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The Role of Serum Calcium Levels in the Progression of Arterial Stiffness: Cross-Sectional and Longitudinal Analyses in a Multicenter Cohort

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ABSTRACT

Increased arterial stiffness measured by brachial-ankle pulse wave velocity (baPWV) is a well-known risk factor for hypertension and future cardiovascular events. The relationship between serum calcium levels and increased arterial stiffness is not well understood. Individuals undergoing baPWV measurements as part of a generalized health examination, with normal serum calcium (8.5–10.5 mg/dL) and phosphate levels and no significant renal dysfunction, were selected from the Korea Initiatives on Coronary Artery (KOICA) registry. The cross-sectional relationship between serum calcium levels and baPWV, and the longitudinal effect of baseline serum calcium levels on baPWV progression in those with repeated baPWV measurements, were analyzed using multivariable regression models. A total of 9150 individuals with baseline baPWV and 2329 individuals (5451 PWV measurements) with follow-up baPWV were selected for cross-sectional and longitudinal analyses, respectively. After adjustment for confounders, higher serum calcium levels were associated with increased baseline baPWV (β-coefficient per 1 mg/dL increase, 19.61; 95% CI 7.77–31.45; $p = 0.001$). Higher serum calcium was also independently associated with a greater annualized baPWV progression rate longitudinally (β-coefficient per 1 mg/dL increase, 5.17; 95% CI, 1.82–8.67; $p = 0.004$). Subgroup analysis showed that the effect of serum calcium on baPWV progression had a significant interaction with baseline baPWV, systolic blood pressure, and the presence of diabetes (interaction $p < 0.001$). In conclusion, higher serum calcium levels within the normal range were associated with faster arterial stiffness progression measured by baPWV. Further studies are required to explore the potential for modulating calcium metabolism to slow arterial stiffness progression.

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1 | Introduction

Increased arterial stiffness is associated with structural and compositional changes in the arterial wall and is an independent predictor of increased cardiovascular risk [1, 2]. Brachial-ankle pulse wave velocity (baPWV) is a noninvasive, reproducible, and relatively simple method for assessing arterial stiffness, and its incremental value for predicting cardiovascular events is well established [3–5]. Increased arterial stiffness causes increases in pulse pressure and afterload, leading to hypertension, left ventricular hypertrophy, and decreased coronary perfusion [5, 6]. Treatments for atherosclerotic risk factors have been reported to improve arterial stiffness; however, there is an unmet need for specific therapies to slow the progression of arterial stiffening [5, 7].

Vascular calcification is a major component of the structural changes causing increased arterial stiffness [8]. Abnormalities in calcium-phosphate metabolism are important factors that cause vascular calcification in patients with chronic kidney disease (CKD). In addition, higher serum calcium levels are associated with more severe vascular calcification and increased cardiovascular risk in the general population [9]. Positive associations have been reported between higher serum calcium levels and direct measures of increased arterial stiffness including baPWV [10–12], suggesting that treatments targeting the modulation of serum calcium may have the potential to slow the progression of arterial stiffness. However, these studies were cross-sectional in design, with limited ability for causal inference. Therefore, this study aimed to analyze the relationship between serum calcium levels and the longitudinal progression of arterial stiffness assessed using baPWV.

2 | Methods

2.1 | Study Design and Population

The Korea Initiatives on Coronary Artery calcification (KOICA) registry is a retrospective, multicenter registry comprising 93 914 individuals who underwent coronary artery calcium (CAC) scoring computed tomography (CT) as part of a generalized health examination at six university hospital healthcare centers in Korea between April 2003 and March 2017. Further details regarding this registry have been described in previous studies [13–16]. From this registry, 9905 individuals with baPWV data were considered for inclusion in this study, after excluding participants with an ankle-brachial index of <0.9. In order to minimize the effect of CKD or primary hormonal disorders, we also excluded individuals with estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2, and those with serum calcium and phosphate values outside the reference range (calcium: 8.5–10.5 mg/dL; phosphate: 2.5–4.5 mg/dL). Individuals without calcium or phosphate measurements and those with no CAC scores owing to previous coronary interventions were also excluded. A total of 9150 individuals were selected for the baseline cross-sectional analysis, and 2329 individuals with follow-up baPWV measurements (total 5451 measurements) were included in the longitudinal analysis (Figure 1). This study was approved by the Institutional Review Board of each participating center (Seoul St. Mary's Hospital IRB No. KC16RIMI0669). The need for written informed consent was waived owing to the retrospective nature of the study. The study complied with the principles of the Declaration of Helsinki.

2.2 | Data Acquisition

During the health examination, demographic data and medical history were collected using a self-reported questionnaire. Laboratory samples were obtained after a 12-h fast, and lipid profiles, including low-density lipoprotein (LDL) cholesterol levels, were measured using direct enzymatic methods. eGFR was calculated using the Modification of Diet in Renal Disease equation [17]. In individuals with hypoalbuminemia (albumin < 3.5 mg/dL), serum calcium levels were corrected using the formula: $Corrected\ calcium = measured\ calcium + 0.8 \times (4 - albumin)$ [18].

