Original Article

Relationship between homeostasis model assessment of insulin resistance and beta cell function and serum 25-hydroxyvitamin D in non-diabetic Korean adults

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The purpose of this study is to look at these relationships in non-diabetic Korean adults. This study was based on data from the KNHANES V-1, which is representative of the population of Korea. A total of 5,492 participants (≥20 years in age) without type 1 or type 2 diabetes, assessed for serum 25-hydroxyvitamin D [25(OH)D], fasting blood glucose and insulin, as well as anthropometric variables, were included in the analyses. The key study results were as follows: First, vitamin D status [vitamin D deficient, 25(OH)D <25 nM; vitamin D insufficient, 25(OH)D ≥25, <50 nM; vitamin D sufficient, 25(OH)D ≥50 nM] was inversely associated with homeostasis model assessment of insulin resistance (HOMA-IR) and beta cell function (HOMA-*B*) in model 2 (adjusted for age and gender) and 3 (further adjusted for smoking, alcohol drinking, regular exercise, systolic and diastolic blood pressure, waist circumference, and body mass index). Second, in model 4, when further adjusted for total cholesterol, triglycerides, and HDL-C, vitamin D status was inversely associated with HOMA-*B*. However, association of vitamin D status and HOMA-IR was no longer significant. In conclusion, vitamin D was inversely associated with beta cell function in non-diabetic Korean adults but was not associated with insulin resistance.

***Key Words*: vitamin D, HOMA-IR, HOMA-*B*, non-diabetic adult**

Diabetes, a disease that results from the interaction of genetic factors and environmental factors, is one of the most common endocrine diseases worldwide.[1,2] Increased insulin resistance and decreased beta cell function are known to play a role in the pathogenesis of type 2 diabetes.[3]

Vitamin D is involved in calcium and phosphate absorption in the intestines, which maintains sufficient concentrations of circulating calcium and phosphate levels and normal mineralization of bone by providing the minerals to bone-forming sites.[4,5] Recently, vitamin D has also received greater attention to additional functions that concerning its effect on insulin secretion and resistance.[6–8]

However, the association of vitamin D and beta cell function and insulin resistance differs among ethnic groups and countries, and its mechanism of action remains unclear. For example, some studies have shown that vitamin D was inversely associated with insulin resistance,[9–11] beta cell function,[12,13] or both.[14] Some studies have shown that vitamin D was positively associated with beta cell function.[15,16] Some studies have shown that vitamin D was not associated with insulin resistance,[17] beta cell function,[9,18] or both.[19,20] In addition, most of the studies were designed to target populations with diseases, such as metabolic syndrome, obesity and especially diabetes.

The Republic of Korea has recently been known as a country that has a severe vitamin D deficiency problem. Among Koreans (age ≥10 years), 65.9% of men and 77.7% of women were deficient [25(OH)D ≤25 nM] or insufficient [25(OH)D ≥25, <50 nM] of vitamin D. In particular, vitamin D deficient or insufficient is serious in the twenties (men, 78.8%; women, 88.3%).[21] However, there still remains a lack of studies on the association of vitamin D with insulin resistance and beta cell function in the population of Korea. Therefore, our objective was to assess the association between vitamin D concentrations and both insulin resistance and beta cell function in non-diabetic Korean adults using data from the fifth Korea National Health and Nutrition Examination Survey (KNHANES), which is representative of the population of Korea.[22]

Materials and Methods

Subjects. This study was based on data from the KNHANES V-1 (2010), which is the most recent data that measured homeostasis model assessment (HOMA) among the KNHANES. The KNHANES is a cross-sectional survey conducted nationwide by the Division of Korean National Health and Welfare. The KNHANES V-1 (2010) was performed from January 2010 to December 2010. The survey includes a representative national sample of the Korean population, selecting from recorded households in the Population and Housing Census in Korea. The survey section is arranged by district and housing type characteristics. Twenty households were selected from each survey section using a stratified, multistage probability cluster sampling method that considers geographical area, age, and gender. In the KNHANES V-1 (2010), 8,958 individuals over 1 year of age were sampled for the survey. Among the 6,665 subjects who participated in the KNHANES V-1, we limited the analyses to adults aged ≥20 years. We excluded 778 subjects whose data were missing important analytic variables, such as serum 25(OH)D levels, various blood chemistry tests, and information about lifestyle. After the exclusion of those individuals with missing values or who suffered from diabetes (395 subjects diagnosed with type 1 or 2 diabetes or with fasting plasma glucose level ≥126 mg/dl), 5,492 adults were

