Original Article
Epidemiology

DIABETES & METABOLISM JOURNAL

Serum 25-Hydroxyvitamin D Concentration Is Independently Inversely Associated with Insulin Resistance in the Healthy, Non-Obese Korean Population

So Young Ock[1], Kyoung Hwa Ha[2,3], Bu Kyung Kim[1], Hyeon Chang Kim[4,5], Jee-Seon Shim[5], Myung Ha Lee[4,5], Young Me Yoon[5], Dae Jung Kim[2,3]

[1]Department of Endocrinology and Metabolism, Kosin University College of Medicine, Busan,
[2]Department of Endocrinology and Metabolism, [3]Cardiovascular and Metabolic Disease Etiology Research Center, Ajou University School of Medicine, Suwon,
[4]Department of Preventive Medicine, [5]Cardiovascular and Metabolic Diseases Etiology Research Center, Yonsei University College of Medicine, Seoul, Korea

Background: We evaluated the associations between 25-hydroxyvitamin D (25(OH)D) concentrations in serum and insulin resistance in the healthy Korean population.

Methods: We conducted this cross-sectional analysis in 1,807 healthy Korean people (628 men and 1,179 women) aged 30 to 64 years in the Cardiovascular and Metabolic Disease Etiologic Research Center study. All participants were assessed for 25(OH)D, fasting glucose, and insulin levels, and completed a health examination and lifestyle questionnaire according to standard procedures. Insulin resistance was defined as the homeostasis model assessment insulin resistance higher than the 75 percentile.

Results: Compared to those in the highest tertile (≥14.3 ng/mL), the odds ratio (OR) for insulin resistance was 1.37 (95% confidence interval [CI], 1.01 to 1.86) for the 1st tertile (<9.7 ng/mL) and 1.19 (95% CI, 0.08 to 1.62) for the 2nd tertile (9.7 to 14.3 ng/mL) after adjusting for age, gender, waist circumference, alcohol consumption, smoking status, physical exercise, season, and cohort. After stratification of the subjects by adiposity, these associations remained only in non-obese subjects (lowest tertile vs. highest tertile, multivariable OR, 1.64; 95% CI, 1.05 to 2.56).

Conclusion: Serum 25(OH)D has an independent inverse association with insulin resistance in the healthy, non-obese Korean population, even among people with vitamin D insufficiency.

Keywords: Insulin resistance; Obesity; Vitamin D

INTRODUCTION

Vitamin D is not only a regulator of calcium-phosphorus metabolism, but it also influences the onset of diseases, including diabetes, cardiovascular disease, and cancer [1,2]. The association between vitamin D and glucose metabolism is particularly important. Some studies have reported that vitamin D insufficiency is more common in people with diabetes risk than people without such risk [3-5]. Other studies have linked lower 25-hydroxyvitamin D (25(OH)D) concentrations, a generally accepted indicator of vitamin D status, with insulin resistance and β-cell dysfunction in Western populations [4,6,7].

However, there are differences in vitamin D metabolism and nutritional status between ethnic groups [3,8-10]. Asian countries, including Korea, have a relatively high prevalence of vitamin D insufficiency compared to other countries [11-13].

However, few studies have examined the relationship between 25(OH)D concentration and insulin resistance in a healthy Asian population. In addition, previous studies suggested that this association may differ by obesity status [14,15].

In this cross-sectional study, we investigated the associations between 25(OH)D levels in serum and insulin resistance (represented by the homeostasis model assessment insulin resistance [HOMA-IR]) in the healthy Korean population.

METHODS

Study design and participants

This study was performed as part of the Cardiovascular and Metabolic Disease Etiologic Research Center (CMERC) study, which was undertaken beginning in 2013 to evaluate traditional risk factors, explore new biomarkers, clarify etiology, and suggest prevention strategies for cardiovascular and metabolic diseases.

The CMERC population is a multicenter prospective cohort, which consists of two community-based cohorts and one hospital-based cohort of people at high risk for cardiovascular diseases. The community-based cohorts included residents of urban and rural areas. Community-based cohort 1 was based in the Seoul, Goyang-si, Gimpo-si, and Ganghwa-gun; community-based cohort 2 was based in the Suwon-si, Yongin-si, and Hwaseong-si. We excluded persons who had been diagnosed with a malignancy within 2 years, were currently being treated, or had a history of myocardial infarction, stroke, or heart failure.

