Plasma 25-hydroxyvitamin D concentration and metabolic syndrome among middle-aged and elderly Chinese individuals

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Accessibility
Plasma 25-Hydroxyvitamin D Concentration and Metabolic Syndrome Among Middle-Aged and Elderly Chinese Individuals

Ling Lu, MSC
Zhijie Yu, PhD
An Pan, MSC
Frank B. Hu, MD, PhD
Oscar H. Franco, MD, DSc, PhD
Huaixing Li, PhD
Xiao Ying Li, MD
Xin Yan Yang, PhD
Yan Chen, PhD
Xu Lin, MD, PhD

OBJECTIVE — To evaluate the association between 25-hydroxyvitamin D (25(OH)D) and metabolic syndrome in the Chinese population.

RESEARCH DESIGN AND METHODS — Plasma 25(OH)D was measured in a cross-sectional sample of 1,443 men and 1,819 women aged 50–70 years from Beijing and Shanghai. Metabolic syndrome was defined according to the updated National Cholesterol Education Program Adult Treatment Panel III criteria for Asian Americans. Fasting plasma glucose, insulin, lipid profile, A1C, and inflammatory markers were measured.

RESULTS — The geometric mean of plasma 25(OH)D was 40.4 nmol/l, and percentages of vitamin D deficiency [25(OH)D <50 nmol/l] and insufficiency [50 ≤ 25(OH)D <75 nmol/l] were 69.2 and 24.4%, respectively. Compared with the highest 25(OH)D quintile (≥57.7 nmol/l), the odds ratio for metabolic syndrome in the lowest quintile (≤28.7 nmol/l) was 1.52 (95% CI 1.17–1.98, P trend = 0.0002) after multiple adjustment. Significant inverse associations also existed between 25(OH)D and individual metabolic syndrome components plus A1C. Moreover, we observed significant inverse associations of 25(OH)D with fasting insulin and the insulin resistance index (homeostasis model assessment of insulin resistance [HOMA-IR]) in overweight and obese individuals (BMI ≥24 kg/m²) but not in their normal-weight counterparts (test for interaction, P = 0.0363 and 0.0187 for insulin and HOMA-IR, respectively).

CONCLUSIONS — Vitamin D deficiency is common in the middle-aged and elderly Chinese population, and a low 25(OH)D level is significantly associated with an increased risk of having metabolic syndrome and insulin resistance. Prospective studies and randomized clinical trials are warranted to determine the role of 25(OH)D in the development of metabolic syndrome and related metabolic diseases.

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Vitamin D deficiency is now recognized as a worldwide concern (1). A growing body of evidence suggests that 25-hydroxyvitamin D [25(OH)D], a generally accepted indicator of vitamin D status, is inversely associated with adiposity, glucose homeostasis, lipid profiles, and blood pressure along with its classic role in calcium homeostasis and bone metabolism (1–6). Even though the underlying mechanism has not been well understood, vitamin D appears to exert effects through direct modulation of gene expression via vitamin D receptors (VDRs) (1) and through regulation of extra- and intracellular calcium (1,7).

Metabolic syndrome, a constellation of cardiometabolic disease risk factors, has become a global epidemic (8). Several epidemiologic studies (5,6,9,10) have suggested that 25(OH)D status is inversely associated with metabolic syndrome in western populations, although data for morbidly obese individuals are inconsistent (11,12). Nevertheless, evidence from the Asian population is limited. Because of ethnic differences in vitamin D metabolism and its nutritional status indicated by previous studies (3,13), it is not clear whether the findings from western populations could be extrapolated directly to Asian individuals. With rapid nutrition and lifestyle transitions in the last 20 years, metabolic syndrome has become one of the most widespread health problems in Asian countries (8). However, little is known regarding whether vitamin D deficiency plays an important role in the heightened prevalence of metabolic syndrome and other metabolic disorders among Asian individuals. Therefore, the aim of our study was to evaluate the plasma 25(OH)D concentration and its association with metabolic syndrome among Chinese individuals aged 50–70 years.

RESEARCH DESIGN AND METHODS — The present study is a part of the Nutrition and Health of Aging Population in China (NHAPC) project, which is a population-based cross-sectional study among noninstitutionalized Chinese individuals aged 50–70 years in Beijing (latitude 40° north) and Shanghai (latitude 31° north), China. The details of the study design have been described previously (14). In brief, the study was conducted simultaneously in both...
geographic locations from April to June 2005. In each city, one rural and two urban districts were selected. A total of 3,289 eligible participants (1,458 men and 1,831 women) were recruited. After excluding those who did not have adequate blood samples for 25(OH)D measurement (n = 27), 3,262 individuals were eligible for the present analysis. The study was approved by the institutional review board of the Institute for Nutritional Sciences, and all participants provided informed consent.

