

Original Article

Low levels of serum 25-hydroxyvitamin D and risk of metabolic syndrome in China

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Abstract: Recent evidence indicates the potential role of vitamin D in the prevention of Metabolic syndrome (MetSyn). This is an analytical cross sectional study. A total of 3275 subjects were investigated. 25-hydroxyvitamin D(25[OH]D) was detected by electrochemiluminescence immunoassay (ECLIA) technology. Metabolic syndrome was defined according to the definition of International Diabetes Federation (IDF). Among the participants, the prevalence of the MetSyn was 6.0%. The prevalence of vitamin D deficiency and insufficiency was 50.1% and 25.0% respectively. Subjects with MetSyn presented with significantly lower 25(OH)Vit D serum levels compared with non-MetSyn group. The results shows that vitamin D deficiency is common in Chinese adults, and subjects with lower serum 25(OH)D have a higher risk of the MetSyn. The cut-off value of serum 25(OH)D that reflected MetSyn in Chinese adults was 15.655 ng/mL.

Keywords: Vitamin D deficiency, metabolic syndrome, cardiovascular risk

Introduction

Metabolic syndrome (MetSyn) is a constellation of CVD risk factors, i.e. abdominal obesity, atherogenic dyslipidemia (high triglycerides and reduced high density lipoprotein cholesterol [HDL-c]), disturbed carbohydrate metabolism, elevated blood pressure, along with a pro-thrombotic and proinflammatory profile [1]. In recent years, there have been marked advances in our understanding of the potential role of vitamin D in the prevention of MetSyn and cardiovascular disease (CVD).

Vitamin D, obtained largely from sunlight exposure and to a lesser extent from dietary and supplemental sources, increases the efficiency of intestinal calcium absorption. Hypovitaminosis D is associated with increased bone turnover, osteoporosis, osteomalacia, and an increased risk of fracture [2-4]. More recent evidence from several lines of research has suggested nontraditional roles for vitamin D in conditions which are frequently observed with MetSyn, including reduced insulin secretion and sensitivity [5, 6], obesity [7], diabetes [8-11], and hypertension [12]. Data from labo-

ratory studies [13], ecologic studies [14], epidemiologic investigations [15-18] and secondary analyses of small randomized trials [4] suggest a protective effect for vitamin D against CVD. Systematic reviews [19, 10, 21] suggest a possible inverse association between Vitamin D and cardiovascular risks. In a meta-analysis by Parkera et al [22], individuals with the highest levels of serum vitamin D were associated with a 43% reduction in cardio-metabolic disorders (OR 0.57, 95% CI: 0.48-0.68).

The purpose of our study was to examine the vitamin D status and the cross-sectional associations of vitamin D status with MetSyn in a large population-based cohort of Chinese adults. In this study, we also try to find the appropriate predictive cut-off value for 25-hydroxyvitamin D(25[OH]D) reflecting MetSyn in Chinese adults.

Material and methods

Ethics statement

This study was conducted according to the guidelines laid down in the Declaration of

Vitamin D status and metabolic syndrome

Helsinki and all procedures involving human subjects were approved by the ethics committee of Chinese PLA General Hospital (S2014-076-01). Written informed consent was obtained from all subjects.

Subjects

A cross-sectional study was conducted of 3330 adults aged 21-97 years who were arranged for an annual regular check-up from March to May 2012 in Chinese PLA general hospital in Beijing, which is located at the latitude of 39°9′N. Participants were excluded if they received glucocorticoid, antituberculous within one year, had severe liver or kidney insufficiency, had overt hyperparathyroidism. Totally there were 3275 adults included in the present study.

Assessments

A standard questionnaire was used by trained interviewers to collect information on age, sex, smoking, alcohol drinking and self-reported diabetes, hypertension, and dyslipidemia. Resting blood pressure was measured. Anthropometric measurements such as weight, height and waist circumference were also taken. Body height was measured to the nearest 0.5 cm and body weight to the nearest 0.1 kg. The waist and hip circumferences were measured with a circumference measurement tape. The waist was defined as the point midway between the iliac crest and the costal margin (lower rib) [23]. All measurements were conducted by trained staff.

