https://doi.org/10.4082/kjfm.2018.39.3.174 • Korean J Fam Med 2018;39:174-179

KJFM

Korean Journal of Family Medicine

eISSN: 2092-6715

■ Original Article

The Association between 10-Year Atherosclerotic Cardiovascular Diseases Risk Score Calculated Using 2013 American College of Cardiology/ American Heart Association Guidelines and Serum 25-Hydroxyvitamin D Level among Aged 40–79 Years in Korea: The Sixth Korea National Health and Nutrition Examination Surveys

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Background: We examined the relationship between 10-year predicted atherosclerosis cardiovascular disease (ASCVD) risk score and 25-hydroxyvitamin D in Koreans aged 40–79 years.

Methods: A population-based, cross-sectional design was used from data based on the Korea National Health and Nutrition Examination Survey 2014.

Results: A total of 1,134 healthy Koreans aged 40–79 years were included. A positive relationship between serum 25-hydroxyvitamin D level and ASCVD score was shown in women (β=0.015) after adjusting for central obesity, physical activity, and supplement intake. The chances of being in the moderate to high risk (risk group, ASCVD score ≥5%) with vitamin D sufficiency (serum 25-hydroxyvitamin D ≥20 ng/mL) was 1.267-fold (95% confidence interval, 1.039–1.595) greater than the chance of being included in the group with vitamin D deficiency (serum 25-hydroxyvitamin D <20 ng/mL) after adjustments in women.

Conclusion: Our research indicated a significantly positive association between 25-hydroxyvitamin D and ASCVD score. Further detailed studies to evaluate this correlation are needed.

Keywords: Cardiovascular Diseases; Atherosclerosis; Vitamin D

Received: March 6, 2017, Revised: June 7, 2017, Accepted: June 15, 2017

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INTRODUCTION

The American College of Cardiology (ACC) and the American Heart Association (AHA) developed new guidelines for cardiovascular risk assessment in 2013 to quantitatively predict the 10-year risk for first atherosclerotic cardiovascular disease event. The recent guidelines included risks such as age, total cholesterol, high-density lipoprotein (HDL) cholesterol, smoking status, diabetes, and hypertension, which are widely accepted to be major risk factors for cardiovascular disease. These guidelines can be also used to predict stroke event or peripheral artery diseases, apart from cardiovascular disease.[1)]

Meanwhile, several studies have reported that lower vitamin D levels are correlated with metabolic syndrome, which is an important risk factor for cardiovascular diseases. There is accumulating epidemiological evidence from observational studies suggesting that cardiovascular diseases are associated with vitamin D deficiency.[2-4)] Examining the association between serum vitamin D concentration and atherosclerosis cardiovascular disease (ASCVD) score can provide strong evidence for the importance of serum vitamin D concentration for predicting the risk for cardiovascular disease occurrence.

To date, no studies have reported the association of 10-year ASCVD risk score and vitamin D concentration in any country. In this study, we aimed to assess whether there is a correlation between the ASCVD score using the 2013 ACC/AHA guidelines and serum 25-hydroxyvitamin D (25[OH]D) levels in Korean adults.

METHODS

1. Study Population

This study was performed based on data from the 2014 6th Korean National Health and Nutrition Examination Survey (KNHANES). Random sampling and a cross-sectional design was used. Participants who had a diagnosis of congestive heart failure, known coronary heart disease, heart attack, or stroke were excluded from the analysis. We also excluded samples with no vitamin D concentration data or individuals who were bedridden and incapable of any physical activity. Thus, 1,134 healthy Korean men (N=564) and women (N=570) participated in our examination. All participants who took part in the study provided written informed consent.

2. Measurements

Systolic blood pressure and diastolic blood pressure were measured on the subjects' right arm with the subject in a sitting position after 10 minutes of rest using an automated sphygmomanometer. Three consecutive readings of systolic and diastolic blood pressure were taken once per minute and the average value was used for the analysis.

Other demographic variables known to affect the results, such as body mass index (BMI), waist circumference, triglyceride, fasting glucose level, oral nutritional supplements, and physical activity were also analyzed in this study. Obesity, central obesity, physical activity, and oral supplementation were considered as confounding factors.

