Table 4). Serum vitamin D levels were inversely associated with WC, SBP, DBP, TG and SUA (p<0.05). Serum vitamin D levels were positively associated with HDL-C. After adjusting for potential confounders including age, sex and BMI, the inverse or positive association

Table 2. Metabolic characteristics of prediabetic patients by vitamin D status.

Metabolic characteristics	Vitamin D status				*p* value
	Total	Vitamin D deficiency (<20 ng/mL)	Vitamin D insufficiency (20 to<30 ng/mL)	Vitamin D sufficiency (≥30 ng/mL)	
Number of subjects	412	126	110	176	
Body mass index (kg/m^2)	24.23±3.44	25.67±3.70	24.52±3.44*	23.01±2.76*#	<0.001
Waist circumference (cm)	75.68±10.72	79.93±10.72	76.54±10.46*	72.10±9.74*#	<0.001
Systolic blood pressure (mmHg)	118.14±15.90	121.87±15.85	118.05±17.08	115.54±14.69*	0.003
Diastolic blood pressure (mmHg)	77.27±9.67	79.69±9.97	77.59±9.76	75.14±8.92*	<0.001
Fasting plasma glucose (mmol/L)	5.98±0.34	6.11±0.35	5.97±0.35*	5.89±0.30*	<0.001
High-density lipoprotein cholesterol (mmol/L)	1.32±0.26	1.26±0.24	1.31±0.25	1.36±0.27*	0.009
Low-density lipoprotein cholesterol (mmol/L)	3.16±0.77	3.29±0.72	3.18±0.81	3.07±0.76*	0.048
Total cholesterol (mmol/L)	5.20±0.91	5.29±0.80	5.23±1.04	5.12±0.89	0.233
Triglyceride (mmol/L)	1.35±0.77	1.54±0.94	1.35±0.63	1.21±0.70*	0.001
Serum uric acid (μmol/L)	274.35±71.42	298.07±75.41	271.38±70.23*	259.23±64.84*	<0.001
Urea nitrogen (mmol/L)	4.44±1.08	4.54±1.20	4.48±1.06	4.35±0.99	0.272
Creatinine (μmol/L)	57.95±11.41	61.18±11.47	56.35±11.44*	56.65±10.92*	0.001

Values are presented as mean±SD.
* Compared with vitamin D deficiency, $p<0.05$;
# Compared with vitamin D insufficiency, $p<0.05$.

Table 3. Comparison of prevalence of metabolic risk factors in prediabetic patients by vitamin D status.

Metabolic risk factors	Vitamin D status				*p* value
	Total	Vitamin D deficiency (<20 ng/mL)	Vitamin D insufficiency (20 to<30 ng/mL)	Vitamin D sufficiency (≥30 ng/mL)	
Number of subjects	412	126	110	176	
Metabolic syndrome (%)	57 (13.83)	34 (26.98)	12 (10.91)*	11 (6.25)*	<0.001
Central obesity (%)	144 (34.95)	70 (55.56)	40 (36.36)*	34 (19.32)*#	<0.001
Hyperglycemia (%)	120 (29.13)	64 (50.79)	28 (25.45)*	28 (15.91)*	<0.001
Hypertension (%)	85 (20.63)	40 (31.75)	19 (17.27)*	26 (14.77)*	0.001
Dyslipidemia (%)	109 (26.46)	47 (37.30)	30 (27.27)	32 (18.18)*	0.001

Values are presented as *n* (%).
* Compared with vitamin D deficiency, $p<0.05$;
# Compared with vitamin D insufficiency, $p<0.05$.

of serum vitamin D levels and MS risk factors (WC, TG, HDL-C and SUA) were still remained ($p<0.05$).

DISCUSSION

In the present study, we observed that Chinese adults with PreDM were more likely to have low serum 25(OH)D_3 levels. There was an inverse relationship between 25(OH)D_3 levels and WC, TG, and SUA, and a positive relationship between 25(OH)D_3 levels and HDL-C. It was demonstrated that a sufficient 25(OH)D_3 level might have possible beneficial effects on metabolic risk factors in Chinese adults with PreDM.

Evidence from observational studies have pointed that the role of vitamin D status and metabolic risk factors with non-diabetic adults (*24*, *25*) or patients with diabetes (*26*), which was assistance with our study among Chinese adults with PreDM. However, the previous study did not find the association between a low serum vitamin D status and central obesity among prediabetic Korean adults (*27*). In the current study, a significant inverse association was found between serum 25(OH)D_3 levels and central obesity. The inverse association between vitamin D levels and central obesity might be explained by the role of vitamin D in absorption of calcium. It has been shown that calcium intake and high levels of calcium are associated with lower adiposity (*32*). In addition, the elevated intact parathyroid hormone (iPTH) observed in subjects with low 25(OH)D_3 levels might play a causal role in the pathogenesis of increased adiposity (*33*).

Table 4. Linear regression coefficients between serum 25(OH)D_3 level and metabolic risk factors in prediabetic patient.

