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Borderline high serum calcium levels are associated with arterial stiffness and 10-year cardiovascular disease risk determined by Framingham risk score

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Abstract

Recent epidemiological data indicate that the concentration of circulating calcium is related to cardiovascular disease (CVD) mortality. We determined whether serum calcium level is related to arterial stiffness and 10-year CVD risk calculated by Framingham risk score (FRS). We examined the association of normal-range serum calcium level with arterial stiffness and FRS in 565 Korean adults participating at the Health Promotion Center of Gangnam Severance Hospital between March 2016 and May 2017. High brachial-ankle pulse wave velocity (baPWV) was defined as >1460 cm/s, and high FRS was defined as ≥10 percent for 10-year CVD risk. Odds ratios (ORs) and 95% confidence intervals (95% CIs) for high baPWV and high FRS were calculated using multiple logistic regression analysis after adjusting for confounding variables. The OR (95% CI) for high baPWV was 3.91 (1.15-7.36) per 1 mg/dL increment of serum calcium after adjusting for age, sex, body mass index, smoking status, exercise regularity, alcohol consumption, mean blood pressure, fasting plasma glucose, triglyceride, HDL-cholesterol, C-reactive protein, γ-glutamyltransferase, uric acid level, phosphate level, potassium level, and presence of hypertension, diabetes and dyslipidemia medications (P = 0.024). A positive association between serum calcium level and high FRS was also observed after adjusting for the same covariables (OR, 3.54 [95% CI, 1.01-12.44], P = 0.048). Serum calcium level was independently and positively associated with baPWV and 10-year CVD risk estimates. Early detection of higher serum calcium level may be important for the assessment of arterial stiffness and future risk of a cardiovascular event.

1 | INTRODUCTION

Cardiovascular disease (CVD) is a leading cause of premature mortality among middle-aged and elderly individuals in both developing and developed countries.[1,2] The burden of CVD has been reported to be a substantial determinant of a lower quality of life among the elderly. Therefore, early identification of individuals at higher risk for CVD may allow utilization of preventive strategies important for slowing the development and progression of CVD.

Calcium is a pervasive divalent cation that is involved in blood coagulation and muscle contraction as well as in skeletal mineralization and nerve excitability.[3,4] Blood calcium concentration is mainly managed by the balance of calcitonin and parathyroid hormone and can be influenced by various factors such as diet, vitamin D level, and daily activity.[5,6] Recently, accrued epidemiological data indicate that the concentration of circulating calcium is positively related to CVD morbidity and mortality in the general population.[7-9] There is also an emerging issue regarding the possible relationship between calcium supplements and increasing CVD risk.[10,11]

In this study, we hypothesized that the link between higher calcium concentrations and increased CVD risk may be explained by prolonged exposure of higher serum calcium to structural and functional changes within the arterial walls, resulting in arterial stiffness. To this end, we investigated the association of serum calcium level with arterial stiffness in Korean adults as measured by brachial-ankle pulse wave velocity (baPWV) and Framingham risk score (FRS), a widely used metric to estimate global risk for a 10-year CVD event.

2 | METHODS

2.1 | Study population

We reviewed the medical records of 641 participants (366 males, 275 females) who underwent a medical examination at the Health Promotion Center of Gangnam Severance Hospital, Yonsei University College of Medicine between March 2016 and May 2017. Subjects meeting any of the following criteria were excluded (n = 76): subjects with any missing covariate information, a history of coronary heart disease or stroke, subjects with C-reactive protein concentration >10.0 mg/L (to rule out acute inflammatory disorders), and subjects with serum calcium concentration >10.5 mg/dL or <8.5 mg/dL (to rule out calcium homeostasis disorders). After exclusions, 565 participants (333 males, 232 females) were included in the final analysis. This study was approved by the Institutional Review Board of Yonsei University College of Medicine, and informed consent was obtained from each participant. The examinations were performed by medical staff according to standard procedures.