BMI was computed using the formula BMI=kg/m^2 with body weight in kilograms divided by height in meters squared. Body weight and height were measured with the subject wearing lightweight clothing without shoes to the nearest 0.1 kg and 0.1 cm. Participants whose BMI ≥25 (kg/m^2) were classified into the obese group. Waist circumference was measured with a flexible tape, at the midpoint between the iliac crest ad the lower rib margin, and was recorded to the nearest millimeter. Individuals whose waist circumference ≥90 cm in men and ≥85 cm in women were classified into the central obesity group.

Blood samples were obtained from the antecubital vein of each participant after overnight fasting, and were then centrifuged and transported daily to the central laboratory (NeoDin Medical Institute, Seoul, Korea). Levels of total cholesterol, triglycerides, HDL cholesterol, and blood glucose were measured via enzymatic methods using the Hitachi Automatic Analyzer 7600 (Hitachi, Tokyo, Japan).

To assess vitamin D status, fasting blood samples were collected and serum 25(OH)D concentrations were measured by RIAKit (DiaSorin, Stillwater, MN, USA) 1470 WIZARD gamma-Counter (PerkinElmer, Turku, Finland). Serum 25(OH)D levels reflected endogenous synthesis, dietary intake of foods, fortified products, and/or supplementation with vitamin D.[5)]

By using cut-offs values according to research on optimal serum concentration of 25(OH)D in Korean adults,[6)] the vitamin D concentration intervals were set at <12, 12–20 and ≥20 ng/mL in this study. Serum 25(OH)D level was measured as ng/mL.

We reviewed questionnaires on antihypertensive treatment, diabetes mellitus, lipid-lowering medication, smoking status, physical activities, and oral supplementation. Participants were also categorized into non-current smokers or current smokers. Regular physical activity was defined as participation in a form of moderate (team tennis, volleyball, or carrying light objects) to vigorous exercise (running, climbing, rapid cycling, single tennis, or carrying heavy objects) for more than 90 minutes (vigorous exercise) or 75 minutes (moderate and vigorous exercise) in a week. Oral nutritional supplementation for more than 2 weeks was included as a variable. Information regarding specific vitamin D supplementation was not documented in the 2014 KNHANES.

3. Atherosclerosis Cardiovascular Disease Risk Score Estimation

The variables in the equation for the 10-year risk assessment for ASCVD event included age, sex, race, total cholesterol, HDL cholesterol, systolic blood pressure, hypertension, diabetes mellitus, and current smoking status. The 10-year ASCVD event risk score was calculated using the published Pooled Cohort Equation-based algorithm.[1)] Participants were divided into two groups according to ASCVD score: low-risk group (risk score <5%) versus moderate to high-risk group (risk score ≥5%, risk group).

4. Statistical Analyses

Continuous variables were analyzed using the t-test and categorical

https://doi.org/10.4082/kjfm.2018.39.3.174

variables were analyzed using chi-square tests. Correlations between serum 25(OH)D levels and metabolic parameters, including ASCVD scoring factors, were analyzed using Spearman analyses. An association between ASCVD score (we took logarithm transformation for ASCVD score) and serum 25(OH)D concentration was examined by using linear regression with adjustments for central obesity, physical activity, and intake of nutritional supplements. The odds ratio (OR) and 95% confidence intervals (CIs) were also analyzed to evaluate the changes in the association between serum 25(OH)D and the high-risk group using a multiple linear regression analyses. All statistical analyses were performed using the IBM SPSS Statistics ver. 24.0 (IBM Corp., Armonk, NY, USA). All results were considered statistically significant at the 5% critical level (P<0.05, 2 sided).

RESULTS

Finally, 1,134 Koreans (564 men and 570 women) were included after excluding subjects with missing data, known severe cardiovascular disease, and physically inactivity. Participants' characteristics were summarized in Table 1. The average level of serum vitamin D was 18.42 ng/mL for men and 16.37 ng/mL for women. The average ASCVD risk score was 9.279% for men and 3.52% for women. More men were included in the high-risk group compared to women. The proportion of regular physical activity was almost evenly distributed in both groups. Oral supplementation was more prevalent in women compared to men.

Table 2 presented the coefficients of serum 25(OH)D levels for each metabolic parameter, including ASCVD scoring factors, through Spearman analysis. In both men and women, age was found to be a factor significantly associated with serum 25(OH)D concentration (correlation coefficient [rho]=0.136 for men, rho=0.145 for women, respectively; P=0.001). Additionally, ASCVD risk score, waist circumference, total cholesterol, and HDL cholesterol were also to be significant factors correlating with serum 25(OH)D levels in women.