**Data collection**

In a home interview, a standardized questionnaire was used by trained health workers to collect information such as age, sex, geographic location (Beijing/Shanghai), residential region (urban/rural), visit date (April or May/June), education level (≤6, 7–9, or ≥10 years in school), smoking (current, former, or never), alcohol drinking (yes/no), and self-reported diabetes, hypertension, dyslipidemia, coronary heart disease (CHD), stroke, and medication use. Physical activity level was classified as low, moderate, or high according to the International Physical Activity Questionnaire (short last 7-day format) scoring protocol with minor modification (14). According to participants’ responses to the corresponding questions, family history of cardiovascular disease (CVD) or diabetes was classified as yes or no.

After the home interview, all participants were invited to attend a physical examination after an overnight fast. Measurements of weight, height, waist circumference, and blood pressure have been described previously (14). BMI was calculated as weight in kilograms divided by the square of height in meters and categorized as normal weight (<24.0 kg/m²) or overweight or obesity (≥24.0 kg/m²), according to the criteria for Chinese individuals (15).

**Laboratory methods**

Peripheral venous blood samples were collected in tubes containing liquid EDTA and centrifuged at 4°C. After being frozen, the samples were shipped on dry ice to the Institute for Nutritional Sciences and stored at −80°C until analysis. Plasma glucose, triglycerides, and HDL cholesterol were measured enzymatically on an automatic analyzer (Hitachi 7080) with reagents purchased from Wako Pure Chemical Industries (Osaka, Japan). A1C was quantified from resolved erythrocytes with an automated immunoassay (Tinaquant Hemoglobin A1C II; Roche Diagnostics, Indianapolis, IN), which was standardized according to the Diabetes Control and Complications Trial/National Glycohemoglobin Standardization Program. Plasma high-sensitive C-reactive protein (CRP) was measured by a particle-enhanced immunoturbidimetric assay (Ultraseensitive CRP kit; Orion Diagnostica, Espoo, Finland). Interleukin-6 (IL-6) was measured using a high-sensitivity ELISA (Quantikine HS IL-6 Immunoassay; R&D Systems, Minneapolis, MN). Fasting insulin was determined using radioimmunoassay (Linco Research, St. Charles, MO). The insulin resistance index (homeostasis model assessment of insulin resistance [HOMA-IR]) was calculated using updated homeostasis model assessment methods (http://www.dtu.ox.ac.uk/). The plasma 25(OH)D concentration was assayed with a radioimmunoassay kit (DiaSorin, Stillwater, MN). Vitamin D nutritional status was assessed as “sufficiency” (≥75 nmol/l), “insufficiency” [50 ≤ 25(OH)D < 75 nmol/l], or “deficiency” (<50 nmol/l) (1). All of the intra- and interassay coefficients of variation were <13%.

**Definition of the metabolic syndrome**

Metabolic syndrome was defined using the updated National Cholesterol Education Program Adult Treatment Panel III criteria for Asian Americans (16) as presentation of three or more of the following components: 1) waist circumference ≥90 cm for men or ≥80 cm for women; 2) triglycerides ≥1.7 mmol/l; 3) HDL cholesterol <1.03 mmol/l for men or <1.30 mmol/l for women; 4) blood pressure ≥130/85 mmHg or current use of antihypertensive medications; and 5) fasting glucose ≥5.6 mmol/l or previously diagnosed type 2 diabetes or using oral hypoglycemic agents or insulin.

**Statistical methods**

The difference in plasma 25(OH)D concentrations between participants with and without metabolic syndrome was tested by the general linear model with controls for age, sex, geographic location, residential region, and visit date. A logistic regression model was used to evaluate the odds ratios (ORs) and 95% CIs of having metabolic syndrome for each quintile of 25(OH)D compared with the highest quintile with adjustment for potential confounders that were suggested in previous studies (3, 5, 6, 9, 17). In addition, effects of inflammatory factors on the association between 25(OH)D and metabolic syndrome were tested by models adjusted for CRP and IL-6. Tests of linear trend across increasing quintiles of 25(OH)D were performed by assigning the median value to each quintile and treating it as a continuous variable. A multiple linear regression model was used to assess the association of 25(OH)D (continuous) with fasting glucose, A1C, waist circumference, triglycerides, HDL cholesterol, blood pressure, fasting insulin, and HOMA-IR. A likelihood ratio test was used to test the potential modifying effect of sex and obesity status (<24 or ≥24 kg/m²). When appropriate, natural log-transformed values were used for the analyses. Statistical inference was made with P < 0.05 (two-sided). The statistical analyses were performed using Stata 9.2 (StataCorp, College Station, TX).

