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ORIGINAL ARTICLE

Age and sex differences in the relationship between serum 25-hydroxyvitamin D and hypertension in the general Korean population

D Kim[1] and J Kim[1,2]

BACKGROUND/OBJECTIVES: Previous studies have suggested that serum 25-hydroxyvitamin D (25(OH)D) is associated with hypertension. However, the effects of age and sex on the relation between serum 25(OH)D and hypertension has not been examined. The present study examined the relationship between serum 25(OH)D and hypertension by age and sex in the general Korean population, considering potential confounders for hypertension.

SUBJECTS/METHODS: We conducted a population-based, cross-sectional study. Twenty thousand four hundred and forty adults aged 19 years or older, who participated in the 2009–2012 Korean National Health and Nutrition Examination Surveys, were selected for the present study. Hypertension was defined as a systolic blood pressure ⩾ 140 mm Hg, diastolic blood pressure ⩾ 90 mm Hg or current use of antihypertensive medication.

RESULTS: We found that serum 25(OH)D levels are inversely associated with hypertension in young and middle-aged adults, but not in the elderly population. In young and middle-aged adults, the adjusted odds ratios (ORs) for hypertension tended to decrease according to the quartiles of serum 25(OH)D after adjustment for potential confounders, although it was only significant in women (OR = 0.73, 95% confidence interval (CI) = 0.58–0.91, *P* for trend = 0.0349). There was no association between serum 25(OH)D concentration and hypertension in elderly subjects of either sex.

CONCLUSIONS: A higher serum 25(OH)D level was strongly associated with a lower prevalence of hypertension in young and middle-aged Korean women, but not in elderly adults.

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INTRODUCTION

Vitamin D in the body is derived from dietary intake or supplementation and from endogenous production of vitamin D in the skin following sun exposure.[1] The primary physiological role of vitamin D is to regulate calcium homeostasis and bone mineralization.[2] Recently, epidemiologic studies suggested that vitamin D has a key role in the regulation of blood pressure and is associated with the risk of hypertension.[3,4] Martins *et al.*[3] observed an inverse association between serum 25-hydroxyvitamin D (25 (OH)D) and the risk of hypertension in 15 088 US adults aged ⩾ 20 years from the National Health and Nutrition Examination Survey data. In a follow-up study of 4–8 years, plasma 25(OH)D levels were shown to be inversely associated with the risk of incident hypertension in middle-aged and older adults.[4] However, some studies show conflicting results in older men[5] or postmenopausal women.[6] Chan *et al.*[5] reported no association between serum 25 (OH)D levels and blood pressure in 939 older Chinese men aged ⩾ 65 years. These inconsistent results across studies could be due to the difference in characteristics of study populations such as age, sex and ethnicity.[7] Thus, it is critical to consider these factors in the analysis of the relationship between vitamin D and the risk of hypertension.

So far, the associations between vitamin D levels and hypertension have been mostly studied in western populations and in certain age groups, especially in older subjects because of the high prevalence of hypertension and relatively low vitamin D levels.[6,8] However, the cause and types of hypertension may vary among age groups, which could affect the association between vitamin D and hypertension.[9]

Therefore, the present study investigated the association between serum 25(OH)D and hypertension in the general Korean population, by age and sex using the most recent nationally representative survey data. This study considered lifestyle factors associated with the risk of hypertension such as dietary intake, physical activity and socioeconomic variables for the analysis.