Anthropometric measurements and serum biochemistry profiles were made for 1,807 subjects, all of whom were included in this study. The level of serum 25(OH)D was 12.5 ng/mL (interquartile range [IQR], 9.8 to 16.1) in men and 11.1 ng/mL (IQR, 8.3 to 16.0) in women. No statistical difference was present ($P=0.481$), so we analyzed them together. The participants were divided into three categories based on 25(OH)D concentration: tertile 1 (<9.7 ng/mL), tertile 2 (9.7 to 14.3 ng/mL), and tertile 3 (≥14.3 ng/mL). The prevalence of high insulin resistance was compared among these three groups. In addition, participants were divided into normal and obese according to body mass index (BMI) and waist circumference. General obesity was defined as a BMI of 25 kg/m² or greater [16]. Abdominal obesity was defined as a waist circumference of 90 cm or greater for male and 85 cm or greater for female [17]. The odds ratios (ORs) of insulin resistance according to 25(OH)D

concentration were also compared among the groups.

This study was approved by the Institutional Review Boards of Severance Hospital at Yonsei University College of Medicine (IRB No. 4-2013-0661) and Ajou University Hospital (AJIRB-BMR-SUR-13-272), and informed consent was obtained from each participant.

Measurements

Information on subjects, including demographics, physical activities, and lifestyles were collected by face-to-face interviews. Trained researchers gathered all information using standardized questionnaires and protocols. All measurements were taken at the health-screening centers in Seoul and Suwon, South Korea.

Body weights and heights were measured using standardized techniques and equipment with participants who were wearing light indoor clothing without shoes (cohort 1, DS-102 Jenix, Seoul, Korea for height; BB-150 CAS, Seongnam, Korea for weight; cohort 2, BSM 330, Biospace, Seoul, Korea). BMI was calculated as weight divided by height squared (kg/m²). Waist circumference was measured over the midpoint between the lower border of the ribs and the iliac crest in a standing position using a plastic tapeline. Blood pressure was measured three times in the right arm using an electronic manometer (HEM-7080IC; Omron Healthcare Co. Ltd., Kyoto, Japan) after 5 minutes of rest in the sitting position, and the average of the final two measurements was used for the analysis.

Blood samples were obtained after a fasting period of at least 8 hours, and all laboratory tests were performed in a central laboratory (Seoul Clinical Laboratories, Seoul, Korea). Serum fasting glucose was measured using the colorimetric method using an autoanalyzer (ADVIA 1800 Auto Analyzer; Siemens Medical Solutions, Malvern, PA, USA). The insulin level in serum was measured using a radioimmunoassay (SR 300; STRATEC, Birkenfeld, Germany) and serum 25(OH)D concentration was measured using chemiluminescence immunoassay (CLIA) method (Liaison; DiaSorin, Dietzenbach, Germany). Insulin resistance was measured using the HOMA-IR: fasting insulin (μIU/mL)×fasting glucose (mg/dL)/405. In both men and women, high insulin resistance was defined as an HOMA-IR score higher than the 75th percentile [18].

Demographic characteristics including age, gender, smoking status, amount of alcohol consumption, physical exercise, and season of sampling (May to October, November to April) were collected by trained interviewers. Smoking status was di-

vided into three categories: never smokers (if the subjects had smoked <100 cigarettes), former smokers (≥100 cigarettes in one's lifetime but not currently a smoker), and current smokers (≥100 cigarettes and reported "currently smoking" in the questionnaire). Alcohol consumption (in g/day) was assessed by inquiring about the frequency and average amount drunk during the most recent year; this was calculated by multiplying the daily intake of each alcoholic beverage by its ethanol content. Physical exercise was measured using the International Physical Activity Questionnaire (IPAQ) and classified into three categories based on standard scoring criteria (http://www.ipaq.ki.se): low, moderate, and high. Season was defined using the date participants completed blood collection and was classified as follows: May to October, November to April.

