

Association between serum 25-hydroxyvitamin D levels and adiposity measurements in the general Korean population

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BACKGROUND/OBJECTIVES: Obesity, which is a known risk factor for many chronic diseases, has also been associated with vitamin D deficiency. This study explored the relationship between serum 25-hydroxy-vitamin D [25(OH)D] concentrations and adiposity measures in a general Korean population using the most recent, nationally representative survey data.

SUBJECTS/METHODS: The study sample consisted of 4,771 Korean adults (≥ 19 years) who participated in the fifth Korean National Health and Nutrition Examination Surveys. Serum 25(OH)D was determined by radioimmunoassay. Body mass index (BMI), waist circumference (WC) and total body fat content were measured as adiposity measurements. Total body fat content was measured by dual-energy X-ray absorptiometry.

RESULTS: The serum 25(OH)D level was significantly higher in men than in women. Serum 25(OH)D concentration was positively correlated with energy intake, and it was negatively correlated with total body fat content ($P < 0.0001$) and percentage body fat ($P < 0.0001$) after adjustment for age in both sexes, while was inversely correlated with BMI only in women. In multivariable regression analysis, serum 25(OH)D was inversely associated with the total body fat content after adjustment for age, BMI, education, region, smoking, alcohol consumption, physical activity, and energy intake only in men ($P = 0.0047$). However, the serum 25(OH)D concentration was not associated with WC or BMI, indicators of adiposity after adjustment for potential risk factors.

CONCLUSIONS: Serum 25(OH)D concentration was independently associated with the total body fat content in a general Korean population, but it may be not associated with the indicators for estimating adiposity, such as WC or BMI.

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INTRODUCTION

Vitamin D is a fat-soluble vitamin that can be produced in the skin following sun exposure or may be ingested through the diet and nutritional supplementations. Recent evidence supports that lower levels of 25-hydroxyvitamin D [25(OH)D], a generally accepted indicator of vitamin D status, have been associated with glucose intolerance, type 2 diabetes, dyslipidemia, and metabolic syndrome or its components [1-6].

Obesity, which is a known risk factor for these chronic conditions, has been inversely associated with vitamin D status in adults [3,7-9], children and adolescents [10]. McGill *et al.* [3] observed that serum vitamin D concentration was inversely related to body mass index (BMI) and waist circumference (WC) in overweight and obese adults. In a clinical-based sample, Hispanic adults with higher BMI, WC, and waist- to -hip ratio had a lower vitamin D status [11]. On the other hand, Arunabh *et al.* [12] reported that serum vitamin D level was negatively

associated with percentage body fat, but it was not correlated with BMI in healthy black and white women. These inconsistent results may be because adiposity measures have been limited to indirect anthropometric measures such as BMI [7,8,13], WC [3,4,14], waist-to-hip ratio [4,14], and fat mass as measured by bioelectrical impedance [4,10]. Few studies have examined a direct measure of adiposity, such as the total body fat content. Thus, the use of indirect approaches for measuring body fat might underestimate the inverse association between vitamin D status and adiposity. Furthermore, it still remains unclear whether adiposity (or percentage body fat) should be taken into consideration while assessing vitamin D requirements in the general population.

The prevalence of vitamin D deficiency ranges from 5% in Caucasian women to as high as 45% in African-American women in the United States (US) [15]. Racial differences could influence vitamin D levels in ethnic groups [16]. Asians typically have lower levels of 25(OH)D than Caucasians as a result of

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their darker skin pigmentation, which decreases the amount of ultraviolet B (UVB) radiation that can penetrate the skin and produce vitamin D [17]. According to the Fourth Korean National Health Nutrition and Examination Survey (KNHANES IV-2), which was conducted in 2008, the prevalence of vitamin D insufficiency (< 50 nmol/L) was 56% in Korean adults over 19 years of age [18].

One study has reported that a lower serum 25(OH)D level is associated with an increased risk of abdominal obesity and overall obesity among Korean adolescents [19]. However, this study employed indirect measures of adiposity, such as WC and BMI. Thus, a direct measurement, such as body fat content, is required to reveal the association between serum 25(OH)D level and adiposity. To the author's knowledge, this study is the first to reveal an association between vitamin D status and adiposity in the general Korean population using a direct measurement.

Therefore, this study examined the association between serum 25(OH)D concentration and adiposity measurements in a general Korean population using the most recent nationally representative survey data.