MATERIALS AND METHODS

Study population

The study was based on the fourth and fifth KNHANES (Korea National Health and Nutrition Examination Survey) (IV-3, V), a cross-sectional and nationally representative survey carried out by the Korean Center for Disease Control and Prevention between 2009 and 2012. The survey used a stratified multistage probability sampling design. Of 36 067 Koreans that participated in KNHANES, 27 492 adults aged 19 years or older were selected for the present study. Among them, 7052 subjects were excluded, because socio-economic, anthropometric or biochemical data were lacking. Ultimately, a total of 20 440 Korean adults (8295 men and 12 145 women) were eligible for the analysis. To investigate the relationship between serum 25(OH)D concentrations and hypertension by age group, the subjects were divided into two age groups (young and

[1]Department of Medical Nutrition, Graduate School of East-West Medical Science, Kyung Hee University, Yongin, South Korea and [2]Research Institute of Medical Nutrition, Kyung Hee University, Seoul, South Korea. Correspondence: Professor J Kim, Department of Medical Nutrition, Graduate School of East-West Medical Science, Kyung Hee University, 1732 Deogyeong-daero, Giheung-gu, Yongin 446-701, Gyeonggi-do, South Korea.
E-mail: kjhye@khu.ac.kr
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middle-aged adults aged 19–64 years and the elderly aged 65 years or older). Informed, written consent for participation was obtained from all study subjects. In addition, the study was approved by the Korea Center for Disease Control and Prevention Institutional Review Board.

Measurements

Height and body weight were measured as part of the health examination. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Blood pressure was measured with a Baumanometer mercury sphygmomanometer (WA Baum, Copiague, NY, USA) after subjects had rested for 5 min in a sitting position. Systolic and diastolic blood pressures (SBPs and DBPs) were measured at phase I and V Korotkoff sound,[10] respectively. Three SBP and DBP readings were recorded and the average of the last two readings was used for data analysis. Hypertension was defined as SBP $\geqslant$ 140 mm Hg or DBP $\geqslant$ 90 mm Hg, or the current use of anti-hypertensive medication.[11] 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, Waltham, Finland) with a radioimmunoassay (25-hydroxyvitamin D ^{125}I RIA kit; DiaSorin, Stillwater, MN, USA).[12] All of the intra- and interassay coefficients of variation for 25(OH)D were $<$ 12.5 and $<$ 11%, respectively.

Covariates

Information about lifestyle factors was obtained using a self-administered questionnaire and verified by personal interview. Subjects were categorized as living in either an urban or rural residential district. The details are described elsewhere.[11] Education levels were categorized into the following three groups: $\leqslant$6 years (elementary school level), 6–12 years (high school level) and $\geqslant$12 years (college level). Smoking status was classified as non-smoker, former smoker (for at least 1 year) or current smoker. Alcohol intake was assessed by a questionnaire regarding the frequency of alcohol use during the previous year; responses were then converted into alcohol intake per week. Alcohol intake was used to categorize the participants into the following three groups: nondrinker, light or moderate drinker ($<$ 2 times/week) and heavy drinker ($\geqslant$2 times/week). Physical activity was categorized into two groups: regular physical activity (hard exercise for $\geqslant$20 min/session, $\geqslant$5 sessions/week; moderate exercise for $\geqslant$30 min/session, $\geqslant$5 sessions/week; or walking for $\geqslant$30 min/sessions, $\geqslant$5 sessions/week) or non-regular physical activity. Cancer and cardiovascular disease were assessed by the question: have you ever had a disease in the last year or more? (Yes/no). Type 2 diabetes mellitus was defined as fasting blood glucose level $\geqslant$126 mg/dl or current use of anti-diabetic medication or insulin therapy, or by a self-report of the physician's diagnosis. The dietary intakes used to calculate nutrient intakes were determined using the 24-h recall method. Nutrient intakes including sodium, potassium and calcium intakes were 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.[13]

Statistical analyses

Statistical analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC, USA). A pooled weight variable, which was calculated considering the number of sample units, was used to analyze the combined data from the 2009 to 2012 KNHANES. Data are expressed as percentage (categorical) or as the means (s.e.) (continuous). The Rao–Scott χ^2-test was used to compare proportions across the groups of categorical variables by the PROC SURVEYFREQ procedure. Mean values and s.e. of continuous variables were calculated by the PROC SURVEYMEANS procedure, and the PROC SURVEYREG procedure was used to compare the differences according to the quartile categories of serum 25(OH)D concentration. Multivariable-adjusted logistic regression analysis was conducted to determine odds ratios (ORs) for hypertension across the quartiles of serum 25(OH)D concentration by the PROC SURVEYLOGISTIC procedure. For the multivariable regression analysis, energy-adjusted nutrient intakes were used as covariates, because most nutrients are correlated with total energy intake.[14] To accomplish energy adjustment, nutrient density was calculated and expressed as intake per 1,000 kcal. *P*-values $<$ 0.05 were considered statistically significant.

