

Low Serum Vitamin D Is Associated with High Risk of Diabetes in Korean Adults^{1,2}

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Abstract

Vitamin D may play a role in glucose metabolism. A low vitamin D level has been associated with increased risk of diabetes mellitus, but the association has not been confirmed in Asians. Our objective was to examine the association of serum 25-hydroxyvitamin D [25(OH)D] levels with insulin resistance and diabetes mellitus in Korean adults based on a large population-based survey. Cross-sectional analyses were carried out on 5787 Korean adults (2453 men and 3334 women) who were 20 y or older and participated in the Fourth Korea NHANES conducted in 2008. Diabetes mellitus was defined as fasting plasma glucose ≥ 7 mmol/L or current use of oral hypoglycemic agents or insulin. Insulin resistance was estimated by homeostatic model assessment for insulin resistance (HOMA-IR) and quantitative insulin sensitivity check index (QUICKI). Compared to individuals with a sufficient serum 25(OH)D concentration ≥ 75 nmol/L, the OR (95% CI) for diabetes mellitus were 1.73 (1.09–2.74), 1.30 (0.91–1.84), and 1.40 (0.99–1.98) for serum 25(OH)D concentrations < 25 , 25 to < 50 , and 50 to < 75 nmol/L, respectively, after multiple adjustments (P -trend < 0.0001). Furthermore, the serum 25(OH)D level was inversely associated with HOMA-IR ($\beta = -0.061$; $P = 0.001$) and positively associated with QUICKI ($\beta = 0.059$; $P = 0.001$) in overweight or obese participants. In conclusion, a low serum vitamin D concentration is associated with a high risk of diabetes mellitus in Korean adults and the concentration is inversely associated with insulin resistance in those who are overweight or obese. *J. Nutr.* 141: 1524–1528, 2011.

Introduction

A traditional role of vitamin D is promoting calcium and phosphate absorption in the intestine. It maintains adequate concentrations of calcium and phosphate in the circulation and enables normal mineralization of bone by providing these minerals to bone-forming sites. Accordingly, vitamin D deficiency is closely associated with metabolic bone diseases such as rickets in children and osteomalacia in adults. Recently, the nonskeletal actions of vitamin D are also drawing interest, as it was discovered that most cells and tissues throughout the body have the receptors for vitamin D and some of them also have the enzyme 25-hydroxyvitamin D [25(OH)D]⁹-1 α -hydroxylase, which converts the primary form of vitamin D to an active form (1–3).

One of the nonskeletal actions under active investigation is a role of vitamin D in glucose metabolism (4). Animal and in vitro studies have provided evidence that vitamin D may play a role in glucose homeostasis through its effects on insulin secretion and insulin sensitivity (5–10). Previous observational studies have reported an inverse association between vitamin D status and risk of diabetes mellitus (11–14), although some others could not find such an association (15,16). The discrepancy may be attributed to ethnic variation. Scragg et al. (11) reported that the serum level of 25(OH)D was inversely associated with insulin resistance and diabetes risk in non-Hispanic whites and Mexican Americans, but not in non-Hispanic blacks. In Arab Americans, a low 25(OH)D level was associated with insulin resistance and glucose intolerance only in men (13). In addition, serum 25(OH)D was not associated with insulin resistance or β cell function in Canadian Cree (16). However, little is known about whether the association also exists in the Asian population.

Thus, we examined the association between the serum 25(OH)D level and the prevalence of diabetes mellitus and insulin resistance estimated by the homeostatic model assessment for insulin resistance (HOMA-IR) and quantitative insulin sensitivity check index (QUICKI) in Korean adults based on a large population-based survey.

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⁹ Abbreviations used: HOMA-IR, homeostatic model assessment for insulin resistance; KNHANES, Korea NHANES; 25(OH)D, 25-hydroxyvitamin D; QUICKI, quantitative insulin sensitivity check index.

