Original Article

Correction of hypovitaminosis D does not improve the metabolic syndrome risk profile in a Chinese population: a randomized controlled trial for 1 year

Xiao Yin PhD, MD[1], Ling Yan MD[2], Yong Lu MD[1], Qiang Jiang MD[1], Ying Pu MD[3], Qiang Sun PhD[4]

[1]*Department of Endocrinology and Metabolism, Shandong University Affiliated Jinan Central Hospital, Jinan, China*
[2]*Healthcare Department, Shandong University Affiliated Jinan Central Hospital, Jinan, China*
[3]*Department of Medicine, Shandong University Affiliated Jinan Central Hospital, Jinan, China*
[4]*Center for Health management and Policy, Shandong University, Jinan, China*

Background and Objectives: Vitamin D deficiency is associated with a variety of chronic metabolic diseases. In vitro and animal studies suggest that vitamin D may play a crucial role in obesity and related metabolic disorders. Limited evidence regarding vitamin D deficiency exists within the Chinese population. The aims of the present study were to assess whether supplementation with vitamin D would improve metabolic indices in a middle-aged urban Chinese population. **Methods and Study Design:** We designed a randomized placebo controlled trial involving 126 metabolic syndrome sufferers with vitamin D deficiency, allocated to receive either a daily oral tablet contain 700 IU vitamin D or a matching placebo. Metabolic indices including body mass index, plasma glucose, lipid profile and other parameters were measured in subjects who completed a 12 months intervention trial. **Results:** There were significantly higher serum 25(OH)D and lower serum parathyroid hormone in vitamin D treatment group after the 12 months intervention, but no significant effect was observed for the metabolic variables which included body mass index, blood pressure, blood glucose and lipids in both treatment and control groups. **Conclusions:** Correction of hypovitaminosis D did not improve the metabolic syndrome in this urban Chinese cohort. Further studies are warranted in order to elucidate the cause-effect relation between vitamin D status, obesity and related metabolic disorders.

Key Words: vitamin D deficiency, metabolic syndrome, vitamin D supplementation, obesity, Chinese

INTRODUCTION

Altered vitamin D homeostasis is associated with increased risk of developing obesity,[1,2] hypertension,[3,4] glucose intolerance and metabolic syndrome.[5-7] It is also a risk factor for increased cardiovascular events.[8,9] Vitamin D status, which is assessed by serum 25-hydroxyvitamin D [25(OH)D] concentration, differs among ethnic groups, with African-Americans, Hispanics and Asians having a greater prevalence of hypovitaminosis D.[10,11] Lower vitamin D among these groups may be explained in part by darker skin pigmentation.[12] The relationship between hypovitaminosis D and metabolic traits, such as insulin resistance, appears to vary among different ethnicities.[13] A number of studies have tested whether vitamin D supplementation improves metabolic disease risk factors, but these trials have yielded mixed results.[14-16]

Cross-sectional human studies have documented association of hypovitaminosis D with increased risk of the metabolic syndrome in Chinese populations.[6,17] To our knowledge, no study has examined the effect of vitamin D supplementation on metabolic syndrome parameters in non-diabetes Chinese populations. The aim of the present study was to determine whether vitamin D supplementation, in a randomized placebo-controlled intervention trial, would improve metabolic disorders in metabolic syndrome individuals with hypovitaminosis D in a northern Chinese population.

MATERIALS AND METHODS

Screening

Between November in 2011 and February in 2012, 601 subjects who had a health examination in Jinan Central Hospital were recruited with detailed inclusion and exclusion criteria as described before.[17] Briefly, the participants were 35-60 years old, living in Jinan (latitude 36.6) for more than 5 years, employed in an office setting, and

Corresponding Author: Dr Xiao Yin, Department of Endocrinology and Metabolism, Shandong University Affiliated Jinan Central Hospital, 8#LiNong Street, 5-1-801, Jinan 250013, China.
Tel: 086-153-18816220; Fax: +86-531-88382693
Email: yinxiao@medmail.com.cn; yxtiantian@gmail.com
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had >13 years of education, free of known diabetes, cardiovascular disease and hypertension, no use of vitamin D and calcium supplementation within 60 days of screening, <1 period of 20 minutes of strenuous physical activity per week, general good health, no smoking, no use of medication that influence body weight.