Table 1. Characteristics of study population[a]

	Non-hypertension (n = *14 324*)	*Hypertension* (n = *6116*)	P-*values*
Age (year) (%)	40.8 ± 0.2	57.3 ± 0.3	< 0.0001
19 ~ 64	93.8	66.7	< 0.0001
⩾65	6.2	33.3	
Sex (%)			
Men	48.0	55.3	< 0.0001
Women	52.0	44.7	
Residential district (%)			
Urban	72.1	66.2	< 0.0001
Rural	27.9	33.8	
Education level, years (%)			
⩽6	11.2	38.9	< 0.0001
6 ~ 12	51.6	43.0	
⩾12	37.1	18.1	
Smoking status (%)			
Never	55.6	49.6	< 0.0001
Former	13.9	20.9	
Current	30.5	29.5	
Alcohol intake (%)			
Never	20.7	30.5	< 0.0001
< 2 times/week	58.7	40.2	
⩾2 times/week	20.6	29.3	
Physical activity (%)			
Regular	50.9	48.7	0.0270
BMI (kg/m^2)	23.2 ± 0.0	25.1 ± 0.1	< 0.0001
SBP (mm Hg)	110.9 ± 0.1	135.4 ± 0.3	< 0.0001
DBP (mm Hg)	72.8 ± 0.1	84.3 ± 0.2	< 0.0001
Serum 25(OH)D (nmol/l)	42.7 ± 0.3	45.9 ± 0.4	< 0.0001
Adjusted serum 25 (OH)D (nmol/l)[b]	43.4 ± 0.3	42.9 ± 0.4	0.2102
Diseases (%)[c]	7.7	24.3	< 0.0001
Sodium intake (mg/day)	5140.7 ± 40.2	4991.0 ± 59.3	0.0280
Potassium intake (mg/day)	3140.1 ± 20.1	3053.6 ± 31.2	0.0112
Calcium intake (mg/day)	524.0 ± 3.9	500.3 ± 6.6	0.0015

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure; 25(OH)D, 25-hydroxyvitamin D. [a]Values are means ± s.e. or percentages. [b]Adjusted for age, BMI and physical activity. [c]Include cancer, cardiovascular disease and type 2 diabetes mellitus.

RESULTS

Characteristics of study population according to the presence of hypertension are shown in Table 1. Among the 20 440 subjects, 30% had hypertension. The proportion of elderly subjects were higher in the hypertensive subjects than normotensive subjects. The hypertensive subjects were older and were more likely to be men, residing in rural areas, less educated, heavy drinkers and were less likely to be a current smoker and to exercise regularly. The average BMI, blood pressures (both SBP and DBP), serum 25 (OH)D concentrations and the prevalence of chronic diseases such as cancer, cardiovascular disease, and type 2 diabetes mellitus were significantly higher in the hypertensive subjects than the normotensive subjects. Furthermore, the hypertensive subjects had significantly lower intakes of sodium, potassium, and calcium compared to the normotensive subjects.