Blood pressures were measured using automated oscillometric devices with participants in the upright position after at least 5 min of rest. baPWV was measured using waveform analyzers (VP-1000 and VP-2000; Colin Co. Komaki, Japan). Pneumatic cuffs were placed on the arms and ankles and linked to a sensor for evaluating volume pulse waveforms and an oscillometric sensor for recording blood pressure. The time interval between the brachial and ankle waveforms was defined as the brachium-to-ankle time interval (ΔTba). The baPWV was calculated using the formula: $baPWV = (La - Lb)/\Delta Tba$, where Lb (the heart-to-brachial artery path length) and La (the heart-to-ankle path length) were estimated using an algorithm based on the patient's height, $Lb = 0.2195 \times patient's\ height - 2.0734$ and $La = 0.8129 \times patient's\ height + 12.328$ [19]. The average values of the right and left baPWV measurements were used for analysis.

CAC CT scans were obtained using multi-detector CT scanners (Brilliance 256 iCT and Brilliance 40, Philips Healthcare, Cleveland, USA; Lightspeed 64, GE Healthcare, Chicago, USA; SOMATOM Sensation 16 and SOMATOM Definition, Siemens, Forchheim, Germany) with standard prospective or retrospective electrocardiogram gating. The CAC score was defined as the sum of the lesion scores for each major coronary artery using the Agatston method and was analyzed by radiologists specializing in cardiac imaging at each center in accordance with standard guidelines [20].

2.3 | Statistical Analysis

For baseline characteristics, participants were stratified into tertiles according to their serum calcium levels. Categorical data are presented as numbers and frequencies and compared using the χ^2 test. Continuous variables are expressed as mean ± standard deviation or median (interquartile range [IQR]), depending on variable distribution, and were compared using analysis of variance.

The cross-sectional association between serum calcium levels and baPWV at baseline was analyzed using multivariable linear regression. The longitudinal association between baseline serum calcium levels and baPWV progression was assessed using multivariable linear mixed models with individual intercepts, where the effect of serum calcium was estimated using the β-

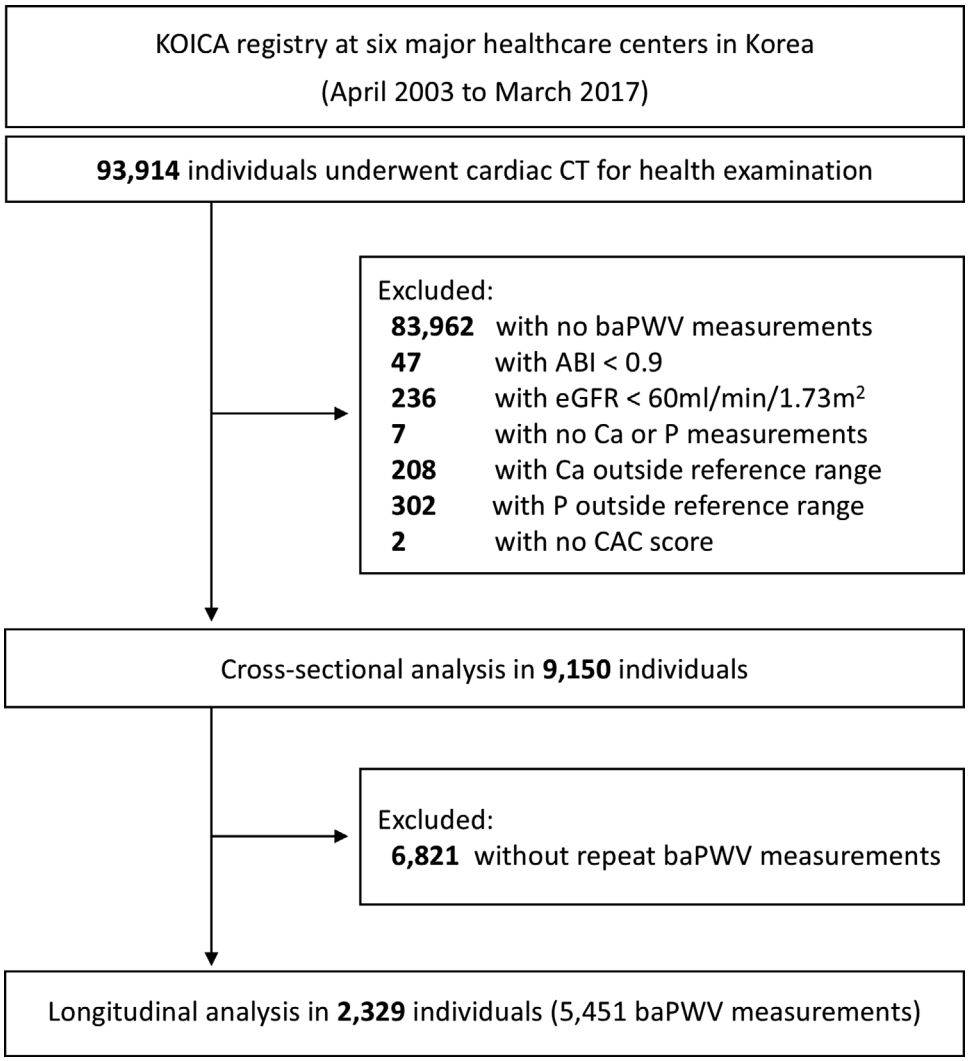

FIGURE 1 | Selection process of the study population. ABI, ankle-brachial index; baPWV, brachial-ankle pulse wave velocity; Ca, calcium; CAC, coronary artery calcification; CT, computed tomography; eGFR, estimated glomerular filtration rate; KOICA, Korea Initiatives on Coronary Artery calcification.