**RESULTS** — The geometric mean of 25(OH)D was 40.4 nmol/l in our study participants. The percentages of vitamin D deficiency, insufficiency, and sufficiency were 69.2, 24.4, and 6.4%, respectively. Across 25(OH)D quintiles, subjects in lower 25(OH)D quintiles were more likely to be northern (Beijing) and urban residents, to have a physical examination in April, to have higher educational levels, and to have a family history of CVD and diabetes. They also tended to have an adverse cardiometabolic profile. In addition, these subjects were less physically active and were less likely to be male and alcohol drinkers than those in higher 25(OH)D quintiles (Table 1).

Plasma 25(OH)D concentrations were lower in participants with metabolic syndrome than in those without metabolic syndrome (39.3 vs. 41.6 nmol/l, P < 0.0001). The risk of having metabolic syndrome increased progressively across the highest to the lowest quintiles of 25(OH)D with the ORs of 1.31 (95% CI 1.03–1.66), 1.36 (95% CI 1.07–1.73), 1.67 (95% CI 1.31–2.13), and 1.62 (95% CI 1.26–2.08), respectively (P trend < 0.0001) (Table 2) after adjustment for age, sex, geographic location, residential region, and visit date (model 1). Further controls for education, behavioral factors, self-reported CHD, and stroke and family history of CVD and diabetes (model 2) did not materially change the inverse associations. After additional adjustment for CRP and IL-6 (model 3), the ORs attenuated slightly, but remained signifi-
cantly (P_trend = 0.0002). The association appeared to be stronger in men than in women (data not shown), although the interaction for sex was not statistically significant (P = 0.1745). When study participants were dichotomized with the cutoff point of 50 nmol/l, the risk of having metabolic syndrome was 27% higher in those with a concentration <50 nmol/l (OR 1.27; 95% CI 1.06–1.53) than in those with a concentration ≥50 nmol/l after controlling for all the covariates in model 3.

In both simple and multiple adjusted linear regression analyses, 25(OH)D was inversely associated with fasting glucose, A1C, triglycerides, waist circumference, and diastolic blood pressure and positively associated with HDL cholesterol (Table 3). Further adjustment for BMI (not for waist circumference) did not substantially alter the associations. Sex-specific interactions were observed in the associations of 25(OH)D with triglycerides and HDL cholesterol (test for interaction: P = 0.0034 and 0.0027 for triglycerides and HDL cholesterol, respectively), and both associations were only significant in men but not in women. There were negative associations of 25(OH)D with fasting insulin and HOMA-IR in the total population (P = 0.0114 and 0.0044 for insulin and HOMA-IR, respectively), after controlling for potential confounding factors (Table 3). We further observed a modifying effect of obesity status on these associations (test for interaction: P = 0.0363 and 0.0187 for insulin and HOMA-IR, respectively). In stratified analyses, 25(OH)D was negatively associated with fasting insulin and HOMA-IR only in participants with BMI ≥24 kg/m² (P = 0.0001 and P < 0.0001 for insulin and HOMA-IR, respectively) but not in those with BMI <24 kg/m² (P = 0.5948 and 0.5874 for insulin and HOMA-IR, respectively).
When overweight and obese participants were divided into 25(OH)D quintiles, the multivariate-adjusted geometric mean of fasting insulin was 13.86 pmol/l lower (P = 0.0003) and HOMA-IR was 0.26 lower (P = 0.0002) for the participants in the highest quintile compared with those in the lowest. Excluding those with diagnosed diabetes and CVD yielded similar results patterns (data not shown).

**CONCLUSIONS** — We observed that ~94% of our study participants had 25(OH)D deficiency or insufficiency. A lower 25(OH)D concentration was associated with increased risk of having metabolic syndrome and its individual components. In addition, poor 25(OH)D status was also significantly associated with increased insulin resistance, especially among those who were overweight or obese.