Biochemistry

All biochemical analysis was conducted by the Clinical Diagnostic Laboratory of the Chinese PLA general hospital. Vitamin D adequacy was evaluated by measuring serum 25(OH)D concentration. This serum concentration of 25(OH)D is a good reflection of cumulative exposure to sunlight and dietary intake of vitamin D, and is widely regarded as a robust “gold standard” indicator of vitamin D status [24]. The biochemical test used was the Roche 25 OH Vitamin D TOTAL Assay. This assay used electrochemiluminescence immunoassay (ECLIA) technology for the quantitative determination of 25(OH)D. Cut-off values for serum 25(OH)Vit D levels in adults include: >30 ng/ml for vitamin D sufficiency, 20-30 ng/ml for insufficiency and <20

ng/ml for deficiency. This definition was based on the fact that the serum iPTH will rise significantly once the serum 25(OH)D level drops to less than 30 ng/ml [25]. Analyses for cholesterol, HDL-C and triglycerides were performed using commercially available enzymatic methods. Fasting plasma glucose (FPG) was measured using standard hexokinase enzymatic assays. All of the intra- and inter-assay coefficients of variation were <10%.

MetSyn

MetSyn was defined according to the definition of International Diabetes Federation (IDF) [26]. Participants were classified as having MetSyn if they had central obesity (waist circumference ≥ 90 cm for South Asian Men or ≥ 80 cm for South Asian women) and had two or more of the following four components: 1) triglycerides ≥ 1.7 mmol/l or receiving drug treatment; 2) HDL-C < 1.03 mmol/l in men, or < 1.29 mmol/l in women; 3) systolic blood pressure (SBP) ≥ 130 mmHg or diastolic blood pressure (DBP) ≥ 85 mmHg or use of antihypertensive medication; 4) FPG ≥ 5.6 mmol/l or receiving drug treatment.

Statistical analysis

Data was entered and analyzed using SPSS for Windows version 19.0 (Somers, NY, USA). Categorical variables were presented as frequencies and percentages while quantitative variables were presented as mean \pm standard deviation (SD) or 95% CI where appropriate. Differences between groups were analyzed using one way analysis of variance or independent samples *t*-test for continuous data and Chi square test for categorical data. A logistic regression model was used to evaluate the odds ratios (ORs) and 95% CIs of having MetSyn for each group of 25(OH)D compared with the highest group with adjustment for potential confounders, such as age, sex, BMI, waist circumference, FPG, triglyceride, HDL-c, LDL cholesterol (LDL-c), SBP and DBP. A Receiver operating characteristic (ROC) curve was designed to identify the best cut-off value of serum 25(OH)D for indicating MetSyn. The sensitivity and specificity for prediction of MetSyn were calculated. The ROC curve was plotted using the sensitivity as the Y-axis and false-positive rate (1-specificity) as the X-axis. The best possible cut-off point was defined as the highest

Vitamin D status and metabolic syndrome

Table 1. Characteristics of the study population by Metsyn status

	ALL	Metsyn	Non-Metsyn	P value
N	3275	184	3091	
Sex n (%)				
Men	2801 (85.53)	154 (83.70)	2647 (85.64)	0.4674
Women	474 (14.47)	30 (16.30)	444 (14.36)	
Age (years), mean (SD)	60.17 (19.68)	47.00 (12.58)	60.96 (19.75)	<.0001
BMI (kg/m ²), mean (SD)	24.77 (3.10)	28.24 (2.85)	24.49 (2.95)	<.0001
Waist circumference (cm), mean (SD)	83.65 (8.97)	93.70 (5.71)	81.72 (8.16)	<.0001
SBP (mmHg), mean (SD)	129.23 (16.44)	140.51 (17.67)	128.20 (15.94)	<.0001
DBP (mmHg), mean (SD)	76.93 (10.72)	86.85 (9.64)	76.02 (10.35)	<.0001
Triglyceride (mmol/L), mean (SD)	1.45 (1.01)	2.47 (1.79)	1.39 (0.91)	<.0001
Total Cholesterol (mmol/L), mean (SD)	4.75 (0.96)	5.14 (0.98)	4.72 (0.95)	<.0001
LDL-c (mmol/L), mean (SD)	2.92 (0.82)	3.13 (0.79)	2.91 (0.82)	<.0001
HDL-c (mmol/L), mean (SD)	1.34 (0.36)	1.11 (0.28)	1.35 (0.35)	<.0001
FPG (mmol/L), mean (SD)	5.51 (1.11)	5.80 (1.57)	5.49 (1.07)	0.0006
25(OH)D (ng/ml), mean (SD)	19.24 (8.56)	15.13 (6.23)	19.48 (8.62)	<.0001
Vitamin D deficiency n (%)	2021 (61.71)	151 (82.07)	1870 (60.50)	<.0001
Vitamin D insufficiency n (%)	893 (27.27)	27 (14.67)	866 (28.02)	
Vitamin D sufficiency n (%)	361 (11.02)	6 (3.26)	355 (11.48)	