Statistical analysis

Differences between continuous variables according to 25(OH)D concentration were evaluated by analysis of variance and Tukey *post hoc* analyses. Categorical variables were compared using chi-square tests. All data are presented as mean±standard deviation or medians with IQRs. Multivariable logistic regression was used to assess the independent association of 25(OH)D concentrations and high insulin resistance. We used three models with progressive degrees of adjustment. Model 1 was the unadjusted analysis. Model 2 adjusted for age and gender. Model 3 additionally adjusted for waist circumference, alcohol consumption, smoking status, physical exercise, season, and cohort (cohort 1 or cohort 2). The results are expressed as ORs and 95% confidence intervals (CIs). Furthermore, stratified analysis between the normal and obese groups was performed. All analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA). *P* values <0.05 were considered statistically significant.

RESULTS

Participant characteristics

This study comprised a total of 1,807 subjects with a mean age of 49.6±8.8 years. Among them, 1,179 (65.2%) were women, and 628 (34.8%) were men. The median concentration of 25(OH)D was 11.7 ng/mL (IQR, 8.8 to 16.0) and HOMA-IR was 1.7 (IQR, 1.4 to 2.2).

Table 1 indicates the characteristics of each group according to serum 25(OH)D. The BMI, waist circumference, fasting glucose, systolic blood pressure, and amount of alcohol con-

sumption did not differ significantly among groups (Table 1). However, the lowest tertile, with the lowest 25(OH)D levels (<9.7 ng/mL), represented a higher proportion of younger people and women, high fasting insulin level, and less frequent physical exercise compared to the other tertiles.

Associations between 25(OH)D concentration and insulin resistance

Insulin resistance was inversely associated with 25(OH)D concentrations (Table 2). Compared to those in the highest tertile, the ORs of those with high insulin resistance was 1.57 (95% CI, 1.21 to 2.04) in the lowest tertile and 1.31 (95% CI, 1.00 to 1.71) in the 2nd tertile (*P* for trend=0.001) in the unadjusted analysis (model 1). This pattern remained after adjustments. After adjusting for age, gender, waist circumference, alcohol intake, smoking status, physical exercise, season, and cohort, model 3 indicated higher ORs for high insulin resistance in the lowest tertile (OR, 1.37; 95% CI, 1.01 to 1.86) and middle tertile (OR, 1.19; 95% CI, 0.88 to 1.62) compared with the highest tertile (*P* for trend=0.042).

The results of the stratified analysis with general obesity by BMI and abdominal obesity by waist circumference are given in Table 3, Supplementary Table 1, Fig. 1. The results are based on the common reference group with serum 25(OH)D in the highest tertile and non-obese. Compared to the reference group, the risk of insulin resistance among subjects with general obesity (BMI ≥25 kg/m^2) and serum 25(OH)D in the lowest tertile was 1.95 times higher, and subjects with normal (BMI <25 kg/m^2) and serum 5(OH)D in the lowest tertile had about a 1.41-fold increase risk of insulin resistance. However, there was no difference in the results according to abdominal obesity (Fig. 1).

Table 3 shows the association between insulin resistance and 25(OH)D concentrations that remained in the non-general obesity group; however, there was no significant association in the general obesity group (lowest tertile vs. highest tertile; normal obesity [OR, 1.64; 95% CI, 1.05 to 2.56]; general obesity [OR, 0.97; 95% CI, 0.63 to 1.48]). After stratification by abdominal obesity, there was no significant association for each of the groups (lowest tertile vs. highest tertile; normal obesity [OR, 1.33; 95% CI, 0.92 to 1.93]; abdominal obesity [OR, 1.38; 95% CI, 0.81 to 2.37]).

