

Association between Serum 25-hydroxyvitamin D Levels and Type 2 Diabetes in Korean Adults

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Previous studies have suggested that a vitamin D deficiency increases the risk of type 2 diabetes. This study evaluated the association between serum vitamin D levels and type 2 diabetes in Korean adults. This study included 9,014 subjects (3,600 males and 5,414 females) aged ≥ 50 years who participated in the Dong-gu Study. The subjects were divided into groups in whom the serum vitamin D level was severely deficient (< 10 ng/mL), deficient (10 to < 20 ng/mL), insufficient (20 to < 30 ng/mL) and sufficient (≥ 30 ng/mL). Type 2 diabetes was defined by a fasting blood glucose level of ≥ 126 mg/dL and/or an HbA1c proportion of $\geq 6.5\%$ and/or self-reported current use of diabetes medication. Multiple logistic regression was performed to evaluate the association between vitamin D status and type 2 diabetes. The age- and sex-adjusted prevalence of type 2 diabetes was 22.6%, 22.5% and 18.4% and 12.7% for severely deficient, deficient, insufficient, and sufficient, respectively. Multivariate modeling revealed that subjects with insufficient or sufficient vitamin D levels were at a lower risk of type 2 diabetes than were subjects with deficient vitamin D levels [odds ratio (OR), 0.82; 95% confidence interval (CI), 0.71-0.94 and OR, 0.51; 95% CI, 0.35-0.74, respectively]. Higher serum vitamin D levels were associated with a reduced risk of diabetes in Korean adults, suggesting that vitamin D may play a role in the pathogenesis of diabetes.

Key Words: *Vitamin D; Diabetes Mellitus, Type 2; Cross-Sectional Study; Vitamin D Deficiency*

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INTRODUCTION

Diabetes mellitus is a very common long-term metabolic condition of older adults; the global burden of the disease is increasing. The number of patients with type 2 diabetes is expected to increase from 381.8 million to 592.0 million worldwide from 2013 to 2035.¹ In South Korea, although age-standardized mortality rates have decreased over the past decade, type 2 diabetes remains the fifth leading cause of death,² and South Korea ranked fourth among OECD countries in terms of the diabetes mortality rate.³ In addition, the Korea National Health and Nutrition Examination Survey (KNHANES) revealed that the prevalence of dia-

betes mellitus increased from 8.6% in 2001 to 11.0% in 2013.⁴ Type 2 diabetes is a complex disorder influenced by genetic, environmental, and nutritional factors. It is thus important to identify environmental and nutritional contributors to the disease.

Vitamin D is a steroid hormone that regulates bone and mineral metabolism by balancing the levels of calcium and phosphorus. Many tissues express vitamin D receptors, suggesting that vitamin D plays physiological roles in a number of organs besides bone. In recent years, it has been suggested that vitamin D may influence several non-skeletal disorders such as cardiovascular disease, cancer, autoimmune disorders, hypertension and diabetes.⁵⁻⁸ Des-

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pite the importance of the vitamin for both skeletal and nonskeletal health, vitamin D deficiency remains a problem worldwide, being very prevalent both in developed countries and populous regions of Asia, India, and the Middle East. Vitamin D deficiency is also very common in South Korea.⁹

Vitamin D may benefit type 2 diabetic patients by improving pancreatic β -cell function, insulin action, and systemic inflammation.¹⁰ Many observational studies have reported associations between the 25-hydroxyvitamin D [25(OH)D] level (the serum levels of which are often used to indicate vitamin D status) and the risk of type 2 diabetes; however, the data are inconsistent.¹⁰⁻¹² Although vitamin D insufficiency is very common in Korea,⁹ only two studies have explored the association between vitamin D levels and type 2 diabetes in Korea.^{13,14} Therefore, the author investigated the association between serum 25(OH)D level and type 2 diabetes in urban Korean adults.