In Table 3, model 2 displayed a positive association between serum vitamin D level and logarithm-transformed ASCVD score in women after adjusting for central obesity, physical activity, and oral supplements (β=0.015, P=0.022) as confounding variables by linear regression analysis, whereas the association was not statistically significant in men.

We also evaluated the association between serum 25(OH)D and

Table 1. Estimated number or average of general characteristics: from the Korean National Health and Nutrition Examination Survey

Characteristic	Men (n=564)	Women (n=570)	P-value*
Age (y)	54.48±8.92	54.51±8.85	0.955
25-Hydroxylated vitamin D (ng/mL)	18.42±6.95	16.37±7.05	<0.001
Deficiency (<12)	14.7 (83)	28.9 (165)	
Insufficiency (12≤ <20)	48.9 (276)	48.8 (278)	
Normal to sufficiency (≥20)	36.3 (205)	22.3 (127)	
BMI (kg/m^2)	24.42±3.063	23.90±3.269	0.006
Waist circumference	85.53±8.794	79.47±9.199	<0.001
Obesity (BMI ≥25 kg/m^2)	41.1 (232)	31.6 (180)	
Central obesity†	28.5 (161)	27.4 (156)	
Triglyceride (mg/dL)	177.14±142.982	122.21±84.59	<0.001
High-density lipoprotein cholesterol (mg/dL)	47.13±10.893	53.37±10.986	<0.001
Total cholesterol (mg/dL)	190.94±32.963	193.83±33.81	0.145
Fasting glucose (mg/dL)	104.40±23.001	99.59±21.939	<0.001
Systolic blood pressure	121.36±15.58	118.88±17.61	0.012
Diastolic blood pressure	78.91±10.22	74.82±9.24	<0.001
Presence of diabetes mellitus			0.054
Yes	10.6 (60)	7.4 (42)	
No	93.3 (504)	92.6 (528)	
Treatment of hypertension			0.538
Yes	19.7 (111)	18.2 (104)	
No	80.3 (453)	81.8 (466)	
Current smoker			<0.001
Yes	40.4 (228)	4.3 (24)	
No	64.9 (336)	95.8 (546)	
ASCVD risk score (%)	9.279±8.04	3.52±4.479	<0.001
ASCVD risk group‡	63.3 (357)	23.9 (136)	
Physical activity			0.479
Yes	49.8 (281)	47.7 (272)	
No	50.2 (283)	52.3 (298)	
Oral supplement	34.2 (193)	53.9 (307)	<0.001

Values are presented as mean±standard deviation or % (number).
BMI, body mass index; ASCVD, atherosclerotic cardiovascular disease.
*Analyzed by t-test, analysis of variance, or chi-square test. †Defined as waist circumference ≥90 cm (in men) and ≥85 cm (in women). ‡ASCVD high risk defined as ≥5%.

Table 2. Coefficient for vitamin D level and each factor related to metabolic parameters including ASCVD risk score factors

Variable	Men		Women	
	Rho*	P-value†	Rho*	P-value†
ASCVD risk score	0.036	0.396	0.103	0.014
Age	0.136	0.001	0.145	0.001
Waist circumstance	0.057	0.176	0.102	0.015
Body mass index	0.039	0.353	0.043	0.308
Fasting glucose	-0.030	0.606	0.017	0.686
Total cholesterol	-0.010	0.913	0.121	0.004
Triglyceride	-0.750	0.076	0.040	0.341
High-density lipoprotein cholesterol	0.067	0.119	0.104	0.014
Systolic blood pressure	0.022	0.606	0.042	0.317
Diastolic blood pressure	-0.005	0.913	0.054	0.201

ASCVD, atherosclerotic cardiovascular disease.
*Correlation coefficient. †By Spearman analysis.

Table 3. Standardized regression coefficient of vitamin D level for ASCVD risk score

Variable	Men		Women	
	β	P-value*	β	P-value*
Model 1	0.005	0.396	0.02	0.004
Model 2	0.003	0.537	0.015	0.022

ASCVD score was log-transformed before performing the analysis. Model 1 was unadjusted. Model 2 was adjusted for central obesity (waist circumstance ≥90 cm for men, ≥85 cm for women), intake of supplements, and physical activity.
ASCVD, atherosclerotic cardiovascular disease; β, standardized regression coefficients.
*By linear regression analysis.