Characteristics of subjects according to age- and sex-specific quartiles of serum 25(OH)D concentration are provided in Table 2. Among the young and middle-aged male subjects aged 19–64

Table 2. Characteristics of subjects according to age- and sex-specific quartiles of serum 25(OH)D concentration[a]

19–64 Years	*Men*				*Women*			
	Q1 (7.5 ~ 35.6 nmol/l)	*Q2 (35.7 ~ 44.6 nmol/l)*	*Q3 (44.6 ~ 55.0 nmol/l)*	*Q4 (55.1 ~ 150.8 nmol/l)*	*Q1 (7.4 ~ 30.8 nmol/l)*	*Q2 (30.8 ~ 38.6 nmol/l)*	*Q3 (38.7 ~ 48.3 nmol/l)*	*Q4 (48.3 ~ 137.3nmol/l)*
N (%)	1557 (7.6)	1558 (7.6)	1553 (7.6)	1554 (7.6)	2363 (11.6)	2360 (11.5)	2368 (11.6)	2355 (11.5)
Age (year)	37.2 ± 0.4	39.8 ± 0.4	41.8 ± 0.4	44.4 ± 0.4***	38.0 ± 0.3	39.9 ± 0.3	41.7 ± 0.3	44.9 ± 0.4***
Residential district (%)								
Urban	78.8	76.1	67.6	59.5***	79.0	77.8	73.5	64.9***
Rural	21.2	23.9	32.4	40.5	21.0	22.2	26.5	35.1
Education level, years (%)								
⩽6	5.0	6.1	6.8	13.0***	21.5	21.8	27.1	27.3***
6 ~ 12	52.8	50.8	54.5	56.1	47.8	54.0	49.9	46.4
⩾12	42.2	43.1	38.7	30.9	30.7	24.3	23.0	26.3
Smoking status (%)								
Never	23.1	22.1	21.6	18.8*	84.9	85.6	87.8	88.6*
Former	20.0	23.2	26.6	26.9	5.6	5.0	5.3	4.6
Current	56.9	54.8	51.9	54.3	9.5	9.4	7.0	6.8
Alcohol intake (%)								
Never	12.4	11.4	10.1	10.7***	28.1	27.0	25.5	28.5
< 2 times/week	57.3	52.6	50.2	48.1	63.4	62.7	62.9	61.8
⩾2 times/week	30.3	36.0	39.7	41.2	8.5	10.4	11.5	9.6
Physical activity (%)								
Regular	51.7	51.4	52.7	57.6*	45.5	48.4	48.1	52.6*
BMI (kg/m^2)	23.9 ± 0.1	24.4 ± 0.1	24.2 ± 0.1	24.1 ± 0.1*	22.7 ± 0.1	23.1 ± 0.1	23.3 ± 0.1	23.3 ± 0.1***
SBP (mm Hg)	117.1 ± 0.4	117.3 ± 0.4	118.8 ± 0.4	119.3 ± 0.5***	110.4 ± 0.4	111.1 ± 0.4	111.7 ± 0.4	112.9 ± 0.4***
Age-adjusted SBP (mm Hg)	118.3 ± 0.4	117.6 ± 0.4	118.4 ± 0.4	118.0 ± 0.4	112.3 ± 0.4	111.8 ± 0.3	111.3 ± 0.3	110.5 ± 0.4*
DBP (mm Hg)	78.3 ± 0.4	78.3 ± 0.3	79.3 ± 0.4	78.9 ± 0.3	72.1 ± 0.3	72.3 ± 0.3	73.0 ± 0.2	73.4 ± 0.3***
Age-adjusted DBP (mm Hg)	78.9 ± 0.4	78.4 ± 0.3	79.1 ± 0.3	78.2 ± 0.3	73.0 ± 0.2	72.6 ± 0.2	72.8 ± 0.2	72.2 ± 0.2
Hypertension (%)	20.5	22.0	24.7	26.7*	11.5	13.2	14.0	16.9***
Serum 25(OH)D (nmol/l)	29.2 ± 0.1	40.2 ± 0.1	49.5 ± 0.1	67.3 ± 0.4***	25.3 ± 0.1	34.7 ± 0.1	43.1 ± 0.1	60.0 ± 0.3***
Diseases (%)[b]	9.4	10.5	10.2	9.6	6.0	7.5	8.3	10.7***
Sodium intake (mg/day)	5799.1 ± 94.5	6203.8 ± 107.5	6542.9 ± 115.3	6296.5 ± 106.9***	4212.9 ± 63.9	4353.7 ± 74.1	4400.3 ± 77.0	4309.5 ± 75.6
Potassium intake (mg/day)	3331.8 ± 49.5	3598.7 ± 43.6	3700.9 ± 55.0	3716.5 ± 55.0***	2653.7 ± 36.7	2809.5 ± 39.4	2916.7 ± 42.5	2956.9 ± 43.7***
Calcium intake (mg/day)	555.8 ± 11.1	588.3 ± 8.7	614.4 ± 10.6	605.0 ± 9.7***	445.5 ± 7.4	472.2 ± 7.5	484.0 ± 8.4	493.9 ± 8.2***