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Research Design and Methods

Study population. We conducted a cross-sectional study based on the data acquired in the second year (2008) of the Fourth Korea NHANES (KNHANES IV), which was conducted from 2007 to 2009. The KNHANES has been periodically conducted since 1998 to assess the health and nutritional status of the civilian, noninstitutionalized population of Korea by the Division of Chronic Disease Surveillance under the Korea Centers for Disease Control and Prevention. The survey consists of a health interview, a nutrition survey, and a health examination. The survey data were collected via household interviews and by direct standardized physical examinations conducted in specially equipped mobile examination centers. The sampling frame was based on the 2005 population and housing census of Korea. A stratified, multistage probability sampling design was used for the selection of household units. In the second year (2008) of the KNHANES IV, there were 264,186 primary sampling units, each of which contained ~60 households. Two hundred units were randomly selected from the primary sampling units and then 23 households from each unit were sampled using a systemic sampling method. Finally, 12,528 individuals in 4600 households were sampled. Among them, 9308 participated in health interviews and health examination surveys and 8641 in nutrition surveys. Among adults who participated in the survey between February and December 2008, 5902 participants (2502 men and 3400 women) aged 20 y or older were tested for fasting glucose, TG, total and HDL cholesterol, insulin, and 25(OH)D levels. Demographic, anthropometric, and behavioral characteristics were also measured. After excluding those who had missing values for analysis, a total of 5787 individuals (2453 men and 3334 women) were eligible for the present analysis. All participants in this survey signed an informed consent form. Diabetes mellitus was defined as fasting glucose ≥ 7 mmol/L or current use of oral hypoglycemic agents or insulin for glucose control. Insulin resistance was indirectly estimated by HOMA-IR and QUICKI (17). The BMI cutoff values for overweight and obesity were 23 and 25 kg/m², respectively, as proposed by the WHO Western Pacific Region (18). The institutional review board of the Korea Centers for Disease Control and Prevention approved the study protocol.

Laboratory methods. For measurements of serum 25(OH)D levels, blood samples of the participants were collected during the survey. Blood samples were properly processed, immediately refrigerated, and transported in cold storage to the Central Testing Institute in Seoul, Korea. Blood samples were analyzed within 24 h after transportation. Serum 25(OH)D levels were measured using a gamma counter (1470 Wizard, Perkin Elmer) with a RIA (DiaSorin). Insulin levels were determined using a gamma counter (1470 Wizard, Perkin Elmer) with an immunoradiometric assay (Biosource). The plasma glucose, total cholesterol, TG, and HDL cholesterol levels were measured using Hitachi Automatic Analyzer 7600 by enzymatic methods using commercially available kits, Pureauto S GLU, Pureauto SCHO-N, Pureauto S TG-N, and CHOLESTEST N HDL, respectively (Daiichi Pure Chemicals).

Statistical analyses. Statistical analyses were carried out using SAS V9.1 (SAS Institute). Demographic characteristics were analyzed according to their serum 25(OH)D levels: <25, 25 to <50, 50 to <75, and ≥ 75 nmol/L. For continuous variables, ANCOVA was used to adjust for age and sex. The Cochran-Armitage test for linear trend of serum 25(OH)D was used in

categorical data analysis. A general linear model using contrast coefficients for linear trend analysis was used in continuous data analysis. A multiple logistic regression model was used to evaluate the OR and 95% CI of having diabetes for each group of serum 25(OH)D levels compared to those with 25(OH)D levels ≥ 75 nmol/L. A multiple linear regression model was used to clarify the relationships between the response variables and serum 25(OH)D. Natural logarithmic transformation was used for skewed variables. Variables for adjustments included age (continuous), sex (men or women), season (spring, summer, fall, or winter), current smoking (yes or no), alcohol drinking (yes or no), regular walking (yes or no), regular exercise (yes or no), region (urban or rural), BMI (continuous), and waist circumference (continuous). Alcohol drinking was indicated as "yes" for participants who consumed at least one glass of alcohol every month over the last 1 y. Regular walking was indicated as "yes" for participants who walked for >30 min at a time and >5 times/wk regardless of indoor or outdoor walking. Regular exercise was indicated as "yes" for participants who exercised on a regular basis regardless of indoor or outdoor exercise (for >30 min at a time and >5 times/wk in the case of moderate exercise, such as swimming slowly, doubles tennis, volleyball, badminton, table tennis, and carrying light objects; and for >20 min at a time and >3 times/wk in the case of vigorous exercise, such as running, climbing, cycling fast, swimming fast, football, basketball, jump rope, squash, singles tennis, and carrying heavy objects). Region was categorized as urban and rural. Among the 16 administrative districts where this survey was conducted, Seoul (the capital city of South Korea) and the surrounding metropolitan area (Gyeonggi) and 6 other metropolitan cities (Busan, Daegu, Incheon, Gwangju, Daejeon, and Ulsan) were grouped as urban areas. The remaining regions (Gangwon, Chungbuk, Chungnam, Jeonbuk, Jeonnam, Gyeongbuk, Gyeongnam, and Jeju) were grouped as rural areas. All statistical tests were 2-sided and the level of significance was 0.05. Values in the text are mean \pm SD.