coefficient for the interaction term with time. Specifically, the equation used was $\Delta baPWV_{ij} = \beta_0 + \Sigma\, \beta_k\, x_{k,i}\, t_{ij} + b_i + \varepsilon_{ij}$, where $\Delta baPWV_{ij}$ represents the change in baPWV for the j-th baPWV measurement in the i-th individual, b_i is the random intercept, and ε_{ij} is the error term. The regression coefficient β_k for the interaction term between the k-th variable of interest ($x_{k,i}$) and the time interval to repeat examination (t_{ij}) indicates the effect of the variable x_k on the longitudinal progression of baPWV. This method has been used in previous longitudinal analyses of PWV and has the advantage of accommodating all possible unequally spaced observations, thus minimizing the possibility of selection bias [21]. A subgroup analysis was performed to assess the possibility of a heterogeneous effect of serum calcium levels on baPWV progression in the selected populations. The primary analysis considered baPWV as a continuous variable; however, a sensitivity analysis using multivariable Cox regression was also performed to assess the progression of baPWV to >1400 cm/s and >1800 cm/s, proposed as indicators of borderline and abnormal arterial stiffness, respectively [22, 23]. We also performed analysis on serum phosphate as well as calcium levels due to the essential correlation between calcium and phosphate metabolism.

For all linear regression analyses, models were adjusted progressively as follows: Model 1, adjusted for age, sex, and baseline baPWV (for longitudinal analyses); Model 2, further adjusted for body mass index, history of smoking, use of antihypertensive and glucose-lowering medications, mean blood pressure, and pulse pressure; Model 3, further adjusted for hemoglobin, platelet count, glycated hemoglobin, high-density lipoprotein (HDL) cholesterol, LDL cholesterol, triglycerides, eGFR, and phosphate; and Model 4, additionally adjusted for the CAC score. Collinearity was assessed using the variance inflation factor, which was <5 for all variables. In the multivariable Cox regression analyses, the initial variables were selected as in Model 4 in the linear regression analysis; however, due to the limited number of individuals whose baPWV increased to >1800 cm/s, backward stepwise elimination was used to select the final variables, where age and sex were retained in the model regardless of significance.

Statistical analyses were performed using R Statistical Software version 4.3.3 (R Foundation for Statistical Computing, Vienna, Austria) and SPSS version 26.0 (IBM, Armonk, New York, USA). A two-sided p value <0.05 was considered statistically significant.

3 | Results

3.1 | Baseline Characteristics

The baseline characteristics of the study population according to serum calcium levels are presented in Table 1. The mean age of the study population was 56.4 years, and 2310 (25.2%) were female. Individuals with higher serum calcium levels demonstrated significantly higher systolic and diastolic blood pressures, higher hemoglobin, platelet count, glucose, glycated hemoglobin, HDL and LDL cholesterol, triglycerides, and phosphate levels, and lower eGFR. Individuals with higher serum calcium levels also had significantly higher baseline baPWV. Similar findings were observed in the longitudinal study population, which included 2329 individuals with at least two baPWV measurements during the study period (Table S1).

3.2 | Baseline Cross-Sectional Analyses

At baseline, the median baPWV was 1370cm/s (IQR −1267 to 1503 cm/s) (Figure S1). Higher serum calcium levels were positively correlated with higher baseline baPWV (Figure S2A), which remained significant after multivariable in all models (Table 2). In the minimally adjusted model (Model 1), each 1 mg/dL increase in serum calcium was associated with a 57.65 cm/s increase in baPWV (95% confidence interval [CI], 45.68–69.62; $p < 0.001$). The strength of the association decreased after progressive adjustment for confounding factors but remained significant even after full adjustment (Model 4) (β coefficient per 1 mg/dL, 19.61; 95% CI 7.77–31.45, $p = 0.001$). A positive association between serum calcium levels and baPWV was also evident when serum calcium levels were assessed according to tertiles. However, no significant relationship was observed between baPWV and serum phosphate levels (Table S3).

3.3 | Longitudinal Analyses

In the participants with follow-up baPWV (median number of measurements 2, IQR 2–3), during a median follow-up duration of 2.4 years (IQR, 2.0–3.9 years), baPWV values increased by a median of 27.5 cm/s (IQR −43.1 to 101.6 cm/s) between the first and last examinations (Figure S1), corresponding to an annual median increase of 10.2 cm/s. Among individuals with an initial baPWV ≤ 1400 cm/s, subsequent increases to >1400 cm/s were found in 345 (23.1%), whereas in those with an initial baPWV ≤ 1800 cm/s, subsequent increases to >1800 cm/s were found in 60 (2.6%).

Higher serum calcium levels were positively correlated with higher baPWV progression rates (Figure S2B), which remained significant after multivariable adjustment in all models (Table 3). In the fully adjusted model, each 1 mg/dL increase in serum calcium level was associated with a 5.17 cm/s/year increase in the progression rate of baPWV (95% CI, 1.82–8.67; $p = 0.004$). Similar results were found when serum calcium level was assessed according to tertiles; even after full adjustment, the highest calcium tertile had a significantly higher baPWV progression rate compared to the lowest tertile (β coefficient per 1 mg/dL, 4.43; 95% CI, 0.20–8.78; p for trend = 0.041). When changes in serum calcium levels were considered in addition to baseline values, both baseline serum calcium levels and their changes showed a significant correlation with baPWV progression (Table S2).