Participants came to the laboratory for a screening evaluation during which blood samples were collected after a 12-hour overnight fast for the measurement of a biochemical profile, including serum 25(OH)D, PTH, plasma glucose, insulin, triglyceride, low density lipoprotein cholesterol (LDL-cholesterol) and high density lipoprotein cholesterol (HDL-cholesterol) concentrations. Anthropometric measures (weight, height, waist circumference) and blood pressure was measured on all participants.

Metabolic syndrome was identified using the updated National Cholesterol Education Program Adult Treatment Panel III criteria for Asian Americans.[18] Vitamin D nutritional status was based on 25(OH)D levels, which were assessed as "deficient" (<20 ng/mL); "insufficient" (20 ng/mL to 30 ng/mL) or "sufficient" (≥30 ng/mL).[19]

On the basis of measurement of anthropometric variables and the results of biochemical profile, we choose participants suffered from both metabolic syndrome and vitamin D deficiency. Subjects with diabetes, serum calcium >2.55 mmol/L, males with serum creatinine >129 mmol/L and females with serum creatinine >104 mmol/L were excluded. After excluding those who required medication for treatment of hypertension (blood pressure >160/95 mmHg), hyperlipidemia (triglyceride >5.5 mmol/L) and those who chose not to participate in the randomized treatment portion of the study, 126 subjects suffered from both the metabolic syndrome and vitamin D deficiency were enrolled in the clinical intervention trial. Insufficiency of calcium status is difficult to document biochemically, but there is concern that Chinese are not meeting the recommended intake of calcium,[20] so in the present study, the participants were all given supplementation with 600 mg elemental calcium as calcium citrate daily.

This study was approved by the Jinan Central Hospital Ethics Committee, and was performed in accordance with the declaration of Helsinki. All subjects provided written informed consent.

Protocol

After the screening procedure, 126 participants suffering from metabolic syndrome and hypovitaminosis D, otherwise healthy, were initially enrolled and randomly assigned to receive either vitamin D treatment (vitamin D treatment group) or placebo (control group). Participants took separate pills containing 700 IU cholecalciferol (vitamin D3) or separate matching placebo tablets containing microcrystalline cellulose. The subjects came to visit every second month for new supply and return of unused medication. During the 12-month trial, 3 participants discontinued treatment (2 and 1 from vitamin D treatment and control groups, respectively); 2 stopped for personal reasons (e.g. they lost interest), 1 subject experienced intestinal discomfort when taking the supplement and decided to stop participation. At the end of the 12th month, 123 participants returned for evaluation of the same parameters measured at baseline.

Laboratory analyses

Serum samples were obtained in the morning after an overnight fast and frozen at -80°C. Serum 25(OH)D and insulin were measured by double antibody radioimmunoassay (DiaSorin, Stillwater, MN, and Linco Research, St. Charles, MO) with quality control materials provided by the manufacturer. The inter-assay coefficient of variation for 25(OH)D and insulin were 9.3% and 6.7% respectively. Serum parathyroid hormone (PTH) was assayed using an electro chemiluminescence immunoassay on the Elecsys 2010 (Roche Diagnostics GmbH). The coefficient of variation for PTH was 6%. Plasma glucose, triglycerides, and HDL cholesterol were measured by enzymatic colorimetric assay on a Bayer 2400 chemistry analyser (Bayer Corporation), LDL cholesterol was calculated using the Friedwald equation. All of the intra- and inter-assay coefficients of variation were <10%. The homeostasis model assessment of insulin resistance (HOMA-IR) and Quantitative Insulin Sensitivity Check Index (QUICKI) were calculated from fasting insulin and glucose levels.[21]

Statistical analyses

Descriptive characteristics for participants were expressed as mean (SD) for continuous variables and percent for categorical variables. The distribution of all variables was determined by measuring skewness and kurtosis, and the skewed variables were logarithmically transformed.