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included in the analyses. The KNHANES V-1 (2010) study has been conducted according to the principles expressed in the Declaration of Helsinki. (Institutional Review Board No. 2010-02CON-21-C). All participants in the survey signed an informed written consent form. Further information can be found in "The KNHANES V-1 (2010) Sample", which is available on the KNHANES website.[22] The data from KNHANES is available on request by email if the applicant logs onto the "Korea National Health and Nutrition Examination Survey" website.

General characteristics and blood chemistry. Research subjects were classified by sex (men or women), smoking (non-smoker or ex-smoker or current smoker), alcohol drinking (yes or no), and regular exercise (yes or no). In the smoking category, participants who smoked more than one cigarette a day, those who had previously smoked but do not presently smoke, and those who never smoked were classified into the current-smoker, ex-smoker, and non-smoker groups, respectively. Alcohol drinking was indicated as "yes" for participants who had consumed at least one glass of alcohol every month over the last year. Regular exercise was indicated as "yes" for participants who had exercised on a regular basis regardless of indoor or outdoor exercise. (Regular exercises was defined as 30 min at a time and 5 times/week 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/week 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). Anthropometric measurements included measurement of body mass index (BMI) and waist circumference (WC), as well as final measurements of systolic blood pressure (SBP) and diastolic blood pressure (DBP). Blood chemistries included measurements of total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), triglycerides (TGs), fasting plasma glucose (FPG), fasting insulin, and 25-hydroxyvitamin D [25(OH)D].

Serum 25(OH)D assessments. Blood samples were collected through an antecubital vein after 10–12 h of fasting to assess serum levels of biochemical markers. Serum levels of 25(OH)D were measured with a radioimmunoassay (25-hydroxy-vitamin D ^{125}I RIA Kit; DiaSorin, Still Water, MN) using a 1470 Wizard Gamma Counter (Perkin Elmer, Turku, Finland). To minimize the analytical variation, serum 25(OH)D levels were analyzed by the same institute, which carried out a quality assurance program through the analysis period. The inter-assay coefficients of variation were 1.9–6.1% for the samples. Serum 25(OH)D levels were classified as either vitamin D deficient [25(OH)D <25 nM], vitamin D insufficient [25(OH)D ≥25, <50 nM], or vitamin D sufficient [25(OH)D ≥50 nM].[23]

HOMA-IR and HOMA-*B*. The homeostasis model assessment of insulin resistance (HOMA-IR) and beta cell function (HOMA-*B*) constitute a method for assessing beta cell function and IR from basal glucose and insulin concentrations.[24] HOMA-IR and HOMA-*B* are also significantly associated with diabetes risk across ethnic groups.[18] The formulas are as follows: HOMA-IR = [fasting insulin (μU/ml) × fasting plasma glucose (mg/dl)]/405; HOMA-*B* = 20 × fasting insulin (μU/ml)/[fasting plasma glucose (mg/dl) – 63].[24]

Data analysis. The collected data were statistically analyzed using SPSS WIN (ver. 18.0). The distributions of the participant characteristics were converted into percentages, and the successive data were presented as averages with standard deviations. The average difference in HOMA-IR and HOMA-*B* for general characteristics and blood chemistries were calculated using an analysis of variance and independent *t* tests. In the case of analysis of covariance test (ANCOVA), the 4 models constructed were: 1) Serum 25(OH)D; 2) Serum 25(OH)D, age, gender; 3) Serum 25(OH)D, age, gender, smoking, alcohol drinking, regular exercise, SBP, DBP, WC, and BMI; and 4) Serum 25(OH)D, age, gender, smoking, alcohol drinking, regular exercise, SBP, DBP, WC, BMI, TC, TGs, and HDL-C. The significance level for all of the statistical data was set as $p<0.05$.