DISCUSSION

We found that lower serum 25(OH)D concentrations are in-

Table 1. Characteristics of study participants: the CMERC study

Characteristic	Serum 25(OH)D, ng/mL			P value[a]
	Tertile 3 (≥14.3)	Tertile 2 (9.7–14.3)	Tertile 1 (<9.7)	
Number	611	595	601	
Age, yr	51.0±8.3	48.7±9.1	48.9±8.8	<0.001
Male sex	237 (38.8)	241 (40.5)	150 (25.0)	<0.001
BMI, kg/m²	23.9±2.8	24.3±3.1	24.2±3.2	0.102
Waist circumference, cm	80.2±8.2	81.2±9.2	80.1±9.2	0.055
SBP, mm Hg	117.4±13.9	118.6±14.8	117.2±15.1	0.188
Fasting glucose, mg/dL	89.0 (84.0–96.0)	89.0 (83.0–97.0)	88.0 (83.0–94.0)	0.583
Fasting insulin, μIU/mL	7.4 (6.1–8.9)	7.8 (6.5–9.7)	7.9 (6.4–10.2)	0.001
HOMA-IR, units	1.67 (1.33–2.10)	1.74 (1.40–2.25)	1.74 (1.35–2.35)	0.009
Alcohol consumption, g/day	0.5 (0.0–11.0)	1.1 (0.0–10.2)	0.0 (0.0–5.5)	0.317
Smoking status				<0.001
Never	407 (66.6)	398 (66.9)	455 (75.7)	
Former smoker	118 (19.3)	101 (17.0)	70 (11.7)	
Current smoker	86 (14.1)	96 (16.1)	76 (12.7)	
Physical exercise				<0.001
Low	219 (35.8)	243 (40.8)	288 (47.2)	
Moderate	244 (39.9)	238 (40.0)	216 (35.9)	
High	148 (24.2)	114 (19.2)	97 (16.1)	
Season				<0.001
May–October	188 (30.8)	118 (19.8)	70 (11.7)	
November–April	423 (69.2)	477 (80.2)	531 (88.4)	

Values are presented as mean±standard deviation, number (%), or median (interquartile range).
CMERC, Cardiovascular and Metabolic Disease Etiologic Research Center; 25(OH)D, 25-hydroxyvitamin D; BMI, body mass index; SBP, systolic blood pressure; HOMA-IR, homeostasis model assessment insulin resistance.
[a]P values were calculated using Tukey *post hoc* analysis for continuous variables and chi-square tests for categorical variables.

Table 2. OR of high insulin resistance (HOMA-IR >75 percentile) according to serum 25(OH)D levels

25(OH)D, ng/mL	Model 1[a]		Model 2[b]		Model 3[c]	
	OR (95% CI)	P for trend[d]	OR (95% CI)	P for trend[d]	OR (95% CI)	P for trend[d]
≥14.3	Reference	0.001	Reference	0.001	Reference	0.042
9.7 to <14.3	1.31 (1.00–1.71)		1.37 (1.04–1.80)		1.19 (0.88–1.62)	
<9.7	1.57 (1.21–2.04)		1.65 (1.26–2.16)		1.37 (1.01–1.86)	

HOMA-IR, homeostasis model assessment insulin resistance; 25(OH)D, 25-hydroxyvitamin D; OR, odds ratio; CI, confidence interval.
[a]Model 1 was the unadjusted model, [b]Model 2 adjusted for age and gender, [c]Model 3 adjusted for age, gender, waist circumference, alcohol consumption, smoking status, physical exercise, season, and cohorts, [d]P for trend indicates the comparison of prevalence of high insulin resistance according to serum 25(OH)D levels.

dependently associated with high insulin resistance even after adjustments. This inverse relationship is consistent with some previous epidemiologic studies [8-10]. A large cross-sectional study from the Third National Health and Nutrition Examination Survey revealed an inverse association between vitamin D status and insulin resistance in non-Hispanic white people and Mexican-Americans [10]. Similarly, studies on Asian populations have indicated that low circulating 25(OH)D levels are correlated with high fasting insulin levels and high HOMA-IR scores [8,9].

Table 3. OR of high insulin resistance (>75 percentile) according to serum 25(OH)D levels stratified by adiposity