To examine differences in baseline characteristics between groups, we used Student's T test for differences in means for continuous variables and the Chi square test for differences in proportions for categorical variables. The primary end points were 12-monthes changes from baseline in metabolic syndrome parameters including body mass index (BMI), waist circumference (WC), plasma glucose, triglycerides, HDL cholesterol and blood pressure. We used two-way ANOVA to assess the effect of supplementation with vitamin D on the primary end point in both treatment and control groups. All analyses were performed using SAS version 9.1.3 (SAS Institute), and a two-tailed p value of <0.05 was considered statistically significant.

RESULTS

A total of 126 subjects met the inclusion criteria, and of these 123 fulfilled the intervention and had complete datasets. The variables fasting insulin, HOMA-IR were severely skewed, and before their inclusion in the statistical analysis the logarithmic transformations were applied. The baseline characteristics of the study population were shown in Table 1. The compliance rate for vitamin D/placebo capsules was 95% in both groups.

We categorized the subjects to obesity and non-obese groups using the cutoff of BMI <28 kg/m^2.[22,23] There was no significant difference in age or sex between the two groups. The obese group had significantly higher waist circumference, BMI, fasting plasma insulin, HOMA-IR compared to non-obese group. Although there were no significant differences in plasma glucose, lipid profile,

serum PTH or blood pressure between obese and non-obese groups, we found a significantly lower serum 25(OH)D in the obese compared to non-obese group (p<0.05) (Table 2).

Baseline physical and biochemical characteristics were not significantly different between vitamin D treatment and control groups (p>0.05). After the 12 months intervention, there was a significant increase in serum 25(OH)D and decrease in serum PTH in the treatment group as expected, with mean serum 25(OH)D levels of 14.6 ng/mL and 33.1 ng/mL, respectively. The serum levels of 25(OH)D and PTH in the control group after the 12 months intervention were similar to baseline. No significant difference was observed after 12 months intervention for any of the variables in either the treatment or control group (p>0.05) (Table 3).

We also compared the improvement of vitamin D status and metabolic syndrome parameters in subjects of treatment group with obesity and non-obesity separately. Although the obesity subgroup had lower baseline serum 25(OH)D level, after vitamin D intervention for 12 months, a significant increase in serum 25(OH)D level was observed in both obesity (with mean serum 25(OH)D levels increased from 11.4 ng/mL to 26.8 ng/mL, p<0.05) and non-obesity subgroup (with mean serum 25(OH)D levels increased from 17.4 ng/mL to 38.7 ng/mL, p<0.05). Similar to the result of the whole treatment group, no significant difference was observed after vitamin D intervention for any of the metabolic syndrome parameters in both the obesity and non-obesity subgroups (p>0.05).

DISCUSSION

Findings from this study suggest that vitamin D treatment sufficient to normalize serum 25(OH)D concentrations does not result in improvement in metabolic syndrome risk factors where there is with vitamin D deficiency.

Based on bone health, the Recommended Dietary Al-

Table 1. Baseline characteristics of the whole study population (n=126)

	Mean±SD or %[†]
Age (years)	49.5 (8.72)
Women	46%
Waist circumference (cm)	94.5±11.5
BMI (kg/m^2)	27.1±3.4
Fasting plasma glucose (mmol/L)	5.88±0.72
Fasting insulin (mu/mL)	13.7±14.3
HOMA-IR	4.17±0.74
QUICKI	0.34±0.04
Triglycerides (mmol/L)	3.23±2.12
HDL cholesterol (mmol/L)	1.04±0.27
LDL cholesterol (mmol/L)	3.24±0.92
Systolic blood pressure (mmHg)	141±21
Diastolic blood pressure (mmHg)	90.0±14.5
Serum PTH (pmol/L)	5.2±2.13
Serum 25(OH)D (ng/mL)	14.5±3.35