Results

The age of participants was 48.5 ± 15.9 y in men and 49.1 ± 16.5 y in women. BMI was 23.9 ± 3.1 kg/m² in men and 23.4 ± 3.4 kg/m² in women. Participants with <25 nmol/L of serum 25(OH)D accounted for 7.9% of the study population, 25 to <50 nmol/L for 48.2%, 50 to <75 nmol/L for 33.8%, and ≥ 75 nmol/L for 10.2%. The prevalence of diabetes mellitus in this study was 9.3% in men and 8.3% in women. After adjusting for age and sex, serum 25(OH)D level was inversely associated with fasting glucose, fasting insulin, and HOMA-IR and positively associated with QUICKI, HDL cholesterol, and total cholesterol (Table 1).

Association between serum 25(OH)D levels and diabetes mellitus. After adjusting for age, sex, and season (model 1), the risk of having diabetes mellitus was higher in participants with low serum 25(OH)D levels (<75 nmol/L) compared with those with a sufficient serum 25(OH)D concentration ≥ 75 nmol/L (P -trend < 0.0001) (Table 2). After further adjustment for additional confounders (models 2 and 3), an increasing risk of diabetes mellitus remained associated with decreasing serum 25(OH)D level (P -trend < 0.0001) (Table 2).

Association between serum 25(OH)D levels and insulin resistance. The relationship between serum 25(OH)D level and fasting glucose, fasting insulin, HOMA-IR, QUICKI, and lipid

TABLE 1 Characteristics of study participants by serum 25-hydroxyvitamin D [25(OH)D] concentrations¹

	Serum 25(OH)D, nmol/L				P-trend
	<25	25 to <50	50 to <75	≥75	
<i>n</i>	455	2790	1954	588	—
Age, <i>y</i>	47.7 ± 0.9	46.5 ± 0.3	50.5 ± 0.4	55.3 ± 0.6	<0.0001 ²
Men	111 (24.4)	995 (35.7)	994 (50.9)	353 (60.0)	<0.0001 ³
Urban residents	349 (76.7)	1918 (68.7)	1105 (56.6)	261 (44.4)	<0.0001 ³
Season of study participation					
Summer	62 (13.6)	693 (24.8)	730 (37.4)	263 (44.7)	<0.0001 ³
Fall	55 (12.1)	658 (23.6)	700 (35.8)	235 (40.0)	
Winter	92 (20.2)	529 (19.0)	196 (10.0)	34 (5.8)	
Spring	246 (54.1)	910 (32.6)	328 (16.8)	56 (9.5)	
Current smoker					
Men	58/111 (52.3)	477/995 (47.9)	407/994 (40.9)	158/353 (44.8)	0.0132 ³
Women	27/344 (7.8)	119/1795 (6.6)	42/960 (4.4)	14/235 (6.0)	0.0280 ³
Alcohol consumer ⁴					
Men	74/111 (66.7)	713/995 (71.7)	748/994 (75.3)	272/353 (77.1)	0.0052 ³
Women	111/344 (32.3)	715/1795 (39.8)	388/960 (40.4)	75/235 (31.9)	0.74 ³
Regular walking ⁵	182 (40.0)	1295 (46.1)	986 (50.5)	337 (57.3)	<0.0001 ³
Regular exercise ⁶	80 (17.6)	679 (24.3)	602 (30.8)	223 (37.9)	<0.0001 ³
Diabetes mellitus	50 (11.0)	219 (7.8)	190 (9.7)	47 (8.0)	0.96 ³
BMI, ⁷ kg/m ²	23.3 ± 0.2	23.6 ± 0.1	23.7 ± 0.1	23.1 ± 0.1	0.68 ²
Waist circumference, ⁷ cm	80.4 ± 0.4	81.5 ± 0.2	82.2 ± 0.2	80.7 ± 0.4	0.37 ²
Systolic blood pressure, ⁷ mm Hg	115 ± 1	116 ± 0	115 ± 0	115 ± 1	0.77 ²
Diastolic blood pressure, ⁷ mm Hg	74 ± 0	75 ± 0	74 ± 0	74 ± 0	0.23 ²
Fasting plasma glucose, ⁷ mmol/L	5.50 ± 0.06	5.49 ± 0.02	5.43 ± 0.03	5.30 ± 0.05	0.0093 ²
Fasting serum insulin, ⁷ pmol/L	70.2 ± 1.7	68.0 ± 0.7	64.1 ± 0.8	62.5 ± 1.5	<0.0001 ²
HOMA-IR ⁷	2.55 ± 0.08	2.46 ± 0.03	2.28 ± 0.04	2.13 ± 0.07	<0.0001 ²
QUICKI ⁷	0.148 ± 0	0.149 ± 0	0.150 ± 0	0.150 ± 0	0.0002 ²
Serum TG, ⁷ mmol/L	1.45 ± 0.06	1.58 ± 0.02	1.49 ± 0.03	1.39 ± 0.05	0.27 ²
Serum HDL cholesterol, ⁷ mmol/L	1.31 ± 0.01	1.34 ± 0.01	1.35 ± 0.01	1.38 ± 0.01	0.0002 ²
Serum total cholesterol, ⁷ mmol/L	4.69 ± 0.04	4.86 ± 0.02	4.87 ± 0.02	4.86 ± 0.04	0.0028 ²