2.2 | Data collection

Participants were asked questions regarding their lifestyles and behaviors, including whether they smoked cigarettes, consumed alcohol, and engaged in physical activity (more or <2 times per week), as well as whether they were currently undergoing treatments for any disease. If so, they were asked for the date of diagnosis and a list of current medications. Trained staff reviewed the completed questionnaires and entered responses into a database. Participants were classified as either non-smokers, ex-smokers, or current smokers and as non-drinkers or current drinkers. Body mass index (BMI) was calculated for each participant as weight divided by height squared (kg/m^2). After a 12-hour overnight fast, blood samples were collected from an antecubital vein. Fasting plasma glucose, total cholesterol, triglyceride, HDL-cholesterol, γ-glutamyltransferase, uric acid, calcium, and potassium levels were measured using a Hitachi 7600-110 Chemistry Autoanalyzer (Hitachi, Tokyo, Japan). High-sensitivity C-reactive protein (CRP) concentration was measured with a Roche/Hitachi 912 System (Roche Diagnostics, Indianapolis, IN, USA) using a latex-enhanced immunoturbidimetric method with a lower limit of detection of 0.02 mg/L. A Type 2 diabetic was defined as a participant with a fasting plasma glucose level ≥ 126 mg/dL or currently using anti-diabetes medication. Hypertension was defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or currently using anti-hypertension medication.

2.3 | BaPWV measurement

We used an automatic waveform analyzer (model BP-203RPE; Colin Co., Komaki, Japan) to measure baPWV. This instrument simultaneously records a phonocardiogram, electrocardiogram, and arterial blood pressure at both brachial arteries as well as both ankles. After 10 minutes of bed rest, participants were examined in the supine position. Electrocardiogram electrodes were placed on both wrists, and a microphone for the phonocardiogram was placed on the left edge of the sternum. Pneumatic cuffs were wrapped around both upper arms and ankles and connected to a plethysmograph to determine the volume pulse waveform. Waveforms for brachial and tibial arteries were stored for 10-second sample times with automatic gain analyses and quality adjustments. Oscillometric pressure sensors were attached to the cuffs to measure blood pressure in the four extremities. The baPWVs were recorded using a semiconductor pressure sensor (1200 Hz sample acquisition frequency) and calculated using the following equation: (La-Lb)/ΔTba, where La and Lb were defined as the distance from the aortic valve to the elbow and to the ankle, respectively, and the time interval between the arm and ankle distance (ΔTba) was defined as the pulse transit time between the brachial and tibial arterial pressure waveforms. The distances from the suprasternal notch to the elbow (La) and to the ankle (Lb) were estimated automatically and expressed by the following equations: La = 0.2195 × participant height (cm) − 2.0734 and Lb = 0.8129 × participant height (cm) + 12.328.

2.4 | Framingham 10-year risk estimation

Framingham risk score is a useful tool for predicting a patient's risk of severe cardiovascular events up to 10 years after estimation. Equations used in risk estimation are based on the individual's description of their age, sex, current blood pressure, reported lipid profile, smoking status, and use of blood pressure lowering drugs. Categories of patient demographics used to calculate FRS were as follows: age—20-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, and 75-79 years; sex—male or female; total cholesterol level—<160, 160-199, 200-239, 240-279, and ≥280 mg/dL; HDL-cholesterol level—≥60, 50-59, 40-49, and <40 mg/dL; smoking status—non-smoker or ex-smoker, and current smoker; and systolic blood pressure—<120, 120-129, 130-139, 140-159, and ≥160 mm Hg according to the presence of hypertension treatment. Estimated risk for 10-year CVD was classified as low risk (<10%) and intermediate risk or high risk (≥10%).[12]

2.5 | Statistical analysis

High baPWV was defined as >1460 cm/s, which corresponded to the 75th percentile of the current sample, and high FRS was defined