Table 4. OR and 95% CI for association between serum 25(OH)D and being at moderate to high risk group of ASCVD* from the Korean National Health and Nutrition Examination Survey

Variable	Men		Women	
	Model 1	Model 2	Model 1	Model 2
25(OH)D (per 1 standard deviation)	1.167 (0.977–1.394)	1.15 (0.960–1.379)	1.205 (1.003–1.448)	1.267 (1.039–1.545)
Central obesity		1.897 (1.266–2.842)		3.589 (2.373–5.427)
Physical activity		1.041 (0.733–1.477)		0.652 (0.432–0.985)
Supplement intake		1.18 (0.810–1.718)		0.922 (0.607–1.40)

Values are presented as OR (95% CI). Multiple logistic regression models were used. Reference group: 25(OH)D concentration <20 ng/mL. Model 1: not adjusted; model 2: adjusted for vitamin D, central obesity (waist circumstance ≥90 cm for men, ≥85 cm for women), physical activity, and supplement intake.
OR, odds ratio; CI, confidence interval; 25(OH)D, 25-hydroxy vitamin D; ASCVD, atherosclerotic cardiovascular disease.
*Moderate to high risk group (analyzed as a dependent variable) defined as ASCVD risk score ≥5%.

high-risk group participants using logistic regression analysis in Table 4. The ORs and 95% CIs were presented. A significant positive relationship between 25(OH)D and the chance of being in the high-risk group was observed with or without adjustments in women (OR,1.267; 95% CI, 1.039–1.595). No significant association was found in men.

DISCUSSION

In this study, central obesity, physical activity, and oral supplements were adjusted, as these factors were considered to relate to serum vitamin D level in previous studies. According to Panagiotakos et al.,[7] a high degree of physical activity is associated with attenuated circulating levels of vitamin D. Obesity may decrease vitamin D release from the skin and from dietary sources into the circulation by storing fat-soluble vitamin D in subcutaneous fat due to the 'sequestration theory,' resulting in an inverse correlation between status of obesity serum 25(OH)D level.[8] Also, waist circumstance was found to be a coefficient for vitamin D level in our research (Table 2). Based on evidence that oral vitamin D supplements increase serum 25(OH)D,[9] we also adjusted for oral supplementation as a confounding factor.

We found the presence of a positive association between 25(OH)D level and ASCVD risk score in women after controlling for confounding factors by using linear regression and logistic regression. Women with higher serum 25(OH)D had a higher ASCVD score and women with vitamin D sufficiency had an approximately 1.267-fold increased risk of being in the high-risk group than individuals with vitamin D deficiency, suggesting that vitamin D levels incurred susceptibility for inclusion in the high-risk group. These results were not in accordance with some previous studies on the favorable relationship of high levels of serum vitamin D with cardiovascular diseases. The latest evidence suggested that lower serum concentrations of 25(OH)D were associated with a number of cardiovascular diseases.[10,11] However, in the present study, it appears that age as a variable would play an influential factor for our results in women. As shown in our Table 2, age was a positive coefficient of serum 25(OH)D levels. In women, total cholesterol, another factor for calculating ASCVD score, was also a positive coefficient of serum 25(OH)D. Some studies indicated a positive correlation between vitamin D and total cholesterol.[12-14] Thus, we surmise that age and total cholesterol may have a pivotal effect on the positive correlation between 25(OH)D levels and ASCVD score in women.

Another potential factor influencing the positive relationship could be the frequency of vitamin D supplement intake. Even though we controlled for oral supplements as a confounding variable, data on oral supplements used in our study included all kinds of nutritional supplements such as various types of vitamin supplementations, omega-3 acid, protein-formula, etc. Thus, exact information on whether participants took vitamin D supplements or not was not provided. Elderly women (age is one of important factors to calculate ASCVD score) are more inclined to take vitamin D fortified products or supplements more often with frequent regular hospital visits and to have a higher prevalence of hypochondriasis than men, resulting in the highest serum vitamin D level in individuals over 75 years.[15] More frequent intake of vitamin D supplements in elderly women could affect the positive relationship between vitamin D and ASCVD score in our study. According to Korean research on healthy food in elderly women, 66.8% of elderly women took nutritional supplements and 30.6% of their supplements were composed of vitamin D and mineral supplements, exhibiting a higher rate of oral supplementation than men.[16] Lee et al.[17] found that men were more passive about taking nutritional supplements than women in their research on healthy food intake in Korean men. Therefore, it seems that more frequent intake of vitamin D supplements in elderly women might have strongly influenced our results. Additionally, we adjusted for general nutrient intake, not specific nutrients (Tables 3, 4). Since data on general nutrient intake was not categorized into sections, and detailed data on vitamin D supplements in KNHANES 2014 were not provided, we could not perfectly analyze the variable. Thus, the possibility of oral supplements affecting our results still remains, unfortunately.