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-c, low density lipoprotein cholesterol; HDL-c, high density lipoprotein cholesterol; FPG, fasting plasma glucose.

Table 2. MetSyn status of the study population according to 25(OH)D groups

	25(OH)D (ng/ml)				P value
	<10 (n, %)	10 to 20 (n, %)	20 to 30 (n, %)	≥30 (n, %)	
Metsyn (n=182)	30 (16.5)	121 (66.5)	25 (13.7)	6 (3.2)	<.0001
Non-Metsyn (n=3083)	275 (8.9)	1595 (51.7)	858 (27.8)	355 (11.5)	

Table 3. Unadjusted and adjusted ORs and 95% CI from logistic regression predicting the likelihood of having MetSyn for each groups of plasma 25(OH)D concentration

25(OH)D (ng/ml)	Number of patients	Number of Metsyn	Incidence of Metsyn (%)	Unadjusted-OR (95% CI)	Adjusted OR (95% CI)*	P-value
<10	305	30	9.84	6.454 (2.649-15.726)	3.137 (1.168-8.424)	0.0233
10 to 20	1716	121	7.05	4.488 (1.962-10.271)	2.317 (0.946-5.673)	0.0659
20 to 30	883	25	2.83	1.724 (0.701-4.238)	1.178 (0.452-3.074)	0.7373
≥30	361	6	1.66	1	1	

*Adjusted ORs: adjusted for age, sex, BMI, waist circumference, FPG, triglyceride, HDL-C, LDL-C, SBP and DBP.

Youden index (specificity+sensitivity-1). All *P* values were 2-tailed, and *p*-value <0.05 was considered to indicate statistical significance.

Results

The study population consisted of 85.53% males and 14.47% females. The mean age of the sample was 60.2 y. Of the 3275 subjects, the prevalence of MetSyn was 6.0%, and the

prevalence of vitamin D deficiency and insufficiency was 50.1% and 25.0% respectively.

Characteristics of the study population by MetSyn status

The clinical and laboratory characteristics of study participants are shown in **Table 1**. As anticipated, subjects with MetSyn exhibited significantly elevated weight, BMI, waist circumfer-