25(OH)D, ng/mL	High insulin resistance	OR (95% CI)		
		Model 1[a]	Model 2[b]	Model 3[c]
General obesity				
Normal				
≥14.7	47 (12.2)	1.00 (reference)	1.00 (reference)	1.00 (reference)
9.8 to <14.7	50 (12.9)	1.07 (0.70–1.63)	1.18 (0.76–1.82)	1.20 (0.76–1.88)
<9.8	63 (16.7)	1.45 (0.96–2.18)	1.53 (1.01–2.32)	1.64 (1.05–2.56)
Obesity				
≥13.9	88 (39.8)	1.00 (reference)	1.00 (reference)	1.00 (reference)
9.6 to <13.9	99 (45.6)	1.27 (0.87–1.85)	1.25 (0.85–1.83)	1.04 (0.68–1.58)
<9.6	104 (47.7)	1.38 (0.94–2.01)	1.30 (0.88–1.91)	0.97 (0.63–1.48)
Abdominal obesity				
Normal				
≥14.6	71 (15.0)	1.00 (reference)	1.00 (reference)	1.00 (reference)
9.8 to <14.6	74 (15.9)	1.06 (0.75–1.52)	1.14 (0.80–1.63)	1.10 (0.76–1.60)
<9.8	90 (19.5)	1.37 (0.97–1.92)	1.42 (1.00–2.01)	1.33 (0.92–1.93)
Obesity				
≥13.8	63 (46.3)	1.00 (reference)	1.00 (reference)	1.00 (reference)
9.4 to <13.8	75 (54.7)	1.40 (0.87–2.26)	1.38 (0.86–2.24)	1.15 (0.68–1.94)
<9.4	78 (58.7)	1.64 (1.01–2.66)	1.57 (0.96–2.55)	1.38 (0.81–2.37)

Values are presented as number (%). General obesity was defined as a body mass index of 25 kg/m² or greater. Abdominal obesity was defined as a waist circumference of 90 cm or greater for men and 85 cm or greater for women.
OR, odds ratio; 25(OH)D, 25-hydroxyvitamin D; CI, confidence interval.
[a]Model 1 was the unadjusted model, [b]Model 2 adjusted for age and gender, [c]Model 3 adjusted for age, gender, waist circumference, alcohol consumption, smoking status, physical exercise, season, and cohort.
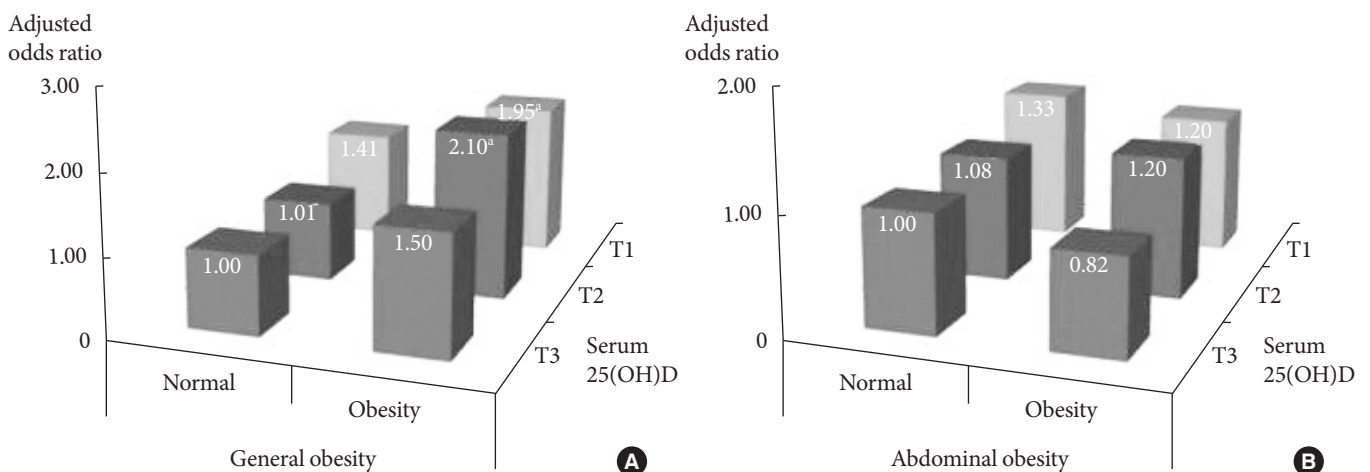

Fig. 1. Adjusted odds ratio of high insulin resistance (>75 percentile) by tertiles (T) of serum 25-hydroxyvitamin D (25(OH)D) and adiposity status. (A) General obesity was defined as a body mass index of 25 kg/m² or greater. (B) Abdominal obesity was defined as a waist circumference of 90 cm or greater for men and 85 cm or greater for women. Serum 25(OH)D was categorized into T. T1, first tertile; T2, second tertile; T3, third tertile. Model adjusted for age, gender, waist circumference, alcohol consumption, smoking status, physical exercise, season, and cohort. [a]P<0.05.