Results

General characteristics of research subjects. General characteristics of the research subjects are shown in Table 1. Among the total set of subjects (5,492 subjects), the serum 25(OH)D, HOMA-IR, and HOMA-*B* levels were 44.95 ± 16.73 nM, 2.39 ± 1.30, and 133.09 ± 70.39, respectively. In the males (2,339 subjects), the mean of serum 25(OH)D levels was 48.68 ± 16.95 nM. According to the classification of vitamin D status, 117 (5.0%), 1,232 (52.7%), and 990 (42.3%) subjects were classified as vitamin D deficient, vitamin D insufficient, and vitamin D sufficient, respectively. The mean values of HOMA-IR and HOMA-*B* for males were 2.45 ± 1.51 and 125.50 ± 66.27, respectively. In the females (3,153 subjects), the mean of serum 25(OH)D levels was 42.21 ± 16.02 nM. According to the classification of vitamin D status, 341 (10.8%), 2,005 (63.6%), and 807 (25.6%) subjects were classified as vitamin D deficient, vitamin D insufficient, and vitamin D sufficient, respectively. The mean values of HOMA-IR and HOMA-*B* for females were 2.36 ± 1.13 and 138.72 ± 72.80, respectively.

HOMA-IR and HOMA-*B* levels by subject characteristics. HOMA-IR and HOMA-*B* levels by subject characteristics are shown in Table 2 and 3. Variables showing a significant difference in the mean of HOMA-IR was age ($p<0.001$), gender ($p = 0.015$), regular exercise ($p = 0.010$), WC ($p<0.001$), BMI ($p<0.001$), SBP ($p = 0.003$), DBP ($p<0.001$), TC ($p<0.001$), TGs ($p<0.001$), HDL-C ($p<0.001$), and FPG ($p<0.001$). However, smoking ($p = 0.057$) and alcohol drinking ($p = 0.191$) showed no significant difference in the mean differences of HOMA-IR. Variables showing a significant difference in the mean of HOMA-*B* was age ($p<0.001$), gender ($p<0.001$), smoking ($p = 0.018$), alcohol drinking ($p<0.001$), WC ($p<0.001$), BMI ($p<0.001$), SBP ($p<0.001$), TGs ($p<0.001$), HDL-C ($p<0.001$), and FPG ($p<0.001$). However, regular exercise ($p = 0.215$), DBP ($p = 0.126$), and TC ($p = 0.185$) showed no significant difference in the mean differences of HOMA-*B*.

Comparisons of HOMA-IR and HOMA-*B* levels according to vitamin D status. Comparisons of HOMA-IR and HOMA-*B* levels according to vitamin D status are shown in Table 4. Vitamin D status [vitamin D deficient, 25(OH)D <25 nM; vitamin D insufficient, 25(OH)D ≥25, <50 nM; vitamin D sufficient, 25(OH)D ≥50 nM] was inversely associated with HOMA-*B* ($p<0.001$) in model 1. However, association of vitamin D status and HOMA-IR was not significant ($p = 0.211$). In model 2, when adjusted for age and gender, Vitamin D status was inversely associated with HOMA-*B* ($p<0.001$) and HOMA-IR ($p = 0.010$). In model 3, when further adjusted for smoking, alcohol drinking, regular exercise, SBP, DBP, WC, and BMI, vitamin D status was inversely associated with HOMA-*B* ($p = 0.002$) and HOMA-IR ($p = 0.035$). In model 4, when further adjusted for TC, TGs, and HDL-C, vitamin D status was inversely associated with HOMA-*B* ($p = 0.006$). However, association of vitamin D status and HOMA-IR was no longer significant ($p = 0.335$).