TABLE 1 Clinical characteristics of the subjects according to presence of high baPWV

	Controls (n = 421)	High baPWV (n = 144)	*P*
Age, y	44.7 (10.2)	57.9 (10.1)	<0.001
Male sex, %	58.9	59.0	0.979
Body mass index, kg/m^2	23.7 (2.9)	24.8 (2.5)	<0.001
Current smoking, %	22.1	24.3	0.583
Ever smoking, %	22.8	22.9	0.977
Alcohol consumption[a], %	75.8	60.4	<0.001
Regular exercise[b], %	59.1	54.2	0.296
Mean blood pressure, mm Hg	86.1 (11.2)	98.2 (12.0)	<0.001
Fasting plasma glucose, mg/dL	94.7 (18.4)	104.3 (26.4)	<0.001
Triglyceride, mg/dL	107.5 (98.6)	145.3 (80.7)	<0.001
HDL-cholesterol, mg/dL	48.3 (12.8)	43.9 (10.4)	<0.001
C-reactive protein, mg/L	0.8 (1.1)	1.4 (1.8)	<0.001
Serum calcium, mg/dL	9.3 (0.3)	9.4 (0.3)	<0.001
Serum phosphate, mg/dL	3.7 (0.5)	3.8 (0.5)	0.006
Serum potassium, mmol/L	4.6 (0.2)	4.7 (0.1)	0.714
γ-glutamyltransferase, U/L	24.3 (16.1)	27.2 (15.6)	0.058
Uric acid, mg/dL	5.2 (1.4)	5.4 (1.2)	0.155
Hypertension medication, %	7.8	28.5	<0.001
Diabetes medication, %	2.9	10.4	<0.001
Dyslipidemia medication, %	4.5	6.9	0.253

Data are expressed as the mean (SD) or percentage.
[a]Alcohol consumption ≥ 140 g/wk.
[b]Regular exercise ≥ twice/wk.

TABLE 2 Clinical characteristics of the subjects according to presence of high FRS

	Controls (n = 428)	High FRS (n = 137)	*P*
Age, y	45.2 (10.9)	56.7 (9.6)	<0.001
Male sex, %	51.9	7.3	<0.001
Body mass index, kg/m^2	23.6 (2.9)	25.3 (2.4)	<0.001
Current smoking, %	10.8	59.9	<0.001
Ever smoking, %	24.3	18.3	0.142
Alcohol consumption[a], %	71.5	73.0	0.734
Regular exercise[b], %	62.4	43.8	<0.001
Mean blood pressure, mm Hg	87.4 (12.7)	94.8 (10.5)	<0.001
Fasting plasma glucose, mg/dL	93.2 (15.4)	109.2 (30.1)	<0.001
Triglyceride, mg/dL	105.6 (95.9)	153.5 (85.8)	<0.001
HDL-cholesterol, mg/dL	48.8 (12.5)	42.1 (10.2)	<0.001
Serum calcium, mg/dL	9.3 (0.3)	9.4 (0.3)	<0.001
Serum phosphate, mg/dL	3.7 (0.5)	3.6 (0.5)	0.039
Serum potassium, mmol/L	4.0 (0.3)	4.1 (0.3)	0.037
C-reactive protein, mg/L	0.8 (1.2)	1.2 (1.6)	0.009
γ-glutamyltransferase, U/L	22.6 (14.9)	32.6 (17.0)	<0.001
Uric acid, mg/dL	5.1 (1.4)	5.8 (1.2)	<0.001
Hypertension medication, %	7.9	29.2	<0.001
Diabetes medication, %	1.6	14.6	<0.001
Dyslipidemia medication, %	3.7	9.5	0.007

Data are expressed as the mean (SD) or percentage.
[a]Alcohol consumption ≥ 140 g/wk.
[b]Regular exercise ≥ twice/wk.