In the subgroup analysis, the effect of serum calcium levels on the progression rate of baPWV did not show evidence of heterogeneity across age, sex, or the presence of dyslipidemia (Figure 2). However, although serum calcium levels did not have a clear effect on the baPWV progression rate in individuals with systolic blood pressure ≤ 120 mmHg, the effect was prominent in those with higher systolic blood pressure, showing a significant interaction according to the systolic blood pressure categories (interaction $p = 0.007$). There was also evidence of heterogeneity according to baseline baPWV; serum calcium levels were associated with faster baPWV progression in those with baseline baPWV > 1400 cm/s, but not in those with lower baPWV (interaction $p < 0.001$). The effect of serum calcium levels on baPWV progression was also more prominent in individuals with diabetes (interaction $p < 0.001$). Interactions for systolic blood pressure (interaction $p < 0.001$) and baseline baPWV (interaction $p < 0.001$) were also observed when these parameters were analyzed as continuous variables.

Consistent with the results of the subgroup analysis, serum calcium levels were not associated with baPWV progression to >1400 cm/s (hazard ratio per 1 mg/dL, 0.77; 95% CI, 0.50–1.20; $p = 0.255$) (Table 4). The main predictors of future baPWV > 1400 cm/s included higher baseline baPWV, older age, use of glucose-lowering medications, higher mean blood pressure, and higher triglyceride levels. In contrast, serum calcium levels were significantly associated with baPWV progression to >1800 cm/s (hazard ratio per 1 mg/dL, 3.02; 95% CI, 1.06–8.61; $p = 0.038$). Other significant predictors of a future baPWV > 1800 cm/s included higher baseline baPWV and older age.

4 | Discussion

4.1 | Main Findings

In a multicenter, retrospective cohort of individuals who participated in a comprehensive health screening program and underwent serial baPWV measurements, increasing serum calcium levels within the normal range were associated with higher blood pressure and worse glycemic and lipid profiles. Higher serum calcium levels were also associated with a higher baPWV cross-sectionally at baseline and more rapid baPWV progression longitudinally. In the subgroup analysis, the effect of calcium levels on baPWV progression was most evident in those with higher blood pressure, higher baseline baPWV, and diabetes. Serum calcium levels were not associated with baPWV progression to >1400 cm/s but were significantly associated with baPWV progression to >1800 cm/s.

4.2 | Comparison With Previous Studies

Since higher baPWV correlates with increased cardiovascular risk [3–5], the findings of our study are consistent with the literature documenting a positive relationship between serum calcium levels and increased cardiovascular events. High serum

TABLE 1 | Baseline characteristics of the study population according to serum calcium levels.

Characteristics	Ca tertile 1 (≤9.0 mg/dL) *n* = 3090	Ca tertile 2 (9.1–9.4 mg/dL) *n* = 3984	Ca tertile 3 (≥9.5 mg/dL) *n* = 2076	*p* value
Age (years)	53.5 ± 7.9	53.2 ± 8.0	52.5 ± 8.4	<0.001
Sex				0.727
Male (n, %)	2316 (75.0)	2986 (74.9)	1538 (74.1)	
Female (n, %)	774 (25.0)	998 (25.1)	538 (25.9)	
BMI (kg/m^2)	24.4 ± 2.8	24.3 ± 3.0	24.4 ± 3.2	0.751
Smoking				0.215
Never smoker (n, %)	1349 (43.7)	1772 (44.5)	969 (46.7)	
Ex-smoker (n, %)	987 (31.9)	1263 (31.7)	649 (31.2)	
Current smoker (n, %)	754 (24.4)	949 (23.8)	458 (22.1)	
Hypertension (n, %)	759 (24.6)	970 (24.3)	562 (27.1)	0.050
Diabetes (n, %)	307 (9.9)	395 (9.9)	211 (10.2)	0.949
Dyslipidemia (n, %)	573 (18.5)	802 (20.1)	406 (19.6)	0.245
Stroke (n, %)	8 (0.3)	10 (0.3)	9 (0.4)	0.416
Antihypertensive medications (n, %)	693 (22.4)	871 (21.9)	460 (22.2)	0.850
Glucose-lowering medications (n, %)	230 (7.4)	242 (6.1)	142 (6.8)	0.071
Systolic blood pressure (mmHg)	120.0 ± 16.7	120.7 ± 15.6	122.6 ± 15.9	<0.001
Diastolic blood pressure (mmHg)	76.6 ± 11.1	77.3 ± 10.5	78.8 ± 10.9	<0.001
Mean blood pressure (mmHg)	91.0 ± 12.0	91.8 ± 11.2	93.4 ± 11.6	<0.001
Pulse pressure (mmHg)	43.4 ± 11.7	43.4 ± 11.4	43.9 ± 11.3	0.271
Hemoglobin (g/dL)	14.6 ± 1.4	14.9 ± 1.3	15.2 ± 1.3	<0.001
Platelet count (10^9/L)	221.2 ± 47.4	231.5 ± 49.4	243.8 ± 52.1	<0.001
Glucose (mg/dL)	96.0 ± 18.3	99.0 ± 21.0	101.6 ± 21.6	<0.001
HbA1c (%)	5.7 ± 0.7	5.7 ± 0.8	5.8 ± 0.8	<0.001
HDL-cholesterol (mg/dL)	52.1 ± 13.3	53.6 ± 13.9	55.4 ± 14.4	<0.001
LDL-cholesterol (mg/dL)	118.5 ± 28.4	124.5 ± 30.3	129.0 ± 32.5	<0.001
Triglycerides (mg/dL)	117.6 ± 64.7	129.0 ± 80.6	139.5 ± 86.7	<0.001
eGFR (mL/min/1.73 m^2)	88.6 ± 15.2	87.3 ± 16.0	85.6 ± 15.2	<0.001
Calcium (mg/dL)	8.8 ± 0.1	9.2 ± 0.1	9.7 ± 0.2	<0.001
Phosphate (mg/dL)	3.3 ± 0.4	3.4 ± 0.4	3.5 ± 0.4	<0.001
CAC score grade				0.128
None (0)	2011 (65.1)	2526 (63.4)	1281 (61.7)	
Mild (1–99)	778 (25.2)	1044 (26.2)	546 (26.3)	
Moderate (100–399)	223 (7.2)	296 (7.4)	183 (8.8)	
Severe (≥400)	78 (2.5)	118 (3.0)	66 (3.2)	
baPWV (cm/s)	1399 ± 217	1408 ± 225	1431 ± 244	<0.001
≤1400	1834 (59.4)	2303 (57.8)	1122 (54.0)	
1401–1800	1105 (35.8)	1462 (36.7)	806 (38.8)	
>1800	151 (4.9)	219 (5.5)	148 (7.1)	