[†]Data are means±SD for continuous variables and % for categorical variables. BMI: Body mass index; HOMA-IR: Homeostasis model of assessment for insulin resistance index; QUICKI: Quantitative Insulin Sensitivity Check Index; LDL: Low density lipoprotein; HDL: High density lipoprotein; PTH: Parathyroid hormone; 25(OH)D: 25-hydroxyvitamin D.

Table 2. Characteristics of samples according to presence or absence of obesity

	Obesity (BMI ≥28 kg/m^2)	
	Absent	Present
n	66	60
Age (years)	50.2 (7.08)	48.1 (8.34)
Sex (M/F)	35/31	33/27
Waist circumference (cm)	91.7 (6.28)	102 (7.95)[*]
BMI (kg/m^2)	25.7 (1.73)	30.7 (2.02)[*]
Fasting plasma glucose (mmol/L)	5.85 (0.58)	5.90 (0.41)
Fasting insulin (mu/mL)	11.3 (13.8)	22.5 (14.5)[*]
HOMA-IR	2.05 (0.71)	5.42 (0.74)[*]
QUICKI	0.36 (0.04)	0.32 (0.03)
Triglycerides (mmol/L)	3.18 (2.01)	3.29 (2.28)
HDL cholesterol (mmol/L)	1.08 (0.29)	0.99 (0.20)
LDL cholesterol (mmol/L)	3.03 (0.81)	3.44 (1.02)
Systolic blood pressure (mmHg)	128 (16.9)	144 (17.2)
Diastolic blood pressure (mmHg)	88.4 (12.7)	94.6 (11.7)
Serum PTH (pmol/L)	5.31 (1.96)	5.14 (2.34)
Serum 25(OH)D (ng/mL)	17.2 (2.57)	11.2 (4.12)[*]

[*]p<0.05 compared to non-obese group. BMI: Body mass index; HOMA-IR: Homeostasis model of assessment for insulin resistance index; QUICKI: Quantitative Insulin Sensitivity Check Index; LDL: Low density lipoprotein; HDL: High density lipoprotein; PTH: Parathyroid hormone; 25(OH)D: 25-hydroxyvitamin D.

Table 3. The effect of vitamin D supplementation on metabolic parameters in treatment and control group

	Treatment group (n=61)		Control group (n=62)	
	Baseline	12 months	Baseline	12 months
Weight (kg)	75.7±3.50	74.1±3.48	75.5±4.26	74.8±4.32
BMI (kg/m^2)	27.0±1.08	26.5±1.07	27.2±0.96	26.9±1.01
Waist circumference (cm)	95.2±3.27	93.5±3.04	93.3±3.84	92.6±3.89
Fasting glucose (mmol/L)	5.91±0.27	5.58±0.23	5.75±0.30	5.51±0.24
Fasting insulin (mu/mL)	14.1±12.5	12.3±14.0	13.2±11.5	11.6±5.43
HOMA-IR	4.73±1.15	3.98±0.93	3.96±1.72	3.28±1.27
QUICKI	0.36±0.06	0.35±0.09	0.33±0.09	0.34±0.08
Triglycerides (mmol/L)	3.34±0.68	2.83±0.41	3.17±0.40	2.88±0.22
HDL cholesterol (mmol/L)	1.07±0.08	1.09±0.07	0.99±0.07	1.04±0.06
LDL cholesterol (mmol/L)	3.26±0.25	3.18±0.24	3.20±0.20	3.14±0.22
Systolic blood pressure (mmHg)	142±4.86	138±4.07	139±5.52	136±3.77
Diastolic blood pressure (mmHg)	90.1±3.86	88.1±2.82	88.9±4.64	87.8±3.64
Serum PTH (pmol/L)	5.2±2.16	3.2±1.62*	5.1±1.8	4.9±2.1
Serum 25(OH)D (ng/mL)	14.6±2.18	33.1±4.37*	14.2±2.55	14.6±2.80