Discussion

In our study population involving non-diabetic Korean adults, vitamin D status was inversely associated with beta cell function indices (HOMA-*B*) and insulin resistance (HOMA-IR) after adjusting for variables (age, gender, smoking, alcohol drinking, regular exercise, SBP, DBP, WC, and BMI). However, when further adjusted for TC, TGs, and HDL-C, vitamin D status was inversely associated with HOMA-*B,* but was not significantly associated with HOMA-IR.

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Table 1. General characteristics

N (%), mean ± SD, (n = 5,492)

Variables	Category	Total (n = 5,492)	Males (n = 2,339)	Females (n = 3,153)	p value
Age (years)	20–29	668 (12.2)	265 (11.3)	403 (12.8)	0.001
	30–39	1,184 (21.6)	494 (21.1)	690 (21.9)	
	40–49	1,084 (19.7)	493 (21.1)	591 (18.7)	
	50–59	1,041 (19.0)	399 (17.1)	642 (20.4)	
	≥60	1,515 (27.6)	688 (29.4)	827 (26.2)	
Smoking	Non-smoker	3,230 (58.8)	433 (18.5)	2,797 (88.7)	<0.001
	Ex-smoker	1,086 (19.8)	898 (38.4)	188 (6.0)	
	Current smoker	1,176 (21.4)	1,008 (43.1)	168 (5.3)	
Alcohol drinking	No	3,086 (56.2)	789 (33.7)	2,297 (72.9)	<0.001
	Yes	2,406 (43.8)	1,550 (66.3)	856 (27.1)	
Regular exercise	No	4,661 (84.9)	1,947 (83.2)	2,714 (86.1)	0.004
	Yes	831 (15.1)	392 (16.8)	439 (13.9)	
[ω]25(OH)D (nM)	<25	458 (8.3)	117 (5.0)	341 (10.8)	<0.001
	≥25, <50	3,237 (58.9)	1,232 (52.7)	2,005 (63.6)	
	≥50	1,797 (32.7)	990 (42.3)	807 (25.6)	
		44.95 ± 16.73	48.68 ± 16.95	42.21 ± 16.02	0.008
[α]WC (cm)		80.69 ± 13.78	84.50 ± 17.16	77.85 ± 9.67	<0.001
[β]BMI (kg/m^2)		23.51 ± 3.30	23.92 ± 3.10	23.21 ± 3.41	<0.001
[γ]SBP (mmHg)		120.46 ± 17.57	123.50 ± 16.11	118.21 ± 18.25	<0.001
[δ]DBP (mmHg)		77.27 ± 10.67	80.51 ± 10.50	74.87 ± 10.15	<0.001
[ε]TC (mg/dl)		188.46 ± 36.42	187.83 ± 37.03	188.92 ± 35.97	0.272
[ζ]TGs (mg/dl)		128.96 ± 103.46	155.48 ± 132.08	109.29 ± 69.27	<0.001
[η]HDL-C (mg/dl)		53.13 ± 12.88	49.65 ± 12.18	55.71 ± 12.77	<0.001
[θ]FPG (mg/dl)		93.08 ± 9.85	94.75 ± 9.99	91.85 ± 9.56	<0.001
[μ]HOMA-IR		2.39 ± 1.30	2.45 ± 1.51	2.36 ± 1.13	0.015
[ψ]HOMA-*B*		133.09 ± 70.39	125.50 ± 66.27	138.72 ± 72.80	<0.001
[§]Insulin (μU/ml)		10.30 ± 4.91	10.33 ± 5.58	10.27 ± 4.35	0.626

[ω]25(OH)D, 25-hydroxyvitamin D; [α]WC, waist circumference; [β]BMI, body mass index; [γ]SBP, systolic blood pressure; [δ]DBP, diastolic blood pressure; [ε]TC, total cholesterol; [ζ]TGs, triglycerides; [η]HDL-C, HDL-cholesterol; [θ]FPG, fasting plasma glucose; [μ]HOMA-IR, homeostasis model assessment of insulin resistance; [ψ]HOMA-*B*, homeostasis model assessment of beta cell function; [§]Insulin, fasting insulin.