Table 2. (Continued)

⩾65 Years	Men				Women			
	Q1 (10.8 ~ 38.7 nmol/l)	Q2 (38.8 ~ 49.4 nmol/l)	Q3 (49.4 ~ 61.9 nmol/l)	Q4 (62.0 ~ 134.0 nmol/l)	Q1 (10.3 ~ 33.6 nmol/l)	Q2 (33.7 ~ 43.7 nmol/l)	Q3 (43.7 ~ 55.8 nmol/l)	Q4 (55.8 ~ 167.1 nmol/l)
N (%)	519 (2.5)	520 (2.5)	516 (2.5)	518 (2.5)	676 (3.3)	674 (3.3)	676 (3.3)	673 (3.3)
Age (year)	72.2 ± 0.3	71.6 ± 0.3	71.8 ± 0.3	71.8 ± 0.3	72.2 ± 0.3	72.8 ± 0.2	72.7 ± 0.3	72.6 ± 0.3
Residential district (%)								
Urban	74.0	63.8	52.7	46.5***	68.3	60.0	47.3	49.9***
Rural	26.0	36.2	47.3	53.5	31.7	40.0	52.7	50.1
Education level, years (%)								
⩽6	40.2	42.9	47.2	58.3***	83.0	86.5	87.7	86.2
6 ~ 12	46.5	42.1	40.5	30.5	16.0	12.5	10.6	11.9
⩾12	13.3	15.0	12.3	11.2	1.0	1.1	1.6	1.9
Smoking status (%)								
Never	14.4	19.0	15.3	13.7	90.2	87.5	90.1	94.4*
Former	43.6	45.5	49.3	45.8	2.7	4.9	4.5	2.2
Current	42.1	35.5	35.5	40.6	7.0	7.6	5.4	3.3
Alcohol intake (%)								
Never	33.0	32.8	29.1	29.3*	65.0	63.7	64.9	63.6
< 2 times/ week	37.7	35.5	30.9	28.9	31.1	31.4	29.5	30.9
⩾2 times/ week	29.2	31.7	39.9	41.8	3.9	4.9	5.7	5.4
Physical activity (%)								
Regular	50.8	55.7	52.2	60.9*	33.1	43.4	42.7	46.0***
BMI (kg/m^2)	23.3 ± 0.2	23.2 ± 0.2	23.3 ± 0.2	22.9 ± 0.2	24.7 ± 0.2	24.6 ± 0.1	24.1 ± 0.2	23.9 ± 0.2***
SBP (mm Hg)	128.6 ± 0.9	128.7 ± 1.0	128.7 ± 1.1	127.9 ± 1.1	131.9 ± 1.0	132.0 ± 0.8	133.2 ± 0.8	131.3 ± 0.9
Age-adjusted SBP (mm Hg)	128.6 ± 0.9	128.8 ± 1.0	128.7 ± 1.1	128.0 ± 1.1	132.0 ± 1.0	131.9 ± 2.0	133.1 ± 3.0	131.3 ± 4.0
DBP (mm Hg)	74.8 ± 0.5	73.8 ± 0.5	74.0 ± 0.7	74.6 ± 0.5	74.5 ± 0.5	74.9 ± 0.5	75.4 ± 0.5	74.5 ± 0.5
Age-adjusted DBP (mm Hg)	74.9 ± 0.5	73.7 ± 0.5	74.0 ± 0.6	74.6 ± 0.5	74.4 ± 0.5	75.0 ± 0.5	75.4 ± 0.5	74.4 ± 0.5
Hypertension (%)	58.0	61.0	59.7	52.8	71.3	66.8	67.0	65.2
Serum 25(OH) D (nmol/l)	30.7 ± 0.3	44.5 ± 0.2	55.0 ± 0.2	74.1 ± 0.7***	27.2 ± 0.2	38.7 ± 0.1	49.6 ± 0.2	69.5 ± 0.7***
Diseases (%)[b]	36.7	33.2	29.9	27.9	31.0	26.3	25.5	34.5*
Sodium intake (mg/day)	4590.0 ± 134.8	4690.0 ± 158.6	4729.2 ± 158.5	5306.2 ± 225.4	3250.9 ± 95.7	3245.8 ± 107.4	3475.4 ± 120.1	3355.8 ± 100.8
Potassium intake (mg/ day)	2759.9 ± 79.5	2830.0 ± 78.7	2902.2 ± 86.2	3108.1 ± 86.5*	2072.3 ± 46.6	2310.9 ± 102.5	2296.2 ± 74.2	2228.7 ± 51.5*
Calcium intake (mg/day)	488.4 ± 19.5	476.8 ± 16.3	470.4 ± 17.0	515.1 ± 20.7	319.7 ± 9.5	408.9 ± 34.7	396.4 ± 16.4	382.1 ± 15.4***