With regard to the Korean population, the Korean Genome Epidemiology Study (KoGES)-Kangwha study reported an inverse relationship between 25(OH)D concentrations and HOMA-IR score, but the association was no longer present after adjusting for sex, age, BMI, smoking status, alcohol intake, and regular exercise [19]. In contrast, in our study, the inverse associations remained after adjustments. However, the KoGES-Kangwha study population consisted of 807 rural subjects aged 40 to 89 years old, and the authors found that 25(OH)D concentrations were much higher than those in both our study and another study based on the Korea National Health and Nutrition Examination Survey (KNHANES IV) [13]. Therefore, the differences in results between the KoGES-Kangwha study and our study might be attributable to differences in 25(OH)D levels.

No significant difference of serum 25(OH)D levels based on gender was present in this study. Although several studies showed serum 25(OH)D levels were higher in males than in females [13,20], other studies showed no difference [21] and even higher serum 25(OH)D levels in females [22]. Statistical adjustment for gender was made as well, with the result that younger people showed much lower serum 25(OH)D levels, which is consistent with other studies [21,23]. This might be the result of their higher indoor activity, lower physical activity, and lower vitamin D supplement intake.

Most previous studies on vitamin D levels and insulin resistance have focused on the categories of vitamin D deficiency (<20 ng/mL), insufficiency (20 to 30 ng/mL), and sufficiency (≥30 ng/mL). However, the KNHANES IV reported that the prevalence of vitamin D insufficiency was very high, impacting more than 60% of Korean adults [13]. Therefore, additional categories of vitamin D deficiency or insufficiency are needed in Korea. We divided subjects based on 25(OH)D concentration, using cutoff points of 9.7 and 14.3 ng/mL, both lower than the level currently defined as vitamin D deficiency (20 ng/mL or 50 nmol/L). To the best of our knowledge, this is the first study to have evaluated the association between subdivisions of vitamin D deficiency and insulin resistance. Similar negative associations were observed between vitamin D levels and insulin resistance in the vitamin D deficiency subdivisions.

Stratified analyses indicated that the association between 25(OH)D levels and insulin resistance is not amplified by abdominal obesity, although it is amplified by general obesity. This result is not consistent with previous studies, which found that abdominal obesity is more strongly associated with insulin resistance than general obesity [24]. Kang et al. [25] reported results that were similar to our study, finding a stronger association between 25(OH)D and insulin resistance when stratified by BMI than when stratified by abdominal obesity. They insisted that BMI is more reflective of subcutaneous fat than waist circumference. Also, previous studies have shown that 25(OH)D and obesity may have a synergistic effect on insulin resistance risk [14]. However, our study showed that the association of 25(OH)D levels with insulin resistance was only present in the normal obesity group. Although the storage of 25(OH)D in fat tissues can cause lower bioavailable vitamin D, obesity may be a greater effect than 25(OH)D because obesity is an established risk factor of insulin resistance [26]. So, the relation of 25(OH)D levels with insulin resistance was only significant in the normal obesity group, not in the obesity group.

Vitamin D is a multifunctional hormone that is essential to many important functions, ranging from calcium and phosphorus homeostasis to glucose regulation [1,2]. Although previous studies have reported that vitamin D deficiency is associated with insulin resistance, the mechanism of this association has not fully been explained. One potential mechanism is that vitamin D may have a direct effect on insulin sensitivity through stimulation of insulin receptor expression, together with improved insulin-dependent glucose transport [27,28]. Another potential mechanism is that vitamin D suppresses chronic inflammation, which is associated with obesity and insulin resistance [28]. Vitamin D has anti-inflammatory actions. It dose-dependently suppresses the release of tumor necrosis factor-α and interleukin 6 (IL-6) [29,30], while upregulating the synthesis of the anti-inflammatory cytokine IL-10, thus potentially partly counteracting the inflammatory consequences of increased adiposity [28].