Table 2. HOMA-IR and HOMA-*B* levels according to general characteristics in non-diabetic subjects

mean ± SD, (n = 5,492)

Variables	Category	HOMA-IR	p value	HOMA-*B*	p value
Gender	Males	2.45 ± 1.51	0.015	125.50 ± 66.27	<0.001
	Females	2.36 ± 1.13		138.72 ± 72.80	
Age (years)	20–29	2.27 ± 1.13	<0.001	165.74 ± 69.87	<0.001
	30–39	2.35 ± 1.55		146.17 ± 70.96	
	40–49	2.36 ± 1.20		128.30 ± 57.74	
	50–59	2.37 ± 1.11		118.48 ± 54.81	
	≥60	2.52 ± 1.36		121.95 ± 80.90	
Smoking	Non-smoker	2.36 ± 1.18	0.057	134.62 ± 62.09	0.018
	Ex-smoker	2.47 ± 1.23		127.68 ± 86.23	
	Current smoker	2.42 ± 1.65		133.89 ± 75.23	
Alcohol drinking	No	2.42 ± 1.29	0.191	137.09 ± 77.18	<0.001
	Yes	2.37 ± 1.32		129.95 ± 64.33	
Regular exercise	No	2.41 ± 1.33	0.01	133.71 ± 71.36	0.215
	Yes	2.26 ± 1.05		129.92 ± 63.85	

Previous studies found inconsistent results in the association between vitamin D and insulin resistance in non diabetic subject (Table 5). These inconsistent results may be caused by different populations due to ethnic groups and countries. In studies on the association between vitamin D and insulin resistance among the healthy subjects, some studies have suggested that insulin resistance is inversely associated with vitamin D level.[11,14,25,26] Ding and his colleagues evaluated the association between serum vitamin D and insulin resistance among Chinese subjects without diabetes mellitus.[11] After adjusting for age, gender, and BMI, they suggested that independent inverse associations existed between the serum level of 25(OH)D and log (HOMA-IR) (p<0.001). Tao and his colleagues evaluated the association between 25(OH)D level and insulin resistance among a healthy Chinese female population.[14] After adjusting for age, parathyroid hormone, Ca^{2+}, and BMI, they suggested that independent inverse associations existed between the serum level of 25(OH)D and HOMA-IR (p<0.001). On the other hand, some previous studies[17,19,27] did not observe an association between serum 25(OH)D and insulin resistance. Gobbo and his colleagues[19]

Table 3. HOMA-IR and HOMA-*B* levels according to anthropometric and blood chemistry tests in non-diabetic subjects

mean ± SD, (n = 5,492)

Variables	Category	HOMA-IR	p value	HOMA-*B*	p value
[α]WC (cm)	Males <90 or Females <80	2.13 ± 1.14	<0.001	128.98 ± 63.26	<0.001
	Males ≥90 or Females ≥80	2.92 ± 1.46		140.54 ± 73.19	
[β]BMI (kg/m^2)	<25	2.14 ± 1.15	<0.001	128.81 ± 68.04	<0.001
	≥25	2.96 ± 1.45		142.27 ± 73.52	
[γ]SBP (mmHg)	<140	2.38 ± 1.32	0.003	135.01 ± 71.79	<0.001
	≥140	2.55 ± 1.13		117.03 ± 54.89	
[δ]DBP (mmHg)	<90	2.37 ± 1.30	<0.001	133.49 ± 71.19	0.126
	≥90	2.65 ± 1.32		127.81 ± 58.81	
[ε]TC (mg/dl)	<200	2.37 ± 1.29	<0.001	132.80 ± 65.57	0.185
	≥200	2.75 ± 1.55		138.42 ± 83.80	
[ζ]TGs (mg/dl)	<150	2.22 ± 1.07	<0.001	131.26 ± 65.76	0.002
	≥150	2.86 ± 1.70		138.03 ± 81.40	
[η]HDL-C (mg/dl)	Males ≥40 or Females ≥50	2.22 ± 0.95	<0.001	128.03 ± 57.94	<0.001
	Males <40 or Females <50	2.57 ± 1.34		137.87 ± 79.89	
[θ]FPG (mg/dl)	<100	2.16 ± 0.91	<0.001	142.90 ± 71.17	<0.001
	≥100	3.22 ± 1.99		98.32 ± 54.91	