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure; 25(OH)D, 25-hydroxyvitamin D. *$P < 0.05$; ***$P < 0.001$. [a]Values are means ± s.e. or percentages. [b]Include cancer, cardiovascular disease and type 2 diabetes mellitus.

years, those in the highest quartile of serum 25(OH)D level were older, more likely to live in rural areas, to be less educated, to drink alcohol and to exercise regularly, and less likely to be non-smokers compared with subjects in the lowest quartile. These associations were similar for young and middle-aged female subjects, except there was no association with alcohol intake and sodium intake. In young and middle-aged men, SBP increased with increasing serum 25(OH)D concentrations, but this association disappeared after adjusting for age. On the other hand, in young and middle-aged women, SBP increased with increasing concentrations of serum 25(OH)D, but it decreased after adjustment for age. Nutrient intakes such as potassium and calcium were significantly higher in the highest quartile of serum 25(OH)D concentration than in the lowest quartile in both men and women. The prevalence of chronic disease significantly increased according to the quartiles of serum 25(OH)D concentration in young and middle-aged women.

Among the elderly subjects, similar to the young and middle-aged adults, those in the highest quartile of serum 25(OH)D level were more likely to live in rural areas, to be less educated and to exercise regularly, and less likely to be non-smokers compared with subjects in the lowest quartile in both men and women. The proportion of heavy drinkers increased according to the quartiles of serum 25(OH)D concentration only in elderly men. BMI was not associated with serum 25(OH)D levels in elderly men, although it decreased as serum 25(OH)D increased in elderly women. SBP, DBP and the prevalence of hypertension were not significantly different across the quartiles of serum 25(OH)D in both elderly men and women. Male subjects in the highest serum 25(OH)D quartile had a higher intake of potassium and female subjects in the highest serum 25(OH)D quartile had higher intakes of potassium and calcium, compared with those in the lowest quartile.

Age- and sex-specific odds ratios (ORs) and 95% confidence intervals (CIs) for hypertension according to serum 25(OH)D concentration are summarized in Table 3. In young and middle-aged adults, the adjusted OR for hypertension tended to decrease according to the quartiles of serum 25(OH)D, after adjustment for potential confounders such as age, BMI, education level, residential district, alcohol intake, smoking status, physical activity and the presence of chronic diseases, although it was only significant in women (OR = 0.72, 95% CI = 0.58–0.90, *P* for trend = 0.0276). This association remained statistically significant after further adjustment for nutrient intakes of sodium, potassium and calcium. (OR = 0.73, 95% CI = 0.58–0.91, *P* for trend = 0.0349). Unlike the young and middle-aged subjects, there was no association between serum 25(OH)D concentration and hypertension in both elderly men and women.