Strengths of this study were the large sample size and the coverage of both rural and urban areas. Thus, our study population may be representative of the Korean general population. In addition, we included many potential confounders (age, gender, BMI, waist circumference, smoking, alcohol consumption, physical activity, and season) that could affect glucose and vitamin D metabolism, and the final results were obtained after adjusting for these confounding factors. However, this study also had some limitations. First, the blood samples were not collected during the same season. So, we adjusted for season (May to October, November to April) to ob-

tain more precise results. Second, data on sunscreen use, sun exposure time, diet pattern, and calcium or vitamin D supplement use were not collected. Third, this study cannot establish causality between 25(OH)D concentrations and insulin resistance due to the cross-sectional design. Finally, there is a possibility that unmeasured confounding factors, such as calcium and parathyroid hormone levels, might have influenced the results.

In conclusion, our study shows that 25(OH)D concentrations in serum have a substantial inverse association with insulin resistance. These results suggest that vitamin D is independently associated with insulin resistance in the healthy, non-obese Korean population.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGMENTS

REFERENCES

1. Lappe JM, Travers-Gustafson D, Davies KM, Recker RR, Heaney RP. Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. Am J Clin Nutr 2007; 85:1586-91.

2. Wang TJ, Pencina MJ, Booth SL, Jacques PF, Ingelsson E, Lanier K, Benjamin EJ, D'Agostino RB, Wolf M, Vasan RS. Vitamin D deficiency and risk of cardiovascular disease. Circulation 2008;117:503-11.

3. Boucher BJ, Mannan N, Noonan K, Hales CN, Evans SJ. Glucose intolerance and impairment of insulin secretion in relation to vitamin D deficiency in east London Asians. Diabetologia 1995;38:1239-45.

4. Chiu KC, Chu A, Go VL, Saad MF. Hypovitaminosis D is associated with insulin resistance and beta cell dysfunction. Am J Clin Nutr 2004;79:820-5.

5. Mattila C, Knekt P, Mannisto S, Rissanen H, Laaksonen MA, Montonen J, Reunanen A. Serum 25-hydroxyvitamin D concentration and subsequent risk of type 2 diabetes. Diabetes Care 2007;30:2569-70.

6. Badawi A, Sayegh S, Sadoun E, Al-Thani M, Arora P, Haddad PS. Relationship between insulin resistance and plasma vitamin D in adults. Diabetes Metab Syndr Obes 2014;7:297-303.

7. Liu E, Meigs JB, Pittas AG, McKeown NM, Economos CD, Booth SL, Jacques PF. Plasma 25-hydroxyvitamin d is associated with markers of the insulin resistant phenotype in nondiabetic adults. J Nutr 2009;139:329-34.

8. Lu L, Yu Z, Pan A, Hu FB, Franco OH, Li H, Li X, Yang X, Chen Y, Lin X. Plasma 25-hydroxyvitamin D concentration and metabolic syndrome among middle-aged and elderly Chinese individuals. Diabetes Care 2009;32:1278-83.

9. Pham NM, Akter S, Kurotani K, Nanri A, Sato M, Hayabuchi H, Yasuda K, Mizoue T. Serum 25-hydroxyvitamin D and markers of insulin resistance in a Japanese working population. Eur J Clin Nutr 2012;66:1323-8.

10. Scragg R, Sowers M, Bell C; Third National Health and Nutrition Examination Survey. Serum 25-hydroxyvitamin D, diabetes, and ethnicity in the Third National Health and Nutrition Examination Survey. Diabetes Care 2004;27:2813-8.

11. Lim SK, Kung AW, Sompongse S, Soontrapa S, Tsai KS. Vitamin D inadequacy in postmenopausal women in Eastern Asia. Curr Med Res Opin 2008;24:99-106.

12. Mithal A, Wahl DA, Bonjour JP, Burckhardt P, Dawson-Hughes B, Eisman JA, El-Hajj Fuleihan G, Josse RG, Lips P, Morales-Torres J; IOF Committee of Scientific Advisors (CSA) Nutrition Working Group. Global vitamin D status and determinants of hypovitaminosis D. Osteoporos Int 2009;20: 1807-20.

13. Rhee SY, Hwang YC, Chung HY, Woo JT. Vitamin D and diabetes in Koreans: analyses based on the Fourth Korea National Health and Nutrition Examination Survey (KNHANES), 2008-2009. Diabet Med 2012;29:1003-10.