Abbreviations: baPWV, brachial-ankle pulse wave velocity; BMI, body-mass index; CAC, coronary artery calcification; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; WBC, white blood cell.

TABLE 2 | Association between serum calcium levels and baseline arterial stiffness measured by brachial-ankle pulse wave velocity.

	Baseline baPWV	
	β coefficient (95% CI)	***p* value**
Model 1[a]		
Per 1mg/dL increase	57.65 (45.68, 69.62)	<0.001
Tertile 1	referent	<0.001[e]
Tertile 2	14.09 (5.02, 23.16)	
Tertile 3	47.74 (36.99, 58.49)	
Model 2[b]		
Per 1mg/dL increase	39.78 (28.79, 50.77)	<0.001
Tertile 1	referent	<0.001[e]
Tertile 2	16.23 (6.53, 25.94)	
Tertile 3	39.24 (27.17, 51.31)	
Model 3[c]		
Per 1mg/dL increase	22.22 (10.35, 34.10)	<0.001
Tertile 1	referent	<0.001[e]
Tertile 2	9.82 (0.01, 19.63)	
Tertile 3	26.61 (13.92, 39.29)	
Model 4[d]		
Per 1mg/dL increase	19.61 (7.77, 31.45)	0.001
Tertile 1	referent	<0.001[e]
Tertile 2	9.43 (−0.34, 19.19)	
Tertile 3	25.10 (12.47, 37.73)	

Abbreviations: baPWV, brachial-ankle pulse wave velocity; CI, confidence interval.

[a]Adjusted for age and sex.

[b]Adjusted for the factors in Model 1 + body mass index, smoking status, antihypertensive medications, glucose-lowering medications, mean blood pressure, and pulse pressure.

[c]Adjusted for the factors in Model 3 + hemoglobin, platelet count, glycated hemoglobin, HDL-cholesterol, LDL-cholesterol, triglycerides, eGFR, and phosphate.

[d]Adjusted for the factors in Model 3 + CAC score.

[e]*p* value for trend.

TABLE 3 | Association between baseline serum calcium levels and the longitudinal progression of arterial stiffness measured by brachial-ankle pulse wave velocity.

	baPWV progression rate	
	β coefficient (95% CI)	***p* value**
Model 1[a]		
Per 1mg/dL increase	3.46 (2.37, 4.59)	<0.001
Tertile 1	referent	0.018[e]
Tertile 2	2.37 (−0.35, 4.94)	
Tertile 3	6.16 (2.69, 9.88)	
Model 2[b]		
Per 1mg/dL increase	5.53 (3.49, 7.58)	<0.001
Tertile 1	referent	0.062[e]
Tertile 2	0.32 (−2.69, 3.31)	
Tertile 3	5.21 (0.38, 9.34)	
Model 3[c]		
Per 1mg/dL increase	5.16 (1.76, 8.99)	0.005
Tertile 1	referent	0.039[e]
Tertile 2	−0.63 (−3.72, 2.56)	
Tertile 3	4.51 (0.10, 8.37)	
Model 4[d]		
Per 1mg/dL increase	5.17 (1.82, 8.67)	0.004
Tertile 1	referent	0.041[e]
Tertile 2	−0.65 (−3.60, 2.28)	
Tertile 3	4.43 (0.20, 8.78)	

Abbreviations: baPWV, brachial-ankle pulse wave velocity; CI, confidence interval.

[a]Adjusted for age, sex, and baseline baPWV.

[b]Adjusted for the factors in Model 1 + body mass index, smoking status, antihypertensive medications, glucose-lowering medications, mean blood pressure, pulse pressure.

[c]Adjusted for the factors in Model 3 + hemoglobin, platelet count, glycated hemoglobin, HDL-cholesterol, LDL-cholesterol, triglycerides, eGFR, and phosphate.