*p<0.05 compared to baseline values in treatment group. BMI: Body mass index; HOMA-IR: Homeostasis model of assessment for insulin resistance index; QUICKI: Quantitative Insulin Sensitivity Check Index; LDL: Low density lipoprotein; HDL: High density lipoprotein; PTH: Parathyroid hormone; 25(OH)D: 25-hydroxyvitamin D.

lowances (RDAs) for calcium and vitamin D are 1000 mg/day and 600 IU/day respectively for age 31-50.[24] Although it is controversial,[25] there is a growing consensus that vitamin D intakes above the current recommendations may be associated with better metabolic outcomes.[26,27] In the Nurses Health Study, female nurses with the highest intake of calcium (>1200 mg/day) and vitamin D (>800 IU/day) had the lowest risk of incidence type 2 diabetes mellitus (T2DM).[28] Chinese in the present study with hypovitaminosis D were made more metabolic equivalent to the Caucasian Americans studies by the provision of calcium 600 mg and vitamin D3 700 IU per day.

Our study consisted of young and middle aged urban metabolic syndrome patients who were office staff and physically inactive. Although cause-and-effect data from human studies are still lacking, the potential benefits of vitamin D supplementation in improvement in insulin sensitivity, glucose homeostasis and reduction in incidence of cardiovascular events and T2DM could have important public health implications. To this end, we sought to determine if vitamin D supplementation had added beneficial effects on markers of metabolic syndrome among metabolic syndrome patients suffering from vitamin D deficiency. Although there was, on average, an approximate doubling of 25(OH)D concentrations following12 months of vitamin D supplementation in the treatment group, the present study did not produce evidence that daily supplementation of vitamin D3 700 IU was able to improve anthropometric measures of adiposity or metabolic markers in this population.

It has been reported in both Chinese[29] and Caucasian populations[30] that correction of vitamin D deficiency does not have great clinical utility as a therapeutic agent for individuals with overt diabetes. In the two studies, the vitamin D treatment dose and observation period were different (109 Chinese patients received cholecalciferol 2,000 IU daily for three months in Luo's study[29] and 5292 participants received 800 IU daily vitamin D3, 1000 mg calcium and followed up for 24-62 months in Avenell's study[30]), but the two studies had similar results, which may be due to the fact that insulin resistance was more severe and less reversible by the time one has established diabetes. Therefore, it is possible that supplementation of vitamin D may be most advantageous in the early stages of metabolic disease. This is supported by previous randomized trials which showed improvements in glucose homeostasis,[31] lipid profile,[32] blood pressure and endothelial function[33] following vitamin D supplementation in healthy populations. The ages of the participants in these studies were younger compared to the participants in the overt diabetes studies, and vitamin D3 interventions were different with 400-700 IU oral daily for 3 years or 15 weeks to 300,000 IU intramascular monthly for 3 months. But results were also mixed, in that the Women's Health Initiative Calcium/Vitamin D Trial did not provide evidence that vitamin D3 supplementation could reduce the risk of developing diabetes in postmenopausal women[34] in which the treatment group received 400 IU of vitamin D3 daily and the median follow-up time was 7 years. Our findings did not support an association between vitamin D supplementation and improvement in metabolic traits in a northern Chinese population meeting the criteria for metabolic syndrome, but without diabetes. The result was similar to the previous studies[35,36] carried out in Caucasian populations.