DISCUSSION

This study found that serum 25(OH)D levels are inversely associated with hypertension in young and middle-aged adults, but not in the elderly subjects, using the most recent nationally representative survey data. In young and middle-aged women, a higher serum 25(OH)D concentration was significantly associated with a decreased prevalence of hypertension after adjusting for potential confounders such as age, BMI, education level, residential district, alcohol intake, smoking status, physical activity, the presence of chronic diseases and nutrient intakes. In young and middle-aged men, the prevalence of hypertension tended to decrease with increasing serum 25(OH)D concentrations, although the relation was not statistically significant. In contrast, there was no association between serum 25(OH)D concentration and hypertension in elderly subjects. These results suggest that the vitamin D level may be an independent risk factor for hypertension in young and middle-aged adults, but not in elderly subjects.

Our findings are consistent with previous observations indicating an inverse association between serum 25(OH)D concentration and hypertension.[6,15–17] A nested case–control study found that the adjusted OR for hypertension was significantly lower among subjects in the highest quartile of plasma 25(OH)D concentration compared with those in the lowest quartile, after adjustment for BMI, physical activity, family history of hypertension, oral contraceptive use, creatinine, parathyroid hormone, calcium phosphorous and uric acid levels among 1484 non-obese young women aged 32–52 years.[15] In a randomized controlled trial of 16 weeks duration conducted in 109 young and healthy women aged 18–35 years, SBP and DBP decreased significantly in the subjects who consumed vitamin D-fortified skimmed milk but not in those assigned to the placebo.[16]

Several clinical and epidemiological studies may help explain that the relationships between vitamin D and blood pressure. The renin–angiotensin system (RAS) has an essential role in the regulation of blood pressure, by affecting blood vessel tone, extracellular fluid volume and electrolyte homeostasis. Therefore, inappropriate overstimulation of the RAS will cause hypertension.[18,19] Vitamin D has been known to regulate blood pressure by suppressing the RAS by inactivating renin gene expression and inhibiting renin synthesis.[20] In addition to this mechanism of vitamin D, lower levels of 25(OH)D are associated with insulin resistance, which has been proposed to be related to

Table 3. Age- and sex-specific ORs and 95% CIs for hypertension according to serum 25(OH)D concentrations

	Men				*Women*			
	Q1	*Q2*	*Q3*	*Q4*	*Q1*	*Q2*	*Q3*	*Q4*
19–64 Years								
Model 1[a]	1.0	0.82 (0.66–1.01)	0.89 (0.73–1.10)	0.87 (0.70–1.08)	1.0	0.93 (0.75–1.15)	0.82 (0.65–1.05)	0.72 (0.58–0.90)
P for trend			0.3155				0.0276	
Model 2[b]	1.0	0.82 (0.66–1.02)	0.90 (0.73–1.10)	0.87 (0.70–1.08)	1.0	0.93 (0.75–1.15)	0.83 (0.65–1.06)	0.73 (0.58–0.91)
P for trend			0.3433				0.0349	
⩾65 Years								
Model 1[a]	1.0	1.20 (0.86–1.67)	1.08 (0.78–1.51)	0.87 (0.64–1.20)	1.0	0.79 (0.59–1.05)	0.89 (0.66–1.20)	0.81 (0.61–1.07)
P for trend			0.2247				0.3313	
Model 2[b]	1.0	1.21 (0.87–1.69)	1.08 (0.77–1.51)	0.89 (0.64–1.22)	1.0	0.77 (0.58–1.03)	0.88 (0.65–1.18)	0.80 (0.61–1.06)
P for trend			0.2369				0.2828	