[d]Adjusted for the factors in Model 3 + CAC score.

[e]*p* value for trend.

calcium levels have been linked to cardiovascular mortality [9, 24–26] and myocardial infarction [9, 26–28]. Serum calcium levels are also positively correlated with the prevalence and severity of coronary artery calcification as assessed by cardiac CT [29, 30] and with increased carotid artery plaque thickness [31]. Therefore, taking into account the well-documented association between serum calcium level and elevated blood pressure, impaired glucose tolerance, and dyslipidemia [9, 28, 32, 33], findings which were also observed in our study, atherosclerosis provides a possible explanation for the increased cardiovascular risk associated with elevated serum calcium. However, although several studies demonstrated that adjustment for atherosclerotic risk factors attenuated the association between calcium and cardiovascular risk [24, 26], others have found that serum calcium was an independent predictor of cardiovascular events even after adjustment for these factors [25, 27], suggesting a possible role of calcium in cardiovascular risk beyond intimal calcification [9].

Several studies have reported a positive association between higher serum calcium levels and increased arterial stiffness. Hagstrom et al. found an association between calcium levels and arterial stiffness measured by common carotid artery distensibility and pulse pressure [12]. In line with our results, two contemporary studies found a relationship between serum calcium levels and baPWV measurements [10, 11]; however,

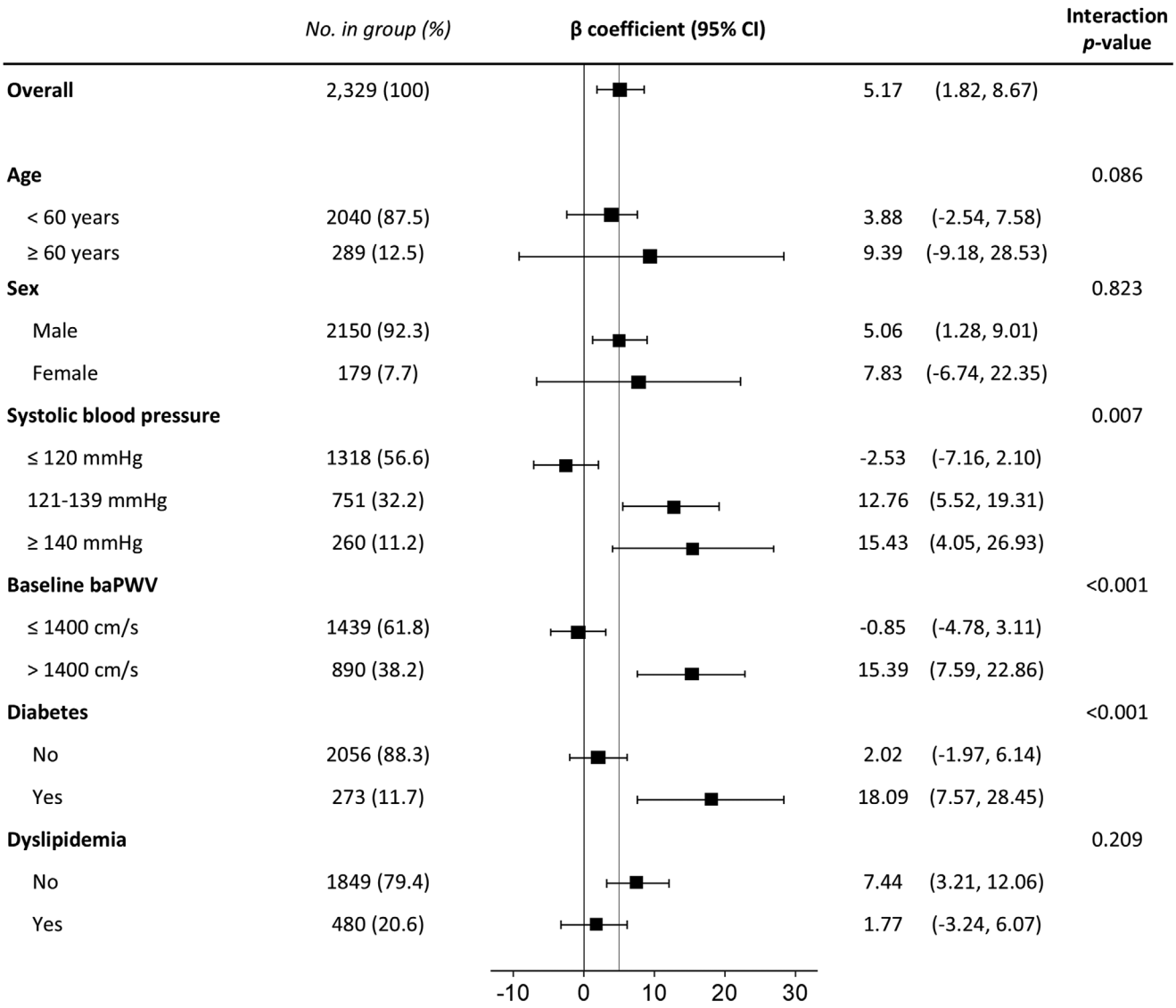

FIGURE 2 | Subgroup analysis for the effect of serum calcium levels on the longitudinal progression rate of brachial-ankle pulse wave velocity. baPWV, brachial pulse wave velocity; CI, confidence interval.

these studies were cross-sectional in design, with limited ability to demonstrate a causal relationship between calcium and arterial stiffness. To the best of our knowledge, this is the first study to demonstrate a correlation between serum calcium levels at baseline and the longitudinal progression of arterial stiffness. Notably, the association between serum calcium levels and baPWV remained significant after adjustment for the CAC score, a powerful indicator of total atherosclerotic burden [34], supporting a role for serum calcium beyond intimal calcification.