Vitamin D status and metabolic syndrome

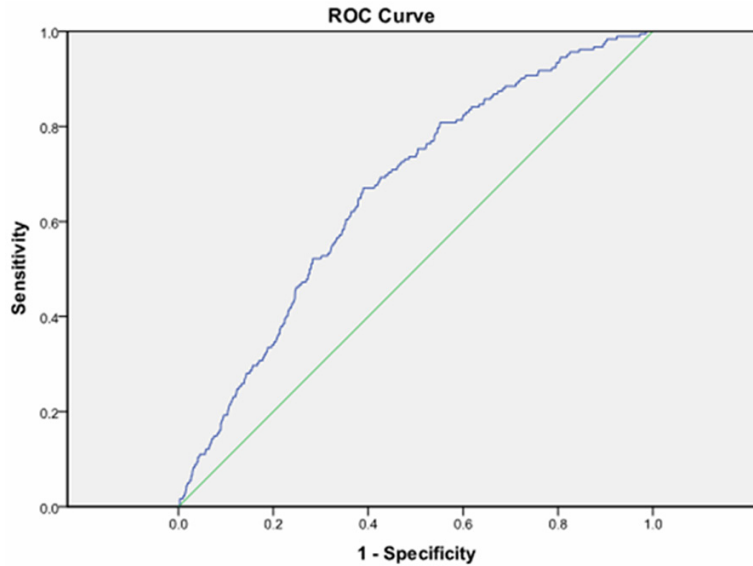


Figure 1. Receiver operating characteristic curve of serum 25(OH)D reflecting MetSyn. The cut-off value of serum 25(OH)D was 15.655 ng/ml (area under the curve = 0.662; 95% CI, 0.624-0.700; $P < 0.001$, sensitivity 67.0%, specificity 39.0%).

ence, SBP, DBP, triglycerides, total cholesterol, LDL-C and FPG, but lower HDL-C compared with non-MetSyn group. Importantly, the prevalence of Vitamin D deficiency was significantly higher in those with MetSyn compared with those without MetSyn (82.07% compared with 60.5%, $P < 0.001$). Subjects with MetSyn presented with significantly lower 25(OH)Vit D serum levels compared with non-MetSyn group (15.13 ± 6.23 ng/ml vs. 19.48 ± 8.62 ng/ml, $P < 0.0001$) (Table 1).

MetSyn status of the study population according to 25(OH)D level

We categorized the subjects using the commonly used cut-off points of serum 25(OH)D (as described in methods) into four groups [25(OH)D < 10 ng/ml, 10 ng/ml \leq 25(OH)D < 20 ng/ml, 20 ng/ml \leq 25(OH)D < 30 ng/ml, 25(OH)D > 30 ng/ml] (Table 2). The proportion of subjects in the lowest 25(OH)D group was significantly higher for females than for males ($P < 0.001$). The proportion of subjects with MetSyn decreased significantly with the increase of 25(OH)D ($P < 0.001$ for chi-squared statistic).

Risk of MetSyn according to 25(OH)D level

The risk of having MetSyn increased progressively across the highest to the lowest groups

of 25(OH)D. As shown in Table 3, after adjustment for potential factors (age, sex, BMI, waist circumference, FPG, triglyceride, HDL-c, LDL-c, SBP and DBP), the multivariable adjusted OR for MetSyn for the lowest 25(OH)D group (< 10 ng/ml) compared with the highest 25(OH)D group (> 30 ng/ml) was 3.14 (95% CI: 1.17-8.43, $P = 0.023$).

The ROC curve reflecting MetSyn from serum 25(OH)D is shown in Figure 1. The AUC of serum 25(OH)D for the prediction of MetSyn was 0.662 (95% CI, 0.624-0.700; $P < 0.001$). The best cut-off value of serum 25(OH)D for indicating MetSyn, according to the maximum of the Youden index, was 15.655 ng/

mL. Sensitivity and specificity were 67.0% and 39.0%, respectively.

Discussion

There are alarming rates of low serum 25(OH)D levels among seemingly healthy populations. In Asia, generally low serum 25(OH)D concentrations have been reported. Our results showed that there were 61.71% subjects with vitamin D deficiency in this population, and the mean serum 25(OH)D was 19.24 ± 8.56 ng/ml. These results are comparable with a population-based cross-sectional study on middle-aged and elderly Chinese population, which showed that their average 25(OH)D level was 16.19 ng/mL with deficiency proportion of 69.2% [27]. In Beijing, China, mean serum 25(OH)D in adolescent girls was 12.0-14.4 ng/ml [28]. In Japan, a low mean serum 25(OH)D of 13.6 ng/ml was observed in women younger than 30 years and 12 ng/ml in immobile older persons [29]. In the Korea National Health and Nutrition Examination Survey (KNHANES), Vitamin D insufficiency (< 20 ng/ml) was found in 47.3% males and 64.5% females [30]. Modern life styles reduce UVB exposure, due to clothing, working and exercising indoors. Air pollution blocks UVB radiation and we increasingly avoid sunshine and use sunscreens to avoid skin aging and

skin cancers. People live longer and skin synthesis and gut absorption of vitamin D fall with age. This has raised several health concerns with regard to the relationship of the low vitamin D levels and the disease consequences of serum 25(OH)D level alterations in these populations. Recently, vitamin D receptors are found in most tissues and cells in the body, which opened a whole new area of research. Since many of the factors leading to increased MetSyn risk also affect vitamin D status, the study on the role of vitamin D in determining MetSyn risks became quite popular.