Abbreviations: BMI, body mass index; CI, confidence interval; OR, oddss ratio; 25(OH)D, 25-hydroxyvitamin D. [a]Adjusted for age, BMI, education level, residential district, smoking status, alcohol intake, physical activity and the presence of diseases. [b]Model 1+further adjusted for energy-adjusted nutrient intakes including sodium intake, potassium intake and calcium intake.

developing hypertension; thus, vitamin D therapy may improve insulin secretion and sensitivity, and may subsequently prevent hypertension.[21,22] A population-based cohort study supported one of our findings with the result that serum 25(OH)D was not significantly associated with the blood pressure or prevalence of hypertension in 1205 older men and women aged 65 years and older.[6] In addition, Scragg *et al.*[17] failed to lower blood pressure through oral supplementation with vitamin D_3 in 95 elderly men and women aged 63–76 years in England over 5 weeks. However, other studies have showed conflicting results with our study, showing an association between serum 25(OH)D concentrations and hypertension in elderly subjects.[23,24]

Meanwhile, the association between serum 25(OH)D concentrations and hypertension was not observed among elderly subjects in the present study. The different results between age groups may be due to age-related processes affecting the pathogenesis of hypertension in the elderly, independent of vitamin D levels.

For instance, an increased arterial stiffness could contribute to hypertension in the elderly, which would result in an increase of peripheral vascular resistance and SBP in elderly adults.[9,25,26] Previous studies have shown that the frequency of hypertension subtypes in patients with uncontrolled hypertension differ in patients older than 60 years of age compared with younger adults,[27] and an increase in arterial stiffness is a contributor to the pathogenesis of systolic hypertension with increasing pulse pressure with aging, which is the most common form of hypertension in the elderly.[28–32]

Another pathophysiological change in the elderly is a reduction of vascular availability of nitric oxide, which has a cardiovascular protective role as an endothelium-derived relaxing factor.[33,34] The alterations in vascular endothelium caused by a decrease in the production of nitric oxide with aging impair vasodilation and can cause hypertension.[34,35] Taken together, we suppose that age-related alterations might have diluted the relationship between serum 25(OH)D concentrations and hypertension in elderly subjects.

Interestingly, an inverse association between serum 25(OH)D concentrations and hypertension was observed only in younger women. This result suggests that a protective effect of vitamin D on hypertension could be more relevant in women than men. Balan and Popescu[36] reported gender differences in the relationship between hypertension and its risk factors. Risk factors related to hypertension such as genetic polymorphisms similar to those of RAS, sex hormones and increased immune inflammatory factors may have a greater impact on women than on men.[36] There is some evidence that the response to a stimulation of the RAS differs in men and in women.[37] Thus, the effect of vitamin D suppressing the RAS may be different between men and women as well. Verdoia *et al.*[38] also showed an independent association between female gender and vitamin D deficiency, and a more relevant role of hypovitaminosis D in the risk of more extensive disease in women as compared with men.

Our study had several limitations. First, the observed association cannot prove a cause-and-effect relationship due to the cross-sectional design. Second, intake of vitamin D from food or supplements was not measured. Third, we could not consider the effect of parathyroid hormone on vitamin D status or hypertension, because parathyroid hormone level was only measured among participants aged 50 years and over.

Despite these limitations, to the best of our knowledge, this is the first study that investigates age and sex differences in the relationship between serum 25(OH)D concentrations and hypertension, adjusting for important confounding factors relevant to hypertension, including nutrient intake in a general Korean population. The strength of our study is the use of the largest and most recent nationally representative survey data among the general Korean population.

In conclusion, the study showed that the serum 25(OH)D concentration was inversely associated with hypertension after adjustment for potential risk factors among young and middle-aged Korean adults, especially in women, but the association was not observed in elderly adults. Prospective studies and randomized controlled trials should be conducted to better understand the relationship between vitamin D status and the risk of hypertension, comparing age, sex or ethnicity differences.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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