¹ Data are means ± SE or *n* (%).

² P-trend was derived from a general linear model using contrast coefficients for linear trend analysis.

³ P-trend was derived from the Cochran-Armitage trend test.

⁴ Alcohol drinking was indicated as "yes" for participants who consumed at least one glass of alcohol every month over the last 1 y.

⁵ Regular walking was indicated as "yes" for participants who walked for more than 30 min at a time and more than 5 times/wk.

⁶ Regular exercise was indicated as "yes" for participants who exercised on a regular basis (for more than 30 min at a time and more than 5 times/wk in the case of moderate exercise and for more than 20 min at a time and more than 3 times/wk in the case of vigorous exercise).

⁷ ANCOVA was used to adjust for age and sex.

concentrations after excluding participants currently using oral hypoglycemic agents or insulin are presented (Table 3). In multivariate regression analyses, including potential confounders, serum 25(OH)D was inversely associated with fasting insulin and HOMA-IR and positively associated with QUICKI, HDL cholesterol, and total cholesterol (Table 3). There was a modifying effect of BMI (<23 or ≥23 kg/m²) on the association

between serum 25(OH)D level and insulin resistance (P-interaction = 0.022 and 0.038 for HOMA-IR and QUICKI, respectively). In stratified analyses, serum 25(OH)D was inversely associated with HOMA-IR and positively associated with QUICKI in overweight and obese participants with BMI ≥23 kg/m², but not in those with BMI <23 kg/m², after multiple adjustments (Table 3).

TABLE 2 Adjusted OR (95% CI) of Korean adults having diabetes by serum 25-hydroxyvitamin D [25(OH)D] concentrations

	Serum 25(OH)D, nmol/L				P-trend ¹
	<25	25 to <50	50 to <75	≥75	
Cases/participants, <i>n/n</i> (%)	50/455 (11.0)	219/2790 (7.8)	190/1954 (9.7)	47/588 (8.0)	
Model 1 ²	1.91 (1.23–2.97)	1.44 (1.03–2.03)	1.55 (1.10–2.18)	1.00 (ref)	<0.0001
Model 2 ³	1.70 (1.09–2.67)	1.34 (0.95–1.90)	1.51 (1.07–2.13)	1.00 (ref)	<0.0001
Model 3 ⁴	1.73 (1.09–2.74)	1.30 (0.91–1.84)	1.40 (0.99–1.98)	1.00 (ref)	<0.0001

¹ The P-trend estimate is the asymptotic Cochran-Armitage trend test in logistic regression. The serum 25(OH)D level was treated as a continuous variable.