SUBJECTS AND METHODS

Study population

The study was based on the Fifth Korean National Health and Nutrition Examination Survey (KNHANES V), a cross-sectional and nationally representative survey carried out by the Korea Center for Disease Control and Prevention (CDC) from October to December of 2010. The survey used a stratified multistage probability sampling design. Of the 8,958 Koreans who participated in the original health examination study, 6,740 adults aged 19 years or over were selected for the present study. However, 1,969 were excluded because socio-economic, anthropometric, or biochemical information was lacking. Therefore, 4,771 Korean adults (1,989 males and 2,782 females) were ultimately eligible for the analysis and constituted the study cohort. Informed written consent for participation was obtained from all study participants. In addition, the study was approved by the Korea CDC Institutional Review Board.

Measurements

Height and body weight were measured as part of the health examination study [18]. BMI was calculated as weight (kg) divided by height squared (m^2). WC was measured to the nearest 0.1 cm at the narrowest point between the lowest rib and the uppermost lateral border of the right iliac crest. Total body fat content was determined by performing a whole-body scan using dual-energy X-ray absorptiometry (DXA) with a radiation densitometer (model DISCOVERY-W, Hologic, Bedford, MA, US). The percentage of total body fat by DXA was calculated using the following formula: $[\text{fat mass (g)}/\text{fat mass (g)} + \text{lean mass (g)} + \text{total bone mineral content (g)}] \times 100$.

The blood samples used to measure 25(OH)D in serum were collected after an overnight fast. All biochemical analyses were carried out within 2 h of blood sampling. Serum 25(OH)D concentrations were measured using a gamma counter (1470 WIZARD gamma-counter, PerkinElmer, Finland) with a radioimmunoassay (25-Hydroxyvitamin D ^{125}I RIA kit; DiaSorin, Stillwater,

US) [20]. All of intra- and interassay coefficients of variation for 25(OH)D were < 12.5% and < 11%, respectively.

Covariates

Information on lifestyle factors was obtained using a self-administered questionnaire and verified with a personal interview. The cutoff points of overweight and obesity were defined by the International Obesity Task Force for Asian adults in the Asian and Pacific regions [21]; underweight (< 18.5 kg/m^2), normal (≥ 18.5 kg/m^2 and < 23 kg/m^2), overweight (≥ 23 kg/m^2 and < 25 kg/m^2), and obese (≥ 25 kg/m^2) based on the BMI. Educational levels were categorized into three groups: ≤ 6 years (elementary school level), 6-12 years (high school level), ≥ 12 years (college level). Participants were classified as non-smokers, former smokers (for at least 1 year) or current smokers. Alcohol consumption was assessed with questionnaires on the frequency of alcohol use during the previous year, and responses were converted into frequencies per week. Alcohol intake was used to divide the participants into three groups: non-drinkers, light or moderate drinkers (< 2 times/week) and heavy drinkers (≥ 2 times/week). Physical activity was classified based on the amount of regular exercise participants completed during their spare time as follows: vigorous exercise for ≥ 20 minutes/time, ≥ 3 times/week; or moderate exercise for ≥ 30 minutes/time, ≥ 5 times/week; or walking for ≥ 30 minutes/time, ≥ 5 times/week. Vitamin D status was classified into three groups: deficient (< 30.0 nmol/L), inadequate (≥ 30 nmol/L and < 50 nmol/L), and adequate (≥ 50 nmol/L) based on serum 25(OH) D level [22]. Participants were categorized as living in either an urban or rural residential district. Seoul, its surrounding metropolitan area (Gyeonggi) and six other metropolitan cities (Busan, Daegu, Incheon, Gwangju, Daejeon, and Ulsan) in South Korea were considered urban areas. The remaining regions (Gangwon, Chungbuk, Chungnam, Jeonbuk, Jeonnam, Gyeonbuk, Gyeongnam, and Jeju) were classified as rural areas. Household income was classified into three groups as low (the first quartile), medium (the second and third quartile), and high (the fourth quartile). The participants' dietary intakes were determined using the 24-hour recall method. Their energy intake was estimated from the food composition table of the Rural Development Administration in combination with the nutrient database of the Korea Health and Industry of Development Institute[23].