Although there is mounting evidence linking vitamin D deficiency with obesity and related metabolic abnormalities, vitamin D intervention trials have had mixed results, likely to be due to different study populations, vitamin D replacement dosage, and intervention length. There is no standard regimen for the correction of vitamin D deficiency; we still do not know what length and duration of vitamin D intervention would be required to improve the metabolic components of the metabolic syndrome.

It is also possible that there is no direct cause-effect relationship between vitamin D and cardiometabolic risk factors. As shown in the present study, the obese metabolic syndrome patients had a significantly lower serum 25(OH)D compared to non-obese patients, even though there was no significant difference in other metabolic syndrome parameters except for BMI, including blood glucose, triglyceride, HDL and blood pressure. So the link between vitamin D deficiency and metabolic disor-

ders may just reflect the fact that both of them are prone to cluster in obese populations.

Several limitations of this study merit consideration. The results of our study may not be generalizable to all racial/ethnic groups or age groups given that our population was northern Chinese and young to middle-aged. The 12 months intervention period may not have been long enough to let us observe the contribution of vitamin D treatment on metabolic improvement. Notwithstanding the above limitations, the present study has several strengths, including the use of a work and lifestyle-based sample. Additionally, the majority of intervention trials have been performed in Caucasians and, to the best of our knowledge, this was the first study to assess hypovitaminosis D correction on the improvement for metabolic disorders in a non-diabetic Chinese population.

Conclusions

Correction of hypovitaminosis D did not improve metabolic disorders in a sample of middle aged Chinese suffering from the metabolic syndrome. The observed associations in humans between vitamin D, adiposity and metabolic traits have not yet been confirmed by intervention studies and, hence, a causal association has not been established. Future prospective studies are needed to establish a cause-effect relationship between vitamin D deficiency, obesity and its metabolic consequences. It is also necessary to establish the optimal therapeutic concentration of 25(OH)D, as basis for vitamin D intervention trials.

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AUTHOR DISCLOSURES

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Original Article

Correction of hypovitaminosis D does not improve the metabolic syndrome risk profile in a Chinese population: a randomized controlled trial for 1 year

Xiao Yin PhD, MD[1], Ling Yan MD[2], Yong Lu MD[1], Qiang Jiang MD[1], Ying Pu MD[3], Qiang Sun PhD[4]

[1]*Department of Endocrinology and Metabolism, Shandong University Affiliated Jinan Central Hospital, Jinan, China*
[2]*Healthcare Department, Shandong University Affiliated Jinan Central Hospital, Jinan, China*
[3]*Department of Medicine, Shandong University Affiliated Jinan Central Hospital, Jinan, China*
[4]*Center for Health management and Policy, Shandong University, Jinan, China*

纠正维生素 D 缺乏没有改善代谢综合征患者的心血管危险因素：中国的一项前瞻性随机对照試驗

背景与目的：维生素 D 缺乏与许多慢性代谢性疾病相关。研究证实血清维生素 D 水平与肥胖症及其相关代谢异常有重要的相关关系，但目前针对中国人群维生素 D 缺乏研究的数据还相对匮乏。本研究选择中国北方地区城市中年人群，研究维生素 D 干预治疗对代谢综合征的影响。**研究设计与方法**：在体检人群中筛选代谢综合征合并维生素 D 缺乏者 126 例，随机分为干预治疗组和安慰剂对照组，治疗组每天口服 700 IU 维生素 D，在基线及干预 12 月后检测两组代谢指标。**结果**：维生素 D 干预治疗组 12 月后血清 25(OH)D 水平显著升高，血清甲状旁腺激素水平显著下降。但体重指数、血压、血糖、血脂等代谢性指标两组在干预前后都没有显著差异。**结论**：在中国城市中年人群中补充维生素 D 可纠正其缺乏状态，但并没有显著改善代谢综合征的各种代谢异常。以后需进一步深入相关研究阐明维生素 D 状态与肥胖及相关代谢异常发生之间的因果关系。

关键词：维生素 D 缺乏、代谢综合征、维生素 D 补充、肥胖症、中国