4.3 | Possible Mechanisms

Increased arterial stiffness involves changes in vascular composition, including the deterioration of elastic fibers and calcium deposition [35]. Vascular smooth muscle cells (VSMCs) have an important role in this process, as VSMC differentiation into an osteogenic phenotype is a key driver in vascular calcification [8]. Serum calcium levels are likely significant in this process, as regulators of calcium-phosphate metabolism, such as calciprotein particles, fetuin-A, fibroblast growth factor 23, and bone morphogenic proteins, are known to induce such transdifferentiation [8, 36–38]. Additionally, increased calcium concentrations have been reported to directly induce VSMC mineral deposition in vitro [39, 40]. Furthermore, higher levels of parathyroid hormone, which increases serum calcium, have been associated with increased arterial stiffness in patients with primary hyperparathyroidism [41] and in the general population [12, 42].

In this study, we were unable to further investigate the mechanisms underlying the association found between serum calcium and arterial stiffness, as data on other regulators of calcium metabolism, aside from serum phosphate, were not collected. However, previous studies have reported associations between all the major modulators of calcium metabolism and the development of cardiovascular diseases [8, 16, 24, 25, 30, 36–44], suggesting that the mechanisms involved are likely multifactorial. Notably, the subgroup analysis indicated that the effect of serum calcium on arterial stiffness progression was more prominent in those with increased baseline baPWV. This implies that serum

TABLE 4 | Association between baseline risk factors and brachial-ankle pulse wave velocity progression.

	baPWV > 1400cm/s		baPWV > 1800cm/s	
	HR (95% CI)	***p* value**	**HR (95% CI)**	***p* value**
Baseline baPWV (per 10cm/s)	1.11 (1.09, 1.14)	<0.001	1.09 (1.06, 1.12)	<0.001
Age (per 10 years)	1.30 (1.00, 1.67)	0.047	2.02 (1.24, 3.29)	0.005
Sex		0.644		0.781
Male	referent		referent	
Female	0.83 (0.37, 1.84)		0.80 (0.16, 3.94)	
Body mass index (per 5 kg/m^2)	0.92 (0.69, 1.23)	0.563		
Smoking	1.02 (0.86, 1.20)	0.850		
Antihypertensive medications	0.83 (0.60, 1.13)	0.231		
Glucose-lowering medications	1.78 (1.03, 3.10)	0.041	1.93 (0.95, 3.93)	0.070
Mean blood pressure (per 10 mmHg)	1.25 (1.07, 1.46)	0.005	1.40 (0.93, 2.11)	0.109
Pulse pressure (per 10 mmHg)	0.94 (0.81, 1.09)	0.420		
Hemoglobin (per 1 g/dL)	1.04 (0.90, 1.19)	0.628		
Platelet count (per 10×10^9/L)	0.99 (0.96, 1.02)	0.490		
HbA1c (per 1%)	0.99 (0.96, 1.02)	0.586		
HDL-cholesterol (per 10 mg/dL)	1.09 (0.98, 1.22)	0.108		
LDL-cholesterol (per 10 mg/dL)	0.99 (0.94, 1.04)	0.669		
Triglycerides (per 10 mg/dL)	1.02 (1.01, 1.04)	0.001		
eGFR (per 10 mL/min/1.73 m^2)	0.96 (0.86, 1.08)	0.530		
CAC score (per 100 AU)	1.01 (0.93, 1.09)	0.875		
Phosphate (per 1 mg/dL)	0.88 (0.65, 1.18)	0.383		
Calcium (per 1 mg/dL)	0.77 (0.50, 1.20)	0.255	3.02 (1.06, 8.61)	0.038

Abbreviations: AU, Agatston unit; baPWV, brachial-ankle pulse wave velocity; CAC, coronary artery calcification; CI, confidence interval; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HR, hazard ratio; LDL, low-density lipoprotein.

calcium may play a more significant role in the later stages of arteriosclerosis after some degree of structural damage has already occurred. The prominent effect of higher serum calcium levels on baPWV progression in those with diabetes may possibly be due to similar mechanisms, as diabetes is also associated with increased arterial stiffness mediated by advanced glycation end-product formation [45, 46]. Further studies are needed to elucidate the pathways through which serum calcium levels influence arterial stiffness.

4.4 | Clinical Implications

Our results demonstrate that serum calcium levels can affect arterial stiffness, suggesting serum calcium as a potential target for slowing the progression of arterial stiffness. Although the amount of dietary calcium intake from food does not correlate with serum calcium levels [30], oral calcium supplements can rapidly and significantly increase serum calcium levels for up to 8 h after ingestion [47]. Such transient increases in serum calcium levels may cause subsequent vascular disease through the mechanisms discussed previously and have been hypothesized to contribute to the increased cardiovascular mortality observed in several trials involving dietary calcium supplements [9, 48]. The subgroups in which we found a greater effect of serum calcium on baPWV progression–those with diabetes, elevated blood pressure, and higher baPWV–represent an elderly population more likely to be prescribed calcium supplements. However, given the important role of oral calcium supplements in maintaining bone health, it is essential to exercise caution when interpreting their potential link to increased arterial stiffness, as this relationship remains uncertain.