as ≥10 percent for 10-year CVD risk. We compared basic characteristics of each demographic group using independent two-sample *t*-tests for continuous variables (age, BMI, mean blood pressure, fasting plasma glucose, triglyceride, HDL-cholesterol, CRP, γ-glutamyltransferase, uric acid, potassium, phosphate, and calcium levels) and a chi-square test for categorical variables (sex, smoking status, alcohol consumption, rate of physical activity, use of hypertension medication, use of diabetes medication, and use of dyslipidemia medication). To determine whether an independent relationship existed between serum calcium level and high baPWV or high FRS, we used multiple logistic regression analysis after adjusting for confounding variables. All analyses were conducted in 2017-2018, using SAS statistical software (version 9.4; SAS Institute Inc, Cary, NC, USA). All statistical tests were two-sided, and statistical significance was determined at $P < 0.05$.

3 | RESULTS

Tables 1 and 2 list the demographic and biochemical characteristics of the study sample (n = 565). The overall prevalence of high baPWV and high FRS was 25.4% and 24.2%, respectively. Mean calcium level was significantly higher in high baPWV and high FRS groups compared with the control group ($P < 0.001$ for both). Mean values for age, BMI, mean blood pressure, fasting plasma glucose, triglycerides, and CRP level were higher in the high baPWV group, but HDL-cholesterol and alcohol consumption were higher for those in the control group. Similar patterns were seen in the high FRS group compared to the control group. Additionally, serum potassium and uric acid levels were higher in the high FRS group, without significant difference in alcohol consumption.

Table 3 shows the risk of high baPWV and high FRS according to changes in serum calcium level. After adjusting for age, sex, BMI, smoking status, exercise regularity, alcohol consumption, mean blood pressure, fasting plasma glucose, triglycerides, HDL-cholesterol,

TABLE 3 Multiple logistic regression analysis showing the independent contribution of serum calcium level to high baPWV and high FRS

	High baPWV		High FRS	
	OR (95% CIs)	*P*	OR (95% CIs)	*P*
Model 1[a]	4.00 (1.86-8.61)	<0.001	3.98 (1.66-9.53)	0.002
Model 2[b]	2.70 (1.07-6.80)	0.035	3.66 (1.09-12.29)	0.036
Model 3[c]	3.91 (1.15-7.36)	0.024	3.54 (1.01-12.44)	0.048

[a]Model 1: adjusted for age and sex.
[b]Model 2: adjusted for age, sex, body mass index, smoking status, alcohol consumption, regular exercise, mean blood pressure, fasting plasma glucose, triglyceride, HDL-cholesterol, C-reactive protein, γ-glutamyltransferase, uric acid, phosphate, and potassium levels.
[c]Model 3: adjusted for age, sex, body mass index, smoking status, alcohol consumption, regular exercise, hypertension medication, diabetes medication, dyslipidemia medication, mean blood pressure, fasting plasma glucose, triglyceride, HDL-cholesterol, C-reactive protein, γ-glutamyltransferase, uric acid, phosphate, and potassium levels.

CRP, γ-glutamyltransferase, uric acid, phosphate, and potassium, the odds ratio (95% CI) for high baPWV was 2.70 (1.07-6.80) and for high FRS was 3.66 (1.09-12.29) per 1 mg/dL increment of serum calcium. These associations remained after adjusting for the presence of medications that could modify vascular function parameters, including anti-hypertension, anti-diabetic drugs, and lipid-lowering medications.

4 | DISCUSSION

For individuals without clinical calcium homeostasis disorders, our cross-sectional study showed a positive association of serum calcium level with baPWV and 10-year CVD risk estimates, independent of classical cardiovascular risk factors. These effects remained after adjusting for the presence of vascular function-modifying drugs such as anti-hypertensive drugs, anti-diabetic drugs, and dyslipidemia medications.