Statistical analysis

Data are expressed as numbers and percentages or as means \pm standard errors (SEs). Specific sampling weight with consideration of sampling probability in a health interview, a health examination, and a nutrition survey was used. The Rao-Scott chi-square test was used to compare proportions of categorical variables between men and women by the PROC SURVEYFREQ procedure. Mean values and standard errors of continuous variables were calculated by the PROC SURVEYMEANS procedure, and the PROC SURVEYREG procedure was used to compare the differences between men and women. We investigated possible interactions between sex and serum 25(OH)D level by including an interaction term in fully adjusted regression model. Age-adjusted correlation analysis of serum 25(OH)D with anthropometric measurements of adiposity and dietary intake were

performed. Multivariable regression analyses were performed to evaluate the independent association of the serum 25(OH)D level with adiposity measures by the PROC SURVEYREC procedure. Regression models were differently adjusted for confounding factors of obesity or serum 25(OH) D level such as age, BMI, education, region, smoking, alcohol consumption, physical activity, and energy intake according to adiposity indicators. However, vitamin D intake was not adjusted as a confounding factor since dietary vitamin D intake has not been measured in this study. Sensitivity analyses were carried out excluding subjects who have chronic diseases such as cardiovascular, type 2 diabetes mellitus, and cancer. Statistical analyses were performed with SAS version 9.3 (SAS Institute, Cary, NC, US). *P*-values < 0.05 were considered statistically significant.

RESULTS

Characteristics of participants

A total of 4,771 Korean adults (1,989 males and 2,782 females) participated in this study. The basic characteristics of participants are shown in Table 1. BMI and WC values for men were greater than those of women ($P < 0.0001$), but the body fat content and the percentage of body fat were higher in women ($P < 0.0001$). The serum 25(OH)D concentration was significantly higher in men than in women ($P < 0.0001$). Men were more likely to be highly educated ($P < 0.0001$), to smoke ($P < 0.0001$) and drink alcohol ($P < 0.0001$), and to exercise regularly ($P = 0.0038$). Furthermore, men had significantly higher energy intake than women ($P < 0.0001$).

Correlation among serum 25(OH)D concentration, adiposity measurements and energy intake

Age-adjusted correlation coefficients between adiposity measures and serum 25(OH)D concentration in Korean adults are provided in Table 2. In men, serum 25(OH)D concentration was positively correlated with energy intake, and it was negatively correlated with the total body fat content ($r = -0.080$, $P < 0.0001$) and the percentage of body fat ($r = -0.114$, $P < 0.0001$) after adjustment for age. These correlations were similar for women, but were stronger for men than women. BMI was negatively correlated with serum 25(OH)D concentration only in women ($r = -0.041$, $P = 0.0309$), while WC was not correlated with serum 25(OH)D in both sexes.

Table 1. Characteristics of subjects¹⁾

	Men (n = 1,989)	Women (n = 2,782)	<i>P</i> -value
Age (yrs)	44.6 ± 0.6	46.0 ± 0.5	0.0168
BMI (kg/m ²)	24.0 ± 0.1	23.2 ± 0.1	< 0.0001
Underweight (%)	2.2	6.0	< 0.0001
Normal weight (%)	35.8	46.2	
Overweight (%)	25.5	21.0	
Obese (%)	36.5	26.8	
WC (cm)	84.1 ± 0.3	77.8 ± 0.3	< 0.0001
Total body fat (kg)	16.4 ± 0.2	19.7 ± 0.15	< 0.0001
% total body fat	23.1 ± 0.3	34.0 ± 0.2	< 0.0001
Serum 25(OH) D (nmol/L)	47.7 ± 0.8	42.1 ± 0.7	< 0.0001
Deficient (%)	13.0	21.5	< 0.0001
Inadequate (%)	47.4	53.5	
Adequate (%)	39.6	25.0	
Residential district (%)			
Urban	68.0	68.3	0.8707
Rural	32.0	31.7	
Income (%)			
Low	25.5	27.3	0.4060
Medium	51.4	49.7	
High	23.1	23.0	
Educational level (%)			
≤ 6 yrs	12.4	26.2	< 0.0001
6-12	50.7	44.5	
≥ 12	36.9	29.3	
Smoking Status (%)			
Never	19.1	87.5	< 0.0001
Former	34.9	6.9	
Current	46.0	5.7	
Alcohol consumption (%)			
Never	12.3	31.3	< 0.0001
< 2 times/week	51.4	59.5	
≥ 2 times/week	36.3	9.2	
Physical activity (%)			
Regular	53.6	48.3	0.0038
Energy intake (kcal/d)	2,501 ± 28	1,751 ± 18	< 0.0001

¹⁾ Values are means ± SE or percentages.
BMI; body mass index, WC; waist circumference

Table 2. Age-adjusted Pearson's correlation coefficients among serum 25(OH) D concentration, adiposity measurements, and energy intake in Korean adults (n = 4,771)