MATERIALS AND METHODS

1. Subjects

The author used data obtained during the Dong-gu Study, which is described in detail elsewhere.¹⁵ In brief, the Dong-gu Study is an ongoing, prospective population-based project exploring risk factors for chronic diseases such as cardiovascular disease, fracture, cognitive decline, and cancer in an elderly urban population. The baseline survey recruited 9,260 participants aged ≥ 50 years from 2007 to 2010 in the Dong-gu district of Gwangju (a metropolitan city of South Korea). After exclusion of subjects for whom data was missing, a total of 8,991 subjects (3,588 males and 5,403 females) were included in the present study. The study was approved by the Institutional Review Board of Chonnam National University Hospital, and carried out in accordance with the guidelines of the Declaration of Helsinki. All participants provided written informed consent.

2. Anthropometric data and lifestyle factors

Information on medical history, demographics, and lifestyle characteristics was collected using interviewer-administered standardized questionnaires. Subjects were categorized as current smokers or nonsmokers (including ex-smokers) and as nondrinkers or current drinkers. Exercise was divided into irregular or regular based on the weekly frequencies of recreational and physical activity. Education status was classified as middle school or below and high school or above. Height was measured to the nearest 0.1 cm. Body weight was measured in light clothing without shoes. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. Blood pressure in the right upper arm was measured on three consecutive occasions at 1-min intervals using a mercury sphygmomanometer (Baumanometer; WA Baum Co., Inc., Copiague, NY, USA) fitted with a cuff of the appropriate size. All blood pressure measurements were performed with the subject seated after having rested for at least 5 min. The average

values were used in the analysis.

3. Laboratory measurements

Venous blood samples were collected in the morning after a 12-h of fasting. Sera were separated and stored at -70°C until use. The levels of serum total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, and fasting blood glucose were measured via enzymatic methods on an automatic analyzer (Model 7600; Hitachi Ltd., Tokyo, Japan). C-reactive protein (CRP) levels were determined using a BN II nephelometer (Dade Behring, Marburg, Germany). Hemoglobin A1c (HbA1c) levels were measured by high-performance liquid chromatography using the VARIANT II system (Bio-Rad, Hercules, CA, USA). 25(OH)D levels were determined by chemiluminescent microparticle immunoassay (ARCHTECT i2000, Abbott, Chicago, IL, USA). The coefficient of variation of analytical precision was $\leq 10\%$. The lower level of detection was 3.0 ng/mL. Diabetes mellitus was defined as having a blood glucose level of ≥ 126 mg/dL or a HbA1c level of $\geq 6.5\%$ or current use of diabetes medication.

4. Statistical analysis

The vitamin D status was categorized based on the serum 25(OH)D level as severely deficient (< 10 ng/mL), deficient (10 to < 20 ng/mL), insufficient (20 to < 30 ng/mL), or sufficient (≥ 30 ng/mL).¹⁶ Baseline characteristics were analyzed by the vitamin D status and compared using analysis of variance and the chi-squared test, as appropriate. Multiple logistic regression was used to obtain odds ratios (ORs) with 95% confidence intervals (95% CIs) for associations between vitamin D status and the risk of type 2 diabetes after adjusting for age, sex, the month of blood collection, BMI, smoking status, alcohol consumption status, performance of regular exercise, use of antihypertensive medication, use of dyslipidemia medication, systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol level, log-transformed triglyceride concentration, HDL cholesterol level, and log-transformed CRP concentration. Sensitivity analysis was performed by excluding participants taking antidiabetic medications to explore the effects of such drugs on the results. All statistical tests were performed at a two-sided significance level of 5%. Stata version 12 software was used for all calculations (StataCorp, College Station, TX, USA).