[ω]25(OH)D, 25-hydroxyvitamin D; [α]WC, waist circumference; [β]BMI, body mass index; [γ]SBP, systolic blood pressure; [δ]DBP, diastolic blood pressure; [ε]TC, total cholesterol; [ζ]TGs, triglycerides; [η]HDL-C, HDL-cholesterol; [θ]FPG, fasting plasma glucose; [μ]HOMA-IR, homeostasis model assessment of insulin resistance; [ψ]HOMA-*B*, homeostasis model assessment of beta cell function; [§]Insulin, fasting insulin.

Table 4. Comparisons of HOMA-IR and HOMA-*B* levels according to serum 25(OH)D in non-diabetic subjects

(n = 5,492)

	Serum 25(OH)D			p value
	<25.0 nmol/L	≥25.0, <50.0 nmol/L	≥50.0 nmol/L	
HOMA-IR				
Model 1	2.37 ± 1.15 (2.26–2.47)	2.42 ± 1.33 (2.37–2.47)	2.35 ± 1.29 (2.36–2.43)	0.211
Model 2	2.44 ± 0.06 (2.28–2.52)	2.44 ± 0.02 (2.39–2.48)	2.32 ± 0.03 (2.25–2.38)	0.010
Model 3	2.47 ± 0.06 (2.36–2.59)	2.41 ± 0.02 (2.37–2.46)	2.33 ± 0.03 (2.76–2.39)	0.035
Model 4	2.41 ± 0.05 (2.31–2.50)	2.37 ± 0.05 (2.31–2.50)	2.34 ± 0.03 (2.31–2.50)	0.335
HOMA-*B*				
Model 1	145.93 ± 103.50 (136.43–155.44)	136.94 ± 68.51 (134.59–139.31)	122.88 ± 61.61 (120.03–125.73)	<0.001
Model 2	141.50 ± 3.24 (135.16–147.84)	134.95 ± 1.22 (132.57–137.34)	127.60 ± 1.66 (124.35–130.85)	<0.001
Model 3	138.63 ± 3.04 (132.67–144.60)	134.34 ± 1.14 (132.11–136.58)	128.66 ± 1.56 (125.61–131.71)	0.002
Model 4	138.09 ± 3.04 (132.14–144.05)	134.24 ± 1.14 (132.02–136.46)	128.99 ± 1.55 (125.95–132.03)	0.006

Model 1 [mean ± SD (95% CI)], Non-adjusted; Model 2 [mean ± SE (95% CI)], adjusted for age and gender; Model 3 [mean ± SE (95% CI)], adjusted for age, gender, smoking, alcohol drinking, regular exercise, SBP, DBP, WC, and BMI; Model 4 [mean ± SE (95% CI)], adjusted for age, gender, smoking, alcohol drinking, regular exercise, SBP, DBP, WC, BMI, TC, TGs, and HDL-C.

Table 5. Studies reporting an association between vitamin D status, insulin resistance, and beta cell function in non-diabetic subjects

Study (country of origin)	Gender (M/F)	Outcomes	Adjustments	Main study results
Ding *et al.*, 2014[11] (China)	M/F (n = 897)	Lg (HOMA-IR)	age, gender, BMI	25(OH)D inversely associated with Lg (HOMA-IR) (p<0.001)
Tao *et al.*, 2013[14] (China)	F (n = 1,382)	HOMA-IR, HOMA-*B*	age, PTH, Ca^{2+}, BMI	25(OH)D inversely associated with HOMA-IR (p<0.001) and HOMA-*B* (p = 0.001)
Del Gobbo *et al.*, 2011[19] (Canada)	M/F (n = 510)	HOMA-IR, HOMA-*B*	age, gender, physical activity, smoking, alcohol, education, BMI, WC, body fat percentage	25(OH)D not associated with HOMA-IR (p = 0.572) and HOMA-*B* (p = 0.498)
Zhao *et al.*, 2010[25] (USA)	M/F (n = 3,206)	HOMA-IR	age, gender, race/ethnicity, education, smoking, heavy alcohol, drinking, physical activity, abdominal obesity, BMI	25(OH)D inversely associated with HOMA-IR (p_{trend}<0.001)
Liu *et al.*, 2009[26] (USA)	M/F (n = 2,803)	HOMA-IR, $ISI_{0,120}$	age, gender, current smoking status, BMI, WC	25(OH)D inversely associated with HOMA-IR (p<0.001), but not associated with $ISI_{0,120}$ (p = 0.310)
Hao *et al.*, 2014[27] (China)	M (n = 567)	HOMA-IR	age, BMI	25(OH)D not associated with HOMA-IR (p = 0.558)