The average ASCVD score and the prevalence of being in the high-risk group were higher in men than in women. One possible reason can be due to the different prevalence of cigarette smoking in men and women, as a smoking is thought to exert an influence on predicting the ASCVD scores in our study. The prevalence of tobacco use is 39.3% and 5.5% in men and women, respectively, from 2015 Korean data showing a lower rate of tobacco use in women.[18] However, the smoking rate among women may be underestimated due to inaccuracies in

https://doi.org/10.4082/kjfm.2018.39.3.174

answers to the questionnaire because Korean society places a taboo on women who smoke, resulting in decreased smoking status and lower ASCVD scores in women. According to Park et al.[19] actual female smoking rate is significantly higher than officially reported, showing discrepancies in smoking rate between self-reported surveys and urinary nicotine levels. Furthermore, we observed a higher prevalence of smoking in men in our study, which was oriented towards elderly individuals, and it influenced the ASCVD scores in men. In addition, a higher prevalence of diabetes mellitus would be another explanation for higher ASCVD score in men than in women.

The strength of this study is that it is the first nationwide research to assess interactions between serum 25(OH)D concentration and 10-year ASCVD risk score. We explored the relationship after adjusting for obesity, physical activity, and oral nutritional supplements by using a large, representative, population-based sample of data from Korea.

There were also several limitations. First, the cross-sectional design of the study is a major weakness. Causality cannot be drawn from present study and our results cannot guarantee being part of future guidelines for physicians. Therefore, a longitudinal controlled trial is required to confirm these findings. Second, since it is based predominantly on randomized placebo controlled trials in Western populations, ASCVD score assessment allows for limited interpretation in Korean populations. Asian-specific ASCVD score guidelines are needed in future studies. Third, the optimal cut-off value for vitamin D deficiency level in the Korean population is still controversial. A consensus is required for Asians, including Koreans, in order to identify the optimal cut-off values. Fourth, the production of vitamin D in the skin depends on various sun exposure conditions such as season, latitude, the use of sun block, and skin pigmentation. These variables should be considered for more detailed and accurate research on serum vitamin D levels. In particular, seasonal variations, the strongest factor affecting serum vitamin D level, needs to be addressed in a subsequent study. Furthermore, more intensive identification of causes for the discrepancy of study results between men and women and the positive correlation between serum 25(OH)D and ASCVD score are required. Although age, total cholesterol, and varying frequencies of oral supplement use were considered as influential factors in this study, more evidence is needed. Moreover, ASCVD score is an indirect prognostic factor and we could not determine arterial stiffness or thickness in our sample. Thus, assessing the extent of coronary stenosis or plaque using ultrasonography matched with the ASCVD scores would be necessary to prove the relationship between ASCVD score and arterial-atherosclerotic status. There are also statistical vulnerabilities. A stratified, multistage, probability sampling design would better for statistical analysis for selecting the household units in KNHANES, instead of using simple data sampling analysis. Finally, our study population included only Koreans. Further studies should be conducted with reference to ethnic differences.

In summary, our data demonstrated that a high prevalence of vitamin D deficiency and insufficiency, in otherwise healthy Korean adults, was associated with higher ASCVD score and a higher probability of being in the high-risk group for men compared to women. In addition, there was a significant positive relationship between ASCVD score and serum 25(OH)D concentrations in women after adjusting for confounding variables. These findings in women are the opposite of what we expected based on previous studies that 25(OH)D levels might be negatively associated with the probability of cardiovascular disease occurrence. Age, total cholesterol, and oral supplementation with vitamin D were considered as possible reasons for these findings. In future studies, analyzing exact ingredients such as dietary intake of vitamin D fortified products, oral vitamin D supplements, and cholecalciferol injection status should be conducted to validate our results.

In conclusion, our research indicated women with higher serum 25(OH)D were likely to show higher ASCVD score and also be in a high-risk group based on ASCVD score in Korea. This article was able to assess the relationship between serum 25(OH)D and ASCVD score for the first time.

CONFLICT OF INTEREST

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

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