² Model 1: adjusted for age (continuous), sex (men or women), and season (spring, summer, fall, or winter).

³ Model 2: adjusted as in model 1 plus current smoking (yes or no), alcohol drinking (yes or no), regular walking (yes or no), and region (urban or rural).

⁴ Model 3: adjusted as in model 2 plus BMI (continuous) and waist circumference (continuous).

TABLE 3 Adjusted regression coefficients of 25-hydroxyvitamin D [25(OH)D] with fasting glucose, insulin, HOMA-IR, QUICK, and lipid concentrations in Korean adults

	Model 1 ¹		Model 2 ²		Model 3 ³	
	Standardized β	P	Standardized β	P	Standardized β	P
All (<i>n</i> = 5462) ⁴						
Fasting glucose	-0.002	0.88	0.001	0.97	-0.002	0.90
Fasting insulin ⁵	-0.066	<0.0001	-0.044	0.002	-0.048	0.0001
HOMA-IR ⁵	-0.057	<0.0001	-0.037	0.012	-0.041	0.002
QUICKI ⁵	0.055	0.0001	0.034	0.020	0.038	0.003
TG ⁵	-0.026	0.05	-0.019	0.17	-0.022	0.09
HDL cholesterol	0.041	0.003	0.031	0.026	0.033	0.014
Total cholesterol	0.028	0.041	0.036	0.012	0.034	0.015
BMI <23 (<i>n</i> = 2494) ⁴						
HOMA-IR ⁵	-0.032	0.14	-0.009	0.68	-0.013	0.53
QUICKI ⁵	0.029	0.17	0.006	0.77	0.011	0.61
BMI \geq 23 (<i>n</i> = 2968) ⁴						
HOMA-IR ⁵	-0.086	<0.0001	-0.063	0.001	-0.061	0.001
QUICKI ⁵	0.084	<0.0001	0.061	0.002	0.059	0.001

¹ Model 1: adjusted for age (continuous), sex (men or women), and season (spring, summer, fall, or winter).

² Model 2: adjusted as in model 1 plus current smoking (yes or no), alcohol drinking (yes or no), regular walking (yes or no), regular exercise (yes or no), and region (urban or rural).

³ Model 3: adjusted as in model 2 plus BMI (continuous) and waist circumference (continuous).

⁴ Excluding those currently using oral hypoglycemic agents or insulin.

⁵ Log transformations.

Discussion

In this study, we demonstrated that low vitamin D status was associated with an increased risk of diabetes mellitus in Korean adults. Although several observational studies have reported an inverse association between vitamin D level and the risk of diabetes mellitus (11–14), few studies reported such an association in the Asian population. Regarding the association between vitamin D level and the risk of metabolic syndrome in Asians, Lu et al. (19) reported that a low serum 25(OH)D level is significantly associated with a high risk of metabolic syndrome in Chinese people between 50 and 70 y of age. They also noted that serum 25(OH)D level was inversely associated with insulin resistance in overweight and obese Chinese people (BMI \geq 24 kg/m²), but not in their normal-weight counterparts, which is consistent with our results. Although there is no clear explanation for this discrepancy in the associations depending on BMI in the Asian population, vitamin D may play a more important role in glucose homeostasis in overweight and obese individuals who already have some degree of insulin resistance.

Potential mechanisms for the effects of vitamin D on glucose homeostasis have been suggested based on the findings from animal and in vitro studies (4–10). It appears that vitamin D may play a role in both insulin secretion and insulin resistance. It was shown that vitamin D receptors are present on pancreatic β -cells (5) and skeletal muscle (6), and the activating enzyme, 25(OH)D-1 α -hydroxylase, is expressed in pancreatic β -cells (7). Vitamin D may directly induce insulin secretion by binding to vitamin D receptors on β -cells, or it may indirectly affect β -cell function by regulating extracellular calcium level and calcium flux through β -cells (4). Vitamin D stimulates the expression of insulin receptor and enhances insulin responsiveness for glucose transport in cells (8). It also indirectly affects insulin sensitivity in tissues such as skeletal muscle and fat by regulating extracellular calcium level and ensuring adequate intracellular cytosolic calcium pool, which is essential for insulin-mediated intracellular processes (4).