### Table 2 — Adjusted ORs (95% CI) of having metabolic syndrome according to quintiles of plasma 25(OH)D concentrations

<table>
<thead>
<tr>
<th>Quintiles of 25(OH)D</th>
<th>Q5: ≥57.7 nmol/l</th>
<th>Q4: 45.6–57.6 nmol/l</th>
<th>Q3: 36.9–45.5 nmol/l</th>
<th>Q2: 28.8–36.8 nmol/l</th>
<th>Q1: ≤28.7 nmol/l</th>
<th>P_{trend}</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. cases/participants</td>
<td>193/652</td>
<td>248/653</td>
<td>279/652</td>
<td>326/653</td>
<td>335/652</td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>1.00 (reference)</td>
<td>1.31 (1.03–1.66)</td>
<td>1.36 (1.07–1.73)</td>
<td>1.67 (1.31–2.13)</td>
<td>1.62 (1.26–2.08)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.31 (1.02–1.66)</td>
<td>1.38 (1.08–1.77)</td>
<td>1.76 (1.37–2.26)</td>
<td>1.64 (1.27–2.13)</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>Model 3</td>
<td>1.28 (1.00–1.64)</td>
<td>1.33 (1.03–1.71)</td>
<td>1.71 (1.32–2.21)</td>
<td>1.52 (1.17–1.98)</td>
<td>0.0002</td>
<td></td>
</tr>
</tbody>
</table>

Model 1: adjusted for age, sex, geographic location (Beijing/Shanghai), residential region (urban/rural), and visit date (April or May/June). Model 2: further adjusted for education (≤6, 7–9, or ≥10 years in school), physical activity (low, moderate, or high), smoking (current, former, or never), alcohol drinking (yes/no), family history of CVD (yes/no) and diabetes (yes/no), and self-reported CHD (yes/no) and stroke (yes/no). Model 3: further adjusted for inflammatory factors (CRP and IL-6). Model 4: further adjusted for BMI (not for waist circumference and obesity status-stratified analysis). *4 participants were excluded with a missing value of fasting insulin, P for interaction between 25(OH)D and obesity status = 0.0363. 723 participants were excluded with a missing value of HOMA-IR, P for interaction between 25(OH)D and sex = 0.0034. 8P for interaction between 25(OH)D and sex = 0.0027.
Although two studies reported that the VDR gene polymorphism was not associated with metabolic syndrome (18,19), the inverse association between 25(OH)D and metabolic syndrome found in our study is consistent with that from three previous cross-sectional reports in American (9,10) and British adults (6). These three studies (6,9,10) were also performed in the general population with large sample sizes; two American studies (9,10) included subjects aged >20 years and the other one (6) comprised participants aged 45 years. In these studies (6,9,10), 25(OH)D concentrations were relatively higher than in our study. A cohort study by Forouhi et al. (5) showed that the baseline concentration of 25(OH)D was inversely associated with an increased metabolic syndrome risk z score. However, a study in southern California residents (17) did not show a significant association between 25(OH)D and metabolic syndrome, which may be attributed to extraordinary high levels of 25(OH)D (mean concentration was 108.9 nmol/l in men and 101.6 nmol/l in women). Whether there is a threshold or a specific range for the association between 25(OH)D and metabolic abnormalities merits further investigation.

Elevated CRP and IL-6 levels have been found to be positively associated with metabolic syndrome (8) and inversely correlated with 25(OH)D in our study and other studies (20). Thus, we further explored whether the observed inverse association between 25(OH)D and metabolic syndrome was mediated by CRP and/or IL-6. In our study, the association was slightly attenuated but remained significant after we control for CRP and IL-6. Our result was in accordance with the data from the Third National Health and Nutrition Examination Survey (NHANES III) (9) in which 25(OH)D was inversely associated with metabolic syndrome independent of CRP levels.

25(OH)D status in our study was shown to be inversely associated with AIC and individual metabolic syndrome features such as fasting glucose, waist circumference, diastolic blood pressure, and triglycerides and positively associated with HDL cholesterol. However, unlike some of the previous studies (6,9,10), we have noticed that plasma 25(OH)D was associated with triglycerides and HDL cholesterol only in men but not in women. These sex-specific associations may partly explain the stronger 25(OH)D–metabolic syndrome association in men than in women in our study. Although the mechanistic role of vitamin D deficiency in the pathogenesis of dyslipidemia is not well understood, vitamin D supplementation was reported to attenuate the beneficial effect of hormone replacement therapy on serum lipid levels (21). Thus, the potential sex-specific effects of vitamin D on metabolic disorders need to be elucidated further.