Furthermore, our findings indicate that pathways in calcium metabolism may be promising targets for the development of treatments aiming to slow arterial stiffness progression. This potential has been supported by several studies; for instance, calcimimetics have the ability to inhibit calcium-induced VSMC mineral deposition in vitro [39], and parathyroidectomy has been reported to improve arterial stiffness in patients with primary parathyroidism [41]. Bisphosphonates have also been shown to reduce arterial calcification and cardiovascular risk [49]. A better understanding of the mechanisms involved may lead to the development of treatments to slow or reverse the progression of arterial stiffness by modulating calcium metabolism, and thus ultimately reducing cardiovascular risk.

Long-term warfarin therapy has been implicated in vascular calcification through its inhibition of vitamin K-dependent matrix Gla-protein, a key inhibitor of arterial calcification, [50, 51] which

in turn increases baPWV and contributes to cardiovascular risk. Considering that elevated serum calcium levels may also increase the risk of atrial fibrillation [52], the rationale for alternatives such as direct oral anticoagulants may be stronger in atrial fibrillation patients with elevated arterial stiffness or at risk for vascular calcification due to higher serum calcium levels.

4.5 | Limitations and Strengths

Several limitations are acknowledged in this study. First, as mentioned previously, data on the regulators of calcium metabolism, such as parathyroid hormone or vitamin D, were not collected, and it is possible that the association between serum calcium levels and arterial stiffness progression may reflect another underlying process. However, individuals with calcium and phosphate levels outside the reference range, as well as those with CKD, were excluded to minimize the possibility of primary hormonal disorders of calcium metabolism. Second, baPWV was used for the assessment of arterial stiffness, whereas the current gold standard is carotid-femoral pulse wave velocity [2]. Third, although important sex differences exist in calcium metabolism [53], a stratified analysis according to sex could not be performed because of the low proportion of females in our registry. Fourth, the study population consisted of individuals who volunteered for health examination, and as such, their characteristics may not be completely representative of the general population. Data on all-cause mortality was collected as part of the registry. However, due to the very low mortality rate (0.5% during a median follow-up duration of 3.7 years) we could not investigate whether the combined information from baseline serum calcium levels and baPWV provides additional prognostic value. Fifth, the examination results, including baPWV, were presumably reported to the participants, which may have prompted treatment with antihypertensive medications, which are known to decrease arterial stiffness [7]. Additionally, analysis was performed according to the patient characteristics assessed at baseline, which may have changed during follow-up. However, given the current absence of treatments aimed at changing serum calcium levels in the general population, it seems unlikely that these changes would be of sufficient magnitude to significantly alter the main results of our study. Sixth, we did not have data on variables such as left ventricular ejection fraction or the presence of atrial fibrillation, which are known to affect baPWV results [54]. Finally, as this was a retrospective study, there was heterogeneity in patient characteristics and follow-up durations. Despite using multivariable regression to adjust for confounders, the possibility of bias cannot be entirely excluded.

5 | Conclusions

In a multicenter cohort of individuals who participated in a comprehensive health screening program and underwent serial baPWV measurements, increasing serum calcium levels within the normal range were associated with higher baPWV cross-sectionally at baseline and more rapid longitudinal baPWV progression. Higher serum calcium levels were also associated with higher blood pressure and worse glycemic and lipid profiles; however, the relationship between serum calcium levels and baPWV persisted after adjusting for atherosclerotic risk factors, including the CAC score. In the subgroup analysis, the effect of serum calcium levels on baPWV progression was more evident in those with higher blood pressure, higher baseline baPWV, and diabetes. Our results have implications for the use of oral calcium supplements in patients with increased arterial stiffness and suggest that pathways in calcium metabolism may be potential targets for the development of treatments aiming to slow the progression of arterial stiffness. Further studies are needed to elucidate the pathways through which serum calcium levels influence arterial stiffness.

Author Contributions

Conceptualization: Kyung An Kim and Hae-Ok Jung. Data curation: Kyung An Kim and So-Young Lee. Formal analysis: Kyung An Kim. Funding acquisition: Hae-Ok Jung. Investigation: Kyung An Kim. Methodology: Kyung An Kim and Hae-Ok Jung. Project administration: Hae-Ok Jung and Hyuk-Jae Chang. Resources: Hae-Ok Jung, Dong-Hyeon Lee, Donghee Han, Hyuk-Jae Chang, Su-Yeon Choi, Jidong Sung, and Eun Ju Chun. Supervision: Hae-Ok Jung. Validation: So-Young Lee. Visualization: Kyung An Kim and So-Young Lee. Writing–original draft: Kyung An Kim. Writing–review & editing: Kyung An Kim, Jidong Sung, and Mi-Jeong Kim. All authors have read and agreed to the published version of the manuscript.

Acknowledgments

The authors have nothing to report.

Ethics Statement

This study was approved by the Institutional Review Board of each participating center (Seoul St. Mary's Hospital IRB No. KC16RIMI0669).

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data are available on reasonable request from the corresponding author.

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Supporting Information

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