Metabolic risk factors	Unadjusted			Adjusted[1]		
	B (SE)	β	*p* value	B (SE)	β	*p* value
Waist circumference (cm)	−0.633 (0.106)	−0.283	<0.001	−0.707 (0.134)	−0.315	<0.001
Systolic blood pressure(mmHg)	−0.179 (0.074)	−0.118	0.016	−0.114 (0.082)	−0.076	0.162
Diastolic blood pressure (mmHg)	−0.358 (0.121)	−0.144	0.003	−0.250 (0.132)	−0.101	0.058
Triglyceride (mmol/L)	−5.042 (1.513)	−0.162	0.001	−4.172 (1.595)	−0.134	0.009
High-density lipoprotein cholesterol (mmol/L)	18.632 (4.453)	0.202	<0.001	18.184 (4.770)	0.197	<0.001
Low-density lipoprotein cholesterol (mmol/L)	−2.906 (1.540)	−0.093	0.060	−2.403 (1.630)	−0.077	0.141
Total cholesterol (mmol/L)	−1.603 (1.303)	−0.061	0.219	−1.323 (1.419)	−0.050	0.352
Serum uric acid (μmol/L)	−0.073 (0.016)	−0.218	<0.001	−0.080 (0.020)	−0.239	<0.001

[1] Adjusted for age, sex and BMI.

Similarly to our results, many studies have reported that patients with insufficient levels of vitamin D have high prevalence of dyslipidemia, they showed that the use of this vitamin might reduce levels of TG, TC, and might improve HDL-C level (*34–37*). Vitamin D is shown to exert a role in the transportation of cholesterol by regulating the apolipoprotein A-1 levels, and it may act in the reduction of LDL-C uptake, may decrease the formation of foam cells, and may enhance the production of HDL-C. The play of vitamin D as an anti-inflammatory and on the reduction of oxidative stress also is important on the improvement of plasma lipids (*38–41*). In addition, sterol regulatory element-binding proteins (SREBPs) plays a crucial role in regulation the transcription and expression of lipid synthetic enzymes in the liver, which are associated with the lipogenesis of cholesterol, fatty acid, and TG. Recently, it was demonstrated that vitamin D metabolite (25-hydroxyvitamin D) impairs SREBP activation by inducing proteolytic processing and ubiquitin-mediated degradation of SREBP cleavage-activating protein (SCAP), thereby decreasing SREBP levels independently of the vitamin D receptor (*42*). The mechanism of vitamin D-mediated lipid control might be useful in the treatment of metabolic diseases.

Moreover, we have observed an inverse relationship between 25(OH)D_3 levels and SUA among PreDM patients, which suggested that vitamin D might have benefit on hyperuricemia. As a predictor of MS, hyperuricemia has been long observed to occur with an increased frequency among population with high risks for MS and its components (*43*). Previous studies have shown a reverse association between vitamin D status and SUA in postmenopausal women (*44*), patients with diabetes (*45*), or stable renal failure (*46*). A number of animal and human studies have indicated that vitamin D and uric acid (UA) metabolism pathways were related (*47–49*). Findings in humans demonstrated a negative association between parathyroid hormone (PTH) and SUA (*48*, *49*), which corresponded to findings from a study in postmenopausal women given teriparatide (*50*). Vitamin D insufficiency could activate parathyroid to induce the release of PTH (*51*) which was considered to raise SUA level (*48*). Evidence from genome-wide association studies (GWAS) have suggested that inherited characteristics played roles in UA and vitamin D metabolism pathways (*52*, *53*). Most genes involved in excretion of UA via the urate transporters. The ATP-binding cassette subfamily G member 2 (ABCG2) loci was the strongest influence in Asian population (*54*). And the group-specific component (GC) at rs2282679 was also most significantly associated with serum vitamin D level in Asian population (*55*). Thakkinstian et al. assessed the birectional causal pathways of vitamin D and UA using a mediation analysis with accounting for GC and ABCG2 polymorphisms and the results suggested potential causal associations between the GC gene and UA through the vitamin D mediator, and the ABCG2 and the vitamin D through the UA mediator (*56*). Results from a meta-analysis (*57*) suggested that the highest levels of serum vitamin D were associated with a 43% reduction in cardiometabolic disorders. Therefore, the impact of vitamin D supplementation on hyperuricemia and consequently the influence of SUA lowering treatment on metabolic risk factors prevention are needed to be clarified.

Firstly due to the cross-sectional nature of study, we cannot confer a causal link between vitamin D status and metabolic risk factors. Secondly, despite several adjustments, further control for confounding variables such as other micronutrients deficiencies, seasonal variations and psychosocial factors will be needed to reach an independent association between vitamin D status and metabolic risk factors. Thirdly, we did not examine the dietary intake of vitamin D. Our results showed that there was no significant difference in sunshine time per day among the vitamin D sufficient group, vitamin D insufficient group and vitamin D deficient group, which suggested that it was possible that the dietary intake of vitamin D could influence the serum vitamin D status among vitamin D sufficient group, vitamin D insufficient group and vitamin D deficient group in PreDM patients.

Further study will be performed to assess the relationship between the dietary vitamin D status and metabolic risk factors in PreDM patients. Finally, future prospective and intervention studies should be performed to demonstrate the causal effect of vitamin D on metabolic risk factors in PreDM patients.

CONCLUSIONS

Our results showed a remarkable prevalence of low levels of vitamin D in prediabetic patients and this deficiency is related to higher values for WC, TG, SUA and low levels of HDL-C. Therefore, the knowledge of the metabolic profile and levels of vitamin D in prediabetic patients with cardiovascular risk may be helpful in the development of an adequate therapeutic approach and modifications in the lifestyle that can prevent future complications and may improve the quality of life of these patients.

Acknowledgments

This research was supported by a grant from the National Natural Science Foundation of China (No. 81502809) and National Science and Technology Support Program (No. 2012BAI02B02). All the authors contributed to study conception and design, acquisition of data, analysis and interpretation of data, drafting of manuscript and critical revision.

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