RESULTS

The general characteristics of the study participants by vitamin D status are shown in Table 1. The mean subject age was 65.2 ± 8.2 years, and males constituted 39.9% of all subjects. The prevalence of type 2 diabetes was 21.3% as defined by a fasting blood glucose level of ≥ 126 mg/dL, an HbA1c concentration of $\geq 6.5\%$, or self-reported current use of diabetes medication. The prevalence of severe vitamin D deficiency, deficiency, insufficiency, and sufficiency were 7.8%, 68.1%, 21.3%, and 2.8%, respectively. Subjects

TABLE 1. Characteristics of study participants according to the vitamin D status

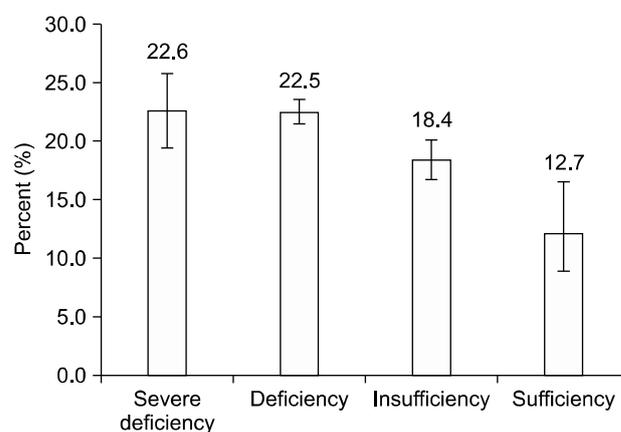
	Severe deficiency	Deficiency	Insufficiency	Sufficiency	p-value
	< 10.0 ng/mL	10.0-19.9 ng/mL	20.0-29.9 ng/mL	≥ 30.0 ng/mL	
N	702	6,136	1,921	255	
Age (years)	66.7±8.5	65.0±8.2	65.0±7.9	65.8±8.2	< 0.001
Men	101 (14.4)	2,056 (33.5)	1,263 (65.8)	180 (70.6)	< 0.001
Education (high school or above)	170 (24.2)	2,205 (35.9)	866 (45.1)	118 (46.3)	< 0.001
Body mass index (kg/m ²)	24.2±3.1	24.4±3.0	24.2±2.7	23.6±2.6	< 0.001
Current smoking	62 (8.8)	600 (9.8)	287 (14.9)	34 (13.3)	< 0.001
Current alcohol consumption	184 (26.2)	2,682 (43.7)	1,133 (59.0)	155 (60.8)	< 0.001
Regular exercise	173 (24.6)	1,943 (31.7)	679 (35.4)	108 (42.4)	< 0.001
Hypertension medication	264 (37.6)	2,213 (36.1)	642 (33.4)	86 (33.7)	0.103
Diabetes medication	102 (14.5)	817 (13.3)	219 (11.4)	24 (9.4)	0.027
Dyslipidemia medication	69 (9.8)	553 (9.0)	127 (6.6)	18 (7.1)	0.004
SBP (mmHg)	124.7±17.6	123.7±17.0	121.9±16.2	122.6±16.5	< 0.001
DBP (mmHg)	75.0±10.9	74.4±10.1	74.0±10.3	73.7±10.3	0.076
Total cholesterol (mg/dL)	218.1±44.6	202.9±39.2	192.3±37.5	186.8±38.2	< 0.001
Triglycerides (mg/dL)	132.0 (93.8-188.0)	118 (85.0-172.0)	113 (79.0-165.0)	108 (75.0-162.0)	< 0.001
HDL cholesterol (mg/dL)	53.6±12.6	51.7±11.9	50.5±11.8	50.1±12.3	< 0.001
CRP (mg/dL)	0.06 (0.02-0.13)	0.06 (0.03-0.13)	0.06 (0.03-0.13)	0.07 (0.03-0.16)	0.055
Glucose (mg/dL)	109.0±27.2	109.7±25.5	109.3±23.1	109.7±23.7	0.855
HbA1c (%)	5.90±1.08	5.85±0.96	5.79±0.86	5.73±0.77	0.010
Month of blood collection					< 0.001
April	241 (34.3)	1,306 (21.3)	235 (12.2)	35 (13.7)	
May	278 (39.6)	2,064 (33.6)	534 (27.8)	54 (21.2)	
June	129 (18.4)	1,793 (29.2)	671 (34.9)	109 (42.8)	
July	54 (7.7)	973 (15.9)	481 (25.0)	57 (22.4)	
Diabetes mellitus	149 (21.2)	1,346 (21.9)	387 (20.2)	37 (14.5)	0.018

Data are means±SD, medians (interquartile range) or number (percentage).

with a sufficient vitamin D status were more likely to be male, highly educated, smokers, drinkers, and physically active. Such subjects had significantly lower BMI, SBP, DBP, total cholesterol, triglycerides, HDL-cholesterol, and HbA1c.