Insulin resistance is a major underlying mechanism for the metabolic syndrome. Experimental studies have suggested that vitamin D may exert its beneficial effects by stimulating the expression of insulin receptor to improve insulin responsiveness for glucose transport or by controlling calcium influx, which is essential for the insulin-mediated intracellular process in insulin-responsive tissues (7). Most epidemiologic studies (3,5,19), but not all (18), suggested that serum 25(OH)D or the VDR polymorphism was associated with insulin sensitivity. Moreover, data from NHANES III documented an ethnic difference in the association between 25(OH)D and insulin resistance (4), with a stronger association in Caucasians than in African Americans, who have much lower levels of 25(OH)D concentrations. Interestingly, in our population, with 25(OH)D levels similar to those of African Americans, 25(OH)D was also negatively associated with fasting insulin and HOMA-IR, and the associations were stronger among overweight and obese subjects.

Obesity is known to be associated with decreased bioavailability of vitamin D, which is sequestered in body fat (2). In fact, Forouhi et al. (5) reported a significant interaction between 25(OH)D and BMI on the risk for a 10-year increase in HOMA-IR. In addition, the release of free fatty acids from adipose tissue can induce insulin resistance, whereas 1,25-dihydroxyvitamin D has been shown to counteract the free fatty acid–induced insulin resistance (22). The stronger association of vitamin D with insulin resistance among the overweight and obese participants suggests that adequate vitamin D status is more important for the prevention of insulin resistance and metabolic syndrome in these individuals.

Our data suggested that vitamin D deficiency was common in middle-aged and elderly Chinese individuals [i.e., 69.2% participants with 25(OH)D ≤30 nmol/l]. Indeed, poor vitamin D status in middle and older Chinese individuals was also reported previously in two small bone-related studies conducted in Beijing (23) and Shenyang (24), respectively. Although little is known regarding to what extent the high prevalence of vitamin D deficiency in our population could be explained by certain environmental and/or genetic factors, plausible explanations include 1) the skin of elderly individuals is less efficient for forming vitamin D3, the major precursor of 25(OH)D (25), 2) use of vitamin D supplements is rare among older Chinese individuals (24), 3) unlike in the United States and other western countries, few vitamin D–fortified foods are available in China, and 4) our study participants were from a relatively high latitude, especially those in Beijing (latitude 40° north), who had lower 25(OH)D levels than their Shanghai counterparts (median 35.6 nmol/l in Beijing vs. 47.6 nmol/l in Shanghai). Hence, attention should be paid to improving vitamin D nutritional status in the Chinese population, particularly for those who are older, female, obese, less physically active, and living in high latitudes and urban areas.

To our knowledge, this is the first study to investigate the distribution and association of 25(OH)D levels with metabolic syndrome in Chinese individuals. The major strength of this study is that we used the data from a large representative sample of middle-aged and older men and women living in the two largest municipalities in China. Our analyses took into account many potential covariates that might confound the observed associations. Furthermore, we completed the field study within a relatively short period, which minimized the seasonal variation in the biomarkers. Nevertheless, several limitations should be acknowledged. A cause-effect relationship between 25(OH)D and metabolic syndrome cannot be inferred because of the cross-sectional nature of the study design. Although data on sun exposure and vitamin D supplementation were not available, we used a direct measure of vitamin D status, which reflects cumulative sun exposure and dietary vitamin D intake. In addition, because we did not measure serum calcium and parathyroid hormone, we could not determine whether the association of 25(OH)D with metabolic syndrome was partly mediated by calcium or secondary hyperparathyroidism. However, data from NHANES 2003–2004 (10) and the Medical Research Council Ely Prospective Study (5) suggested that the associations

25(OH)D and metabolic syndrome
between 25(OH)D and insulin resistance and metabolic syndrome were independent of calcium and parathyroid hormone.

In summary, our findings suggested that reduced 25(OH)D is associated with an increased risk of having metabolic syndrome and adverse values for metabolic syndrome components. The association of 25(OH)D with insulin resistance is stronger in overweight and obese individuals than in normal-weight individuals. Because there is evidence of ethnic variations in the 25(OH)D effect and limited data on the association of 25(OH)D with metabolic syndrome in Asians, our data provide novel insights into the nature of this association among Asians. Moreover, because of the high prevalence of metabolic syndrome and vitamin D deficiency in the middle-aged and elderly Chinese population, our results may have important public health implications. Increased sun exposure and use of vitamin D supplements or fortified foods are simple and inexpensive means to prevent vitamin D deficiency and related health problems. Nevertheless, the benefits of vitamin D on metabolic syndrome and related diseases such as type 2 diabetes need to be confirmed in future prospective studies and clinical trials.

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