	Men						Women					
	Serum 25(OH)D	BMI	WC	Body fat	% body fat	Energy intake	Serum 25(OH)D	BMI	WC	Body fat	% body fat	Energy intake
Serum 25(OH)D	1						1					
BMI	-0.002	1					-0.041**	1				
WC	0.016	0.852***	1				-0.011	0.848***	1			
Body fat	-0.080***	0.812***	0.799***	1			-0.063**	0.876***	0.806***	1		
% body fat	-0.114***	0.617***	0.637***	0.922***	1		-0.084***	0.636***	0.587***	0.866***	1	
Energy intake	0.072**	0.036	0.035	-0.024	-0.007	1	0.050**	-0.016	0.003	-0.025	-0.068***	1

BMI; body mass index, WC; waist circumference

** $P < 0.05$, *** $P < 0.001$

Table 3. Multivariable regression model of predicting adiposity indicators with serum 25(OH)D in Korean adults (n = 4,771)

	Men				Women			
	β	P-value	SE	R ²	β	P-value	SE	R ²
BMI								
Model 1	0.0039	0.3943	0.0046	0.2%	-0.0083	0.1273	0.0054	8.9%
Model 2 ¹⁾	0.0055	0.2127	0.0044	3.6%	-0.0093	0.0877	0.0055	10.8%
Waist circumference								
Model 1	0.0200	0.1663	0.0144	2.7%	-0.0003	0.9795	0.0154	19.9%
Model 2 ²⁾	0.0073	0.4043	0.0088	76.8%	0.0138	0.0902	0.0081	79.7%
Total body fat content								
Model 1	-16.8319	0.0833	9.6607	1.2%	-20.9554	0.0244	9.2255	1.7%
Model 2 ³⁾	-17.5770	0.0047	6.1327	69.8%	-8.3720	0.0774	4.7121	78.2%

Model 1 adjusted for age

Model 2¹⁾ adjusted for age, education region, smoking, alcohol consumption, and energy intake

Model 2²⁾ adjusted for age, BMI, education, region, income, smoking, alcohol consumption, and energy intake

Model 2³⁾ adjusted for age, BMI, education, region, smoking, alcohol consumption, physical activity, and energy intake

The association between serum 25(OH)D concentration and adiposity measurements

A multivariable regression model of predicting obesity with the serum 25(OH)D level is shown in Table 3. The confounding factors for obesity or serum 25(OH)D level were differently adjusted according to adiposity indicators. Among men, serum 25(OH)D concentration was inversely associated with the total body fat content after adjustment for age, BMI, education, region, smoking, alcohol consumption, physical activity, and energy intake ($P=0.0047$). Although an inverse association between serum 25(OH)D concentrations and total body fat content was also shown in women after adjustment for age ($P=0.0244$), the association became weaker after further adjustment for the confounding factors. BMI and WC were not associated with serum 25(OH)D concentration in our subjects of either sex. Furthermore, sensitivity analyses were conducted to determine the robustness of the results after excluding subjects who have chronic diseases ($n=700$), and the results were not meaningfully changed (data not shown).

DISCUSSION

This study found an inverse association between serum 25(OH)D and body fat content in Korean adults using the most recent nationally representative survey data. The serum 25(OH)D concentration was negatively correlated with the total body fat content and the percentage of body fat after adjusting for age in both sexes. Upon multivariable regression analysis, the serum 25(OH)D concentration was inversely associated with total body fat content after adjustment for age, BMI, education, region, smoking, alcohol consumption, physical activity, and energy intake in men. However, the serum 25(OH)D concentration was not associated with WC or BMI, indicators of adiposity, after adjustment for potential risk factors regardless of sex. These results suggest that the serum 25(OH)D concentration may be independently associated with adiposity but not with the indicators used to estimate adiposity, such as WC or BMI.

Our findings are consistent with previous studies reporting an inverse relationship between vitamin D levels and adiposity [4,12,17,24]. The percentage of body fat was independently associated with serum 25(OH)D in healthy Caucasian and

African-American women between 20 and 80 years of age regardless of other well-known factors, such as dietary vitamin D intake, season, age, and race [12]. In Caucasian and African-American adults, the serum 25(OH)D concentration in the obese group was significantly lower than that of the non-obese group, and it was also negatively correlated with DXA fat mass [24]. The plasma 25(OH)D concentration was negatively associated with body fat when bioelectrical impedance was used and also after adjusting for age, BMI and the waist-hip ratio in Caucasian women [4]. The plasma 25(OH)D concentration was inversely associated with visceral fat and subcutaneous fat in Hispanic and African-Americans at baseline, but no significant associations were seen between adiposity and 25(OH)D concentration at the 5-year follow-up visit [17]. However, direct comparison could be difficult because the studies used different measurements for adiposity and also explored members of different ethnic groups.