The age- and sex-adjusted prevalences of type 2 diabetes by vitamin D status are presented in Fig. 1. These prevalences were 22.6%, 22.5%, 18.4%, and 12.7% for those with severely deficient, deficient, insufficient, and sufficient vitamin D levels, respectively. Table 2 shows the findings of logistic regression analysis, revealing an association between vitamin D status and type 2 diabetes. Higher serum 25(OH)D levels were significantly associated with a decreased risk of type 2 diabetes. In the age- and sex-adjusted model, compared with those who were vitamin D-deficient, subjects who were vitamin D-insufficient or -sufficient were at a reduced risk of type 2 diabetes [OR (95% CI)=0.78 (0.69-0.90) and 0.50 (0.35-0.71), respectively]. After further adjustment for cardiovascular risk factors, these associations were slightly attenuated but remained significant. Compared with subjects who were vitamin D-deficient, those who were vitamin D-insufficient and -sufficient were at a decreased risk of type 2 diabetes [OR (95% CIs)=0.82 (0.71-0.94) and 0.51 (0.35-0.74), respectively].

In sensitivity analyses excluding patients taking dia-

**FIG. 1.** Age and sex adjusted prevalence of type 2 diabetes according to serum vitamin D levels.

betic medication, similar results were found, except that subjects who were severely vitamin D-deficient tended to have a lower prevalence of type 2 diabetes than did those who were vitamin D-insufficient (data not shown).

TABLE 2. Odds ratio with 95% confidence interval of diabetes according to the vitamin D status.

	Model 1	Model 2
The vitamin D status		
Severe deficiency (< 10.0 ng/mL)	0.99 (0.81-1.20)	1.04 (0.85-1.28)
Deficiency (10.0-19.9 ng/mL)	1.00 (reference)	1.00 (reference)
Insufficiency (20.0-29.9 ng/mL)	0.78 (0.69-0.90)	0.82 (0.71-0.94)
Sufficiency (≥ 30.0 ng/mL)	0.50 (0.35-0.71)	0.51 (0.35-0.74)
Age (years)	1.03 (1.02-1.04)	1.01 (1.00-1.02)
Men	1.59 (1.43-1.78)	1.73 (1.51-1.99)
Education (high school or above)		0.91 (0.81-1.03)
Body mass index (kg/m ²)		1.08 (1.06-1.10)
Current smoking		1.20 (1.01-1.42)
Current alcohol consumption		0.93 (0.82-1.04)
Regular exercise		1.08 (0.96-1.21)
Hypertension medication		1.59 (1.42-1.79)
Dyslipidemia medication		1.72 (1.45-2.05)
SBP (mmHg)		1.02 (1.02-1.03)
DBP (mmHg)		0.96 (0.96-0.97)
Total cholesterol (mg/dL)		1.00 (0.99-1.00)
Log-transformed triglycerides (mg/dL)		3.27 (2.51-4.26)
HDL cholesterol (mg/dL)		1.00 (0.99-1.01)
Log-transformed CRP (mg/dL)		3.57 (2.02-6.28)
Month of blood collection		
April	1.00 (reference)	1.00 (reference)
May	0.83 (0.73-0.96)	0.80 (0.69-0.93)
June	0.86 (0.74-0.99)	0.84 (0.72-0.98)
July	0.83 (0.70-0.99)	0.73 (0.61-0.88)

OR: odds ratio, CI: confidence interval.

DISCUSSION

In this population-based cross-sectional study, a good vitamin D status was associated with a significantly decreased risk of type 2 diabetes. In addition, this association persisted in subjects who were not taking diabetes medications. As far as we know, this is the largest study to explore such associations in Korea.