Many previous studies have investigated the associations among circulating calcium level and overt vascular events and mortality.[7-9] A recent meta-analysis of studies performed to assess the association between serum calcium level and coronary heart disease mortality showed that the hazard risk for death was 1.13 when serum calcium concentration increased by one standard deviation.[8] Also, a prospective study that examined 16 000 people over 12.6 years demonstrated that the hazard risk for stroke increased 1.37 units with each standard deviation increase in serum calcium concentration.[9] A distinguishing feature of our study is that it examined the impact of serum calcium on vascular health status and future CVD risk in preclinical stage CVD. In our study, high baPWV was defined as >1460 cm/s, which has been shown to be a useful predictor of CVD.[13] High FRS was defined as an estimated risk >10% for a 10-year CVD event, which was classified as low risk (<10%) and intermediate risk or high risk (≥10%).[12] Recently, the use of statin or aspirin has been proposed to prevent future CVD morbidity and mortality based on risk estimation of a 10-year CVD event.[14,15]

Some biological mechanisms may help to explain associations of serum calcium with arterial stiffness and 10-year CVD risk. Increased serum calcium level could induce alterations to blood coagulation mechanisms and lead to endothelial dysfunction, binding to calcium-sensing receptors, or interaction with pyrophosphates, which are important inhibitors of tissue calcification; higher serum calcium levels result in smaller concentrations of serum pyrophosphates and greater tissue calcification.[11,16] Gene expression alterations may be induced by prolonged exposure to and increased concentration of circulating calcium in vascular smooth muscle cells, which can lead to mutations in calcium-sensing receptors with subsequent enhanced cardiovascular risk.[17,18] Further, increased serum calcium level has also been shown to be related to a deteriorated lipid profile.[19,20] It is also known that the higher is the intracellular free calcium level, a secondary messenger system, the greater are the catecholamine secretion, vasoconstrictor tone, and arterial blood pressure.[21,22] Lastly, Vitamin D and parathyroid hormone (PTH) levels are involved in the relationship between serum calcium level and CVD.[5,6] Vitamin D plays a role in regulating many genes for vascular health involving cell proliferation, apoptosis, oxidative stress, and cell adhesion and also can lead to activation of the renin-angiotensin-aldosterone system, predisposing the individual to high blood pressure and left ventricular remodeling. Furthermore, chronic vitamin D deficiency can induce elevation of PTH, which in turn increases vascular inflammation and may be implicated in adverse CVD events.[23,24] Vitamin D deficiency is a worldwide epidemic and is not limited to East Asians.[25-27] In a nationally representative survey conducted by the Korean Ministry of Health and Welfare, 65.9% of men and 77.7% of women had <20 ng/mL of 25-hydroxyvitamin D among Koreans aged 10 years or older.[28]

4.1 | Limitations

Our study had several limitations. Caution should be used in causal and temporal interpretations due to its cross-sectional design. Further, study participants were volunteers visiting for health promotion screenings in a single hospital and appeared to be slightly healthier individuals than most community-based cohorts, indicating that the study population may not be representative of the general population. We did not take into consideration the effects of vitamin D and PTH because these biomarkers were not measured

at the beginning of this study, although chronic vitamin D deficiency has been a prevalent and nationwide problem over the last decade in Korea. Lastly, genetic susceptibility factors in calcium metabolism were not considered. To minimize genetic effects on calcium homeostasis, we excluded individuals with serum calcium >10.5 mg/dL or <8.5 mg/dL.

5 | CONCLUSION

We found serum calcium level to be independently and positively associated with baPWV, a surrogate for arterial stiffness, and 10-year CVD risk estimates calculated by FRS. This finding suggests that it may be possible to slow the development and progression of CVD in individuals with borderline high serum calcium level by practicing preventive strategies.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

All authors take full responsibility for the work as a whole, including the study design, and the decision to submit and publish the manuscript. B. P. and Y. L. helped design the study and participated in data acquisition, analysis, and interpretation. All authors reviewed and approved the final manuscript.

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