evaluated the association between serum 25(OH)D levels and insulin resistance in non-diabetic Canadian Cree. They suggested that the serum 25(OH)D level was not associated with HOMA-IR in models adjusted for age, gender, physical activity, education, alcohol consumption, smoking, and BMI (p = 0.572). Song and her colleagues evaluated the association between serum 25(OH)D levels and insulin resistance in a Korean rural population.[17] After adjusting for potential confounders, such as age, gender, BMI,

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smoking status, alcohol intake, and regular exercise, vitamin D was not independently associated with insulin resistance ($p = 0.247$). In addition, there is a study that the association between vitamin D and HOMA-IR differ in the results according to gender. Choi and his colleagues[28] evaluated the association between 25(OH)D level and insulin resistance among an apparently healthy Korean adolescent population. In male adolescents, after adjusting for age, body mass index, smoking, drinking, and regular exercise, the lowest 25(OH)D quartile was significantly associated with increased insulin resistance (odds ratio 3.54; 95% CI 1.01 to 12.41). Continuous measure (per 10 ng/ml decrease) of 25(OH)D level was also significantly ($p = 0.003$) and inversely associated with insulin resistance among male participants. However, this association was not observed among female participants ($p = 0.752$). In the present study, when adjusted for age, gender, smoking, alcohol drinking, regular exercise, SBP, DBP, WC, and BMI, our results are consistent with previous studies[11,14,25,26] that serum 25(OH)D levels were inversely associated with HOMA-IR levels. However, in the results after adjustments for TC, TGs, and HDL-C, association of vitamin D status and HOMA-IR was no longer significant (Table 4). These results was similar the results of Gulseth and colleagues.[29] They evaluated the relation between serum concentration of 25(OH)D and insulin action and secretion. In multiple linear analyses, when adjusted for age, gender, geographic location, 25(OH)D concentrations were inversely associated with HOMA-IR ($p = 0.016$). However, when further adjusted for all of the variables, the association of 25(OH)D concentrations and HOMA-IR was no longer significant ($p = 0.240$). Dyslipidemia, such as decrease of HDL-C or increase of total cholesterol and triglycerides, is a consistently strong risk factors of insulin resistance, and is associated with the reduction of vitamin D. In the present results, we conclude that insulin resistance and reduction of vitamin D were increased by effect of the serum lipid contents in the non-diabetic Korean adults. Therefore, when further adjusted for serum lipid contents, such significance has disappeared.

In studies on the association between vitamin D and beta cell function, previous results were not consistent according to ethnicity and country, healthy subjects and subjects with disease.[16–20,30–32] Kayaniyil and his colleagues[16] evaluated the association between 25(OH)D and beta cell dysfunction in type 2 diabetes and suggested that the serum 25(OH)D level was positively associated with beta cell function ($p<0.001$). On the other hand, some studies reported that the association of serum 25(OH)D level and HOMA-*B* is not relevant.[19,20] In the study of Del Gobbo and his colleagues,[19] the serum 25(OH)D level was not associated with HOMA-*B* in non-diabetic Canadian Cree ($p = 0.498$). Cai and his colleagues[20] evaluated the associations between vitamin D and beta cell function in type 2 diabetes in a Chinese population. After adjusting for multiple variables, the serum 25(OH)D level was not associated with either beta cell function ($p = 0.206$) or insulin resistance ($p = 0.150$).