Many observational studies of the association between the serum 25(OH)D level and the risk of diabetes have been conducted, but the results have been inconsistent.¹⁰⁻¹² In a meta-analysis of 11 prospective studies (4 positive and 7 negative), Forouhi et al.¹¹ found an inverse association between the 25(OH)D level and the incidence of type 2 diabetes. The combined relative risk (95% CI) of type 2 diabetes when subjects in the highest and lowest quartiles of 25(OH)D levels were compared was 0.59 (0.52-0.67). In a recent updated meta-analysis of 22 prospective studies,¹² each fall of one standard deviation of the 25(OH)D concen-

tration was associated with an increased risk of type 2 diabetes (relative risk, 1.21; 95% CI, 1.16-1.27). Two studies on Korean subjects revealed associations between low serum 25(OH)D levels and diabetes. In a Korean cross-sectional study using data from the third KNHANES, subjects with the lowest 25(OH)D level were at a 1.75-fold greater risk of diabetes than were those with the highest level.¹⁴ In another Korean study on 1,080 participants with a 5-year follow-up, 25(OH)D-deficiency was associated with a 3.4-fold greater risk of diabetes than that in subjects with sufficient 25(OH)D.¹³

Although many observational studies have thus found that low serum 25(OH)D levels are associated with an increased risk of type 2 diabetes, any cause-and-effect relationship remains unclear. Randomized controlled trials (RCTs), which minimize bias and confounding, are considered to be more definitive.¹⁷ However, in contrast to the results of many observational studies, RCTs have revealed no effect of vitamin D supplementation on the incidence of type 2 diabetes.⁵ In the Women's Health Initiative Trial, vitamin D supplementation was not associated with the risk of diabetes in a follow-up period of 7 years.¹⁸ Avenell et al. performed a community-based trial assessing bone outcomes and found that vitamin supplementation did not change the risk of self-reported type 2 diabetes.¹⁹ In addition, a recent study used a Mendelian randomization approach to explore whether the association between 25(OH)D levels and the risk of type 2 diabetes was causal.¹² Such randomization employs genetic variants that influence disease status as instrumental variables to identify causal relationships between an "exposure" and associated outcomes.²⁰ Genetically low 25(OH)D levels were not associated with the risk of type 2 diabetes. Therefore, given this negative finding and those of RCTs, the associations noted in observational studies (including the present study) are unlikely to reflect any causal relationship.

In the present study, the vitamin D sufficient group had lower BMI, blood pressure, total cholesterol, triglyceride and HDL cholesterol than the vitamin D deficient group. After adjusting for age and gender, there was still a difference between the deficiency and sufficiency groups at all levels except for HDL cholesterol (data not shown). Similar to our study, in a meta-study,²¹ serum 25(OH)D levels showed an inverse weak correlation with BMI. In addition, in a bidirectional Mendelian randomization study,²² the BMI allele score was associated with lower vitamin D levels, but the vitamin D allele scores were not associated with BMI. The study suggests that high BMI can lead to vitamin D deficiency, but vitamin deficiency does not cause obesity. Although many observational studies have shown that low vitamin D concentrations were associated with high blood pressure and cholesterol levels, in clinical trials, vitamin D supplementation did not lower cholesterol levels and blood pressure.^{23,24} Therefore, it is unclear whether the relationships found in observational studies are causal.

The strengths of our study are the population-based design and the relatively large sample size, which minimize

selection bias and afford good statistical strength. However, several limitations are apparent. First, because this study is a cross-sectional study, the inverse association noted may be attributable to reverse causation or residual confounding. Second, serum 25(OH)D concentrations were measured only once and therefore may not reflect the long-term vitamin D status. Third, no data on sun exposure, the use of sunscreen, or dietary or vitamin D supplementation were available. Fourth, the baseline survey of the cohort study was conducted on voluntary participants in a community, with a response rate of 27.2%. Therefore, this study cannot be seen as representative of Koreans. In conclusion, we found that a good vitamin D status was associated with a decreased risk of type 2 diabetes in Korean urban adults, suggesting that serum vitamin D may play a role in the pathogenesis of diabetes.

CONFLICT OF INTEREST STATEMENT

None declared.

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