The large NHANES III and NHANES 2003-2004 have shown a significant inverse association between serum 25(OH)Vit D concentration and MetSyn [31, 32]. Our results are in accordance with these studies showing that subjects with MetSyn have significantly lower 25(OH)Vit D levels compared with non-MetSyn (15.13 ± 6.23 vs. 19.48 ± 8.62 , $P < 0.0001$). In the MetSyn group, 82.07% of the people suffered from vitamin D deficiency. A possible explanation for this observation could be that vitamin D is fat soluble and is readily stored in adipose tissue and it could be sequestered in the larger body pool of fat of obese individuals [33], since obesity is quite common in MetSyn subjects. Interestingly, vitamin D may also play a role in the maintenance of a healthy body weight, as women randomized to calcium and vitamin D in the Women's Health Initiative clinical trial, experienced less weight gain compared to women on placebo [34].

Our results showed that age was positively associated with vitamin D status, where older participants had higher vitamin D levels. However, this finding concurs with that from the study among Malay adults [35] and the national study from Korea [30], which found Vitamin D insufficiency most prevalent in the relatively younger age groups. The reason for this result remains unclear. Possibly, the older subjects in this study was not representative of the general population because they were with high education, better income, and maybe they spend more time outdoors and usually pay more attention to their health, while younger people sit in their cars and offices. Maybe low levels of physical activity is the reason for increased body weight, dyslipidemia, hypertension and high blood glucose, and also for lower 25(OH)D

concentrations. Further studies are needed to investigate whether there are some other more logical reasons for this paradoxical finding.

Over 40 studies show inverse correlations of vitamin D status with MetSyn risk or with the incidence or severity of its components [36]. Our results are in accordance with these studies showing that 25(OH)D concentrations were inversely associated with MetSyn risk, and subjects with 25(OH)D levels < 10 ng/mL had a more than 3-fold higher prevalence of MetSyn compared to those with 25(OH)D levels ≥ 30 ng/mL after adjustment. In the Canadian Health Measures Survey [37], OR for MetSyn = 0.5, but 95% CI, 0.24-1.06, for those in the highest quartile of 25(OH)D vs. the rest. Inverse associations of MetSyn risk with 25(OH)D reported in the Netherlands ($n = 1286$ community dwelling subjects aged 65-88 y [mean 25(OH)D = 53.5 nmol/l and 47.8% subjects < 50 nmol/L], gave an adjusted OR for MetSyn for lowest vs. highest strata of 25(OH)D of 1.54 (95% CI 1.23-1.94) [38].

Our study showed that the OR for the MetSyn increased abruptly in subjects with 25(OH)D decreasing. The predictive cut-off value for 25(OH)D reflecting MetSyn was 15.66 ng/ml (sensitivity = 0.670, specificity = 0.390). To our knowledge, this is the first study that has performed a ROC curve in investigating the effect of 25(OH)D levels on METS, and find a cut-off point for 25(OH)D to predict MetSyn, and vitamin D supplementation maybe necessary at this level.

Our study has some limitations, it was just cross-sectional and lack of life style data, further prospective, randomized placebo controlled trials are quite important. We also did not measure the parathyroid hormone and additional markers of islet β cell function or inflammation markers, which may have provided more information of MetSyn. Strengths of this study include the large cohort and the assessment of a cutoff point of 25(OH)D to detect MetSyn, in which level subjects should consider vitamin D supplementation.

Vitamin D deficiency is common in Chinese adults, and subjects with lower serum 25 (OH) D have a higher risk of the MetSyn. The cut-off value of serum 25(OH)D that reflected MetSyn in Chinese adults was 15.655 ng/mL, and vita-

min D supplementation should be considered at this level.

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Disclosure of conflict of interest

None.

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Vitamin D status and metabolic syndrome

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