14. Kabadi SM, Lee BK, Liu L. Joint effects of obesity and vitamin D insufficiency on insulin resistance and type 2 diabetes: results from the NHANES 2001-2006. Diabetes Care 2012;35: 2048-54.

15. Earthman CP, Beckman LM, Masodkar K, Sibley SD. The link between obesity and low circulating 25-hydroxyvitamin D concentrations: considerations and implications. Int J Obes (Lond) 2012;36:387-96.

16. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 2004;363:157-63.

17. Lee S, Park HS, Kim SM, Kwon HS, Kim DY, Kim DJ, Cho GJ, Han JH, Kim SR, Park CY, Oh SJ, Lee CB, Kim KS, Oh SW, Kim YS, Choi WH, Yoo HJ. Cut-off points of waist circumference for defining abdominal obesity in the Korean population. Korean J Obes 2006;15:1-9.

18. Li C, Ford ES, Zhao G, Mokdad AH. Prevalence of pre-diabetes and its association with clustering of cardiometabolic risk factors and hyperinsulinemia among U.S. adolescents: National Health and Nutrition Examination Survey 2005-2006. Diabetes Care 2009;32:342-7.

19. Song BM, Kim HC, Choi DP, Oh SM, Suh I. Association between serum 25-hydroxyvitamin D level and insulin resistance in a rural population. Yonsei Med J 2014;55:1036-41.

20. Choi HS, Oh HJ, Choi H, Choi WH, Kim JG, Kim KM, Kim KJ, Rhee Y, Lim SK. Vitamin D insufficiency in Korea: a greater threat to younger generation: the Korea National Health and Nutrition Examination Survey (KNHANES) 2008. J Clin Endocrinol Metab 2011;96:643-51.

21. Hintzpeter B, Mensink GB, Thierfelder W, Muller MJ, Scheidt-Nave C. Vitamin D status and health correlates among German adults. Eur J Clin Nutr 2008;62:1079-89.

22. Hagenau T, Vest R, Gissel TN, Poulsen CS, Erlandsen M, Mosekilde L, Vestergaard P. Global vitamin D levels in relation to age, gender, skin pigmentation and latitude: an ecologic meta-regression analysis. Osteoporos Int 2009;20:133-40.

23. Rhee EJ, Kim MK, Park SE, Park CY, Baek KH, Lee WY, Kang MI, Park SW, Kim SW, Oh KW. High serum vitamin D levels reduce the risk for nonalcoholic fatty liver disease in healthy men independent of metabolic syndrome. Endocr J 2013;60:743-52.

24. Westphal SA. Obesity, abdominal obesity, and insulin resistance. Clin Cornerstone 2008;9:23-9.

25. Kang JH, Kim SS, Moon SS, Kim WJ, Bae MJ, Choi BG, Jeon YK, Kim BH, Kim YK, Kim IJ. Adiposity in the relationship between serum vitamin D level and insulin resistance in middle-aged and elderly Korean adults: the Korea National Health and Nutrition Examination Survey 2008. Endocrinol Metab (Seoul) 2013;28:96-102.

26. Pittas AG, Lau J, Hu FB, Dawson-Hughes B. The role of vitamin D and calcium in type 2 diabetes. A systematic review and meta-analysis. J Clin Endocrinol Metab 2007;92:2017-29.

27. Tai K, Need AG, Horowitz M, Chapman IM. Vitamin D, glucose, insulin, and insulin sensitivity. Nutrition 2008;24:279-85.

28. von Hurst PR, Stonehouse W, Coad J. Vitamin D supplementation reduces insulin resistance in South Asian women living in New Zealand who are insulin resistant and vitamin D deficient: a randomised, placebo-controlled trial. Br J Nutr 2010;103:549-55.

29. Muller K, Haahr PM, Diamant M, Rieneck K, Kharazmi A, Bendtzen K. 1,25-Dihydroxyvitamin D3 inhibits cytokine production by human blood monocytes at the post-transcriptional level. Cytokine 1992;4:506-12.

30. Schleithoff SS, Zittermann A, Tenderich G, Berthold HK, Stehle P, Koerfer R. Vitamin D supplementation improves cytokine profiles in patients with congestive heart failure: a double-blind, randomized, placebo-controlled trial. Am J Clin Nutr 2006;83:754-9.