There is still no definite consensus on optimal serum levels of 25(OH)D. Estimates of the optimal serum 25(OH)D level,

which has been defined as the concentration that maximally suppresses serum parathyroid hormone, widely vary from 20 to 110 nmol/L (20). Bischoff-Ferrari et al. (20) reviewed evidence from studies that evaluated thresholds for serum 25(OH)D levels in relation to skeletal and nonskeletal outcomes, including bone mineral density, fractures, dental health, risk of falls, lower extremity function, and colorectal cancer. For all endpoints, they found that the most advantageous serum levels of 25(OH)D begin at 75 nmol/L and the optimal level ranged between 90 and 100 nmol/L. Based on these findings, they recommended that the vitamin D intake for adults should be \geq 1000 IU/d (to convert IU of vitamin D to mg, divide by 40,000). However, a recent report by the Institute of Medicine suggested that a serum 25(OH)D level of 50 nmol/L is sufficient to ensure bone health and set the recommended dietary allowances of vitamin D at 600 IU/d for everyone aged 1–70 y and 800 IU/d for adults age 71 y and older (21), as it caused a controversy over the optimal serum 25(OH)D level and adequate vitamin D intake. Meanwhile, an optimal vitamin D level should also be determined based on health outcomes other than bone health, such as diabetes mellitus and cardiovascular diseases, considering various potential effects of vitamin D on health. In the present study, the risk of having diabetes mellitus was higher in participants with low serum 25(OH)D levels compared with those with a sufficient serum 25(OH)D concentration \geq 75 nmol/L. There should be more studies to estimate optimal serum 25(OH)D concentrations in various health outcomes.

As we previously reported (22), vitamin D insufficiency, which is defined as a serum 25(OH)D level <50 nmol/L, is very common in Koreans (47.3% of men and 64.5% of women). With a serum 25(OH)D level of 75 nmol/L as the threshold, the prevalence of vitamin D insufficiency rises to 86.8% in men and 93.3% in women. Meanwhile, diabetes mellitus and impaired fasting glucose have become very common conditions in Korea. In 2005, the prevalence of diabetes mellitus and impaired fasting glucose was estimated at 9.1 and 17.4%, respectively (23). Although the high prevalence of such conditions are mainly attributed to increasing obesity and other environmental factors

such as unhealthy dietary habits and inactivity, vitamin D insufficiency may also partly explain this phenomenon in Korea, considering the possible role of vitamin D in glucose homeostasis.

The major strength of our study is that we included a large number of Koreans aged 20 y or older from all administrative areas of South Korea. To our knowledge, this is the first study that demonstrated the association between a low serum level of 25(OH)D and a high risk of having diabetes mellitus in the Asian population. The present study has some limitations. First, because it is a cross-sectional observation study, the association found in this study is not proof of a causal relationship and might be confounded by many unmeasured and unaccounted-for variables even after multiple adjustments. Previously, only a few intervention studies have shown that vitamin D supplementation can improve insulin secretion or sensitivity (24–26). We suggest a well-designed, randomized, controlled trial with a primary endpoint of prevention of diabetes mellitus is also necessary. Second, insulin resistance was estimated by only indirect methods such as HOMA-IR and QUICKI. Third, diabetes mellitus was defined as fasting glucose ≥ 7 mmol/L or current use of oral hypoglycemic agents or insulin. Because measurement of the hemoglobin A1c level or an oral glucose tolerance test was not used in this study, a considerable number of diabetics might have been missed in the analyses.

In conclusion, we found that a low serum 25(OH)D concentration is significantly associated with a high risk of diabetes mellitus in Korean adults and that the serum 25(OH)D level is inversely associated with insulin resistance in overweight and obese Korean adults. These results suggest that maintaining a sufficient level of vitamin D might be important for glucose homeostasis in Korean adults, especially in those with overweight and obesity. Further investigation into whether vitamin D supplementation may prevent the development of insulin resistance or diabetes mellitus in Koreans is necessary.

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