Vitamin D is essential for insulin secretion and peripheral action through binding to the vitamin D receptor in the pancreatic beta cell.[15] Therefore, vitamin D is necessary for beta cell function in the synthesis of insulin in the subjects with insulin resistance. In our results, although an inverse association between vitamin D and HOMA-*B* may seem contradictory, the subjects of our study included a non-diabetic population. In healthy subjects, beta cells sense changes in plasma glucose concentration and are activated to secrete insulin by corresponding elevated levels of plasma glucose.[33] Tao and his colleagues[14] evaluated the association between 25(OH)D level and beta cell function in non-diabetic female Chinese adults. The serum 25(OH)D level (51.75 ± 16.75 nM) and HOMA-*B* (means: 134.6 [89.7–186.0]) were similar to those of the Korean adults of our study (serum 25(OH)D levels, 44.95 ± 16.73 nM; HOMA-*B*, 133.09 ± 70.39), and serum 25(OH)D level was inversely associated with HOMA-*B* ($p<0.001$). In addition, Rhee and his colleagues[12] evaluated the association between 25(OH)D and diabetes in Korean adults, and suggested that the serum 25(OH)D level was inversely associated with HOMA-*B* ($p<0.001$). Several studies reported that vitamin D was inversely associated with blood glucose.[34–36] Research findings on the association between vitamin D and beta cell function were not consistent according to ethnicity, country, or study. These inconsistencies may be attributed to differences of measurements of beta cell function (e.g., clamps, IVGTT, ISSI, IS_{OGTT}, HOMA indices). Although HOMA indices were not the "gold-standard" method (e.g., hyperinsulinemic-euglycemic clamp and the hyperglycemic clamp test), HOMA may be more appropriate for use in large epidemiological studies.[37] In addition, one of the difficulties in conducting the extensive research required to determine the clinical utility of measures of insulin resistance, sensitivity, and secretion is the lack of standardized insulin assays. Results reported from one study to the next are not comparable, which makes only qualitative comparisons between studies possible.[38] Therefore, the introduction of a sustainable insulin assay standardization program is necessary.

The association between beta cell function and vitamin D in non-diabetic subjects continues to be debated. In the present study results, it is unclear whether the increased beta cell function decreases the vitamin D levels, or the reduction of vitamin D increases beta cell function. In either case, the serum 25(OH)D level was inversely associated with beta cell function in non-diabetic Korean adults. In conclusion, the serum 25(OH)D level was inversely associated with beta cell function in non-diabetic Korean adults, but was not associated with insulin resistance.

The present study has a few limitations. First, the OGTTs are more sensitive than the FPG test in the diagnosis of diabetes. However, the OGGTs were not employed in the KNHANES V-1 study (2010). Second, season is the most important determinant of serum 25(OH)D levels, but the data of the KNHANES V-1 study did not specify serum 25(OH)D levels according to season. Therefore, season could not be used as adjustment variable. Third, serum calcium concentration and daily intake volume of vitamin D are important determinant of serum 25(OH)D levels, but the KNHANES V-1 did not measure serum calcium concentration and daily intake volume of vitamin D. Therefore, serum calcium concentration and daily intake volume of vitamin D could not be used as adjustment variable. Fourth, parathyroid hormone (PTH) is an important determinant of serum vitamin D levels. Increased PTH promotes calcium influx into adipocytes, where intracellular calcium enhances lipogenesis.[39] Therefore, the serum vitamin D levels could change depending on serum PTH. However, the data of the KNHANES V-1 study also failed to measure the PTH of these participants (adults ≥20 years of age). The serum 25(OH)D levels for each season, along with calcium and PTH levels, should be included as variables of vitamin D status in future studies. Although the present study has these limitations, this is the first reported study to determine the relationship between vitamin D and insulin resistance and beta cell function in non-diabetic Korean adults. Therefore, more accurate results might be obtained by performing a cohort study by adding these variables.

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