The inverse association between serum 25(OH)D concentration and adiposity could be explained by the increased storage of 25(OH)D in the adipose tissue of obese participants. Low 25(OH)D levels are associated with increased adiposity, possibly due to enhanced uptake by adipose tissue, thus decreasing the bioavailability of vitamin D3 from cutaneous and dietary sources because of its deposition in body fat compartments [13]. Some experimental data suggest that vitamin D deficiency could promote greater adiposity. Moderate-to-severe vitamin D deficiency leads to elevated parathyroid hormone, which may promote calcium influx into adipocytes and thereby enhance lipogenesis [25]. Furthermore, evidence suggests that 1,25hydroxyvitamin D modulates adipogenesis through vitamin D receptor-dependent inhibition of critical molecular components of adipogenesis, such as peroxisome proliferator-activated receptor γ and C/EBP α [26]. Therefore, depletion of vitamin D stores may lead to excess differentiation of preadipocytes to adipocytes.

In this study, the serum 25(OH)D concentration was associated with total body fat, but not with other indicators of estimating adiposity, such as WC or BMI although those were correlated with body fat. It may be due to intermediate factors between body fat and indirect measures such as age. Although BMI and WC are commonly used to estimate obesity, the indicators are

inaccurate and can lead to bias in measuring adiposity. For example, BMI, an indirect measure of adiposity, is traditionally weaker than direct measures of adiposity because it does not take age, sex, bone structure, fat distribution or muscle mass into consideration [27]. Thus the association between vitamin D and overall adiposity can be underestimated when BMI is used as an estimate of adiposity. Among overweight and obese Puerto Rican adults aged 40-65 years old, serum 25(OH)D was negatively correlated with percent body fat, but it was not correlated with the waist-to-hip ratio or BMI [28]. Bhatt *et al.* reported that serum 25(OH)D was significantly correlated with intra-abdominal adipose tissue depots by using DXA in obese Asian Indians aged 18-60 years, but it was not correlated with WC or waist-to-hip ratio, which are the typical indicators of abdominal obesity [29]. Arunabh *et al.* [12] showed that serum 25(OH)D levels are more strongly correlated with the percentage of total body fat compared with other indicators of adiposity such as body weight or BMI. The percentage of total body fat was more strongly associated with the 25(OH)D level compared with anthropometric measures such as BMI, WC and the sum of skin folds after adjustment for potential confounders in older men and women aged 65 years and older [14]. These results propose that the use of direct measurement for adiposity such as total body fat content may be more proper than the indirect measurements such as BMI and WC in the association between serum 25(OH)D level and adiposity.

Meanwhile, the association between serum 25(OH)D concentrations and total body fat content was much stronger in men compared with women. The different result between men and women may be due to the effect of sex hormones. Estrogen might play a role in these gender differences, because it has a favorable effect on insulin and glucose homeostasis, adipose tissue distribution, and proinflammatory markers [30]. Systemic loss of estrogen at menopause is associated with increased adiposity, which is implicated in the elevated risk of age-related metabolic disease in women [31]. Therefore, the relationship serum 25(OH)D and adiposity could be attenuated by hormonal changes in women.

This study has some limitations. First, the study does not prove a causal relationship because the study was designed cross-sectionally. Second, sunlight exposure and vitamin D intake were not measured, and both of these may affect serum 25(OH)D levels. Despite these limitations, our study examined the total body fat by using DXA, a direct measure of adiposity, although few previous studies have examined direct measures of body fat content. To the best of the author's knowledge, this is the first study to investigate the association of serum 25(OH)D and adiposity in Korean adults using nationally representative survey data.

In conclusion, the serum 25(OH)D concentration was inversely associated with the total body fat content (but not with BMI or WC) after adjustment for potential risk factors in Korean adults, suggesting that the vitamin D level is independently associated with adiposity. Taken together, individuals with a higher percentage of body fat may require a greater vitamin D intake to attain optimal 25(OH)D levels compared with lean individuals; therefore, body fat should be considered when assessing vitamin D requirements. Longitudinal studies or

clinical trials will be needed to confirm the causal relationship between vitamin D status and adiposity, and additional studies will also be required to identify the association between vitamin D status and body fat characteristics in populations with various disease states as well as in healthy people.

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