Research Article

Arterial Stiffness as a Risk Factor for Subclinical Coronary Artery Calcification in Predialysis Chronic Kidney Disease: From the KNOW-CKD Study

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Keywords

Arterial stiffness · Pulse wave velocity · Coronary calcification · Vascular calcification · Chronic kidney disease

Abstract

Background/Aims: Both arterial stiffness and coronary artery calcification (CAC) are important predictors of cardiovascular disease in the general population and in chronic kidney disease (CKD) patients. Recent studies on arterial stiffness and CAC in subjects with preserved renal function have verified the association between the two. However, the relationship is not well evaluated in CKD patients. **Methods:** This cross-sectional study analyzed 1,385 predialysis CKD patients from the KNOW-CKD cohort. Participants were divided into four groups according to brachial-ankle pulse wave velocity (baPWV) quartile. Coronary artery calcium scores (CACS) were assessed using cardiac computed tomography and CAC was defined as a CACS

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> 100. **Results:** CAC prevalence was higher in the higher baPWV groups (6.4, 9.8, 23.7, and 43.8% for the 1st to 4th quartiles of baPWV, respectively, $p < 0.001$). In Tobit regression analyses that were fully adjusted for traditional and renal cardiovascular risk factors, the CACS ratio comparing the highest and lowest baPWV quartiles was 3.03 (95% CI, 1.59–6.87). Similarly, the OR for CAC in the highest baPWV quartile compared to the lowest quartile was 1.98 (95% CI, 1.09–3.60) in a fully adjusted multivariate logistic model. Results were consistent across analyses with different cutoffs for CAC or with different clinically relevant subgroups. **Conclusion:** Increased arterial stiffness measured by high baPWV was associated with CAC in a predialysis CKD cohort. Longitudinal studies are needed to determine the effect of arterial stiffness on the development or progression of CAC in CKD.

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Introduction

Cardiovascular disease (CVD) is a major cause of death in patients with chronic kidney disease (CKD) [1]. Therefore, prevention and early detection of cardiovascular (CV) complications are critical for successful treatment of CKD patients and for slowing renal function deterioration. Arterial stiffness and vascular calcification are important predictors of CVD in the general population and in CKD patients.

Arterial stiffness refers to the loss of ability of arteries to accommodate stroke volume [2]. It is well known that arterial stiffness increases with decreasing renal function [3], which is thought to be the result of complex actions, such as alterations in the extracellular matrix, advanced glycation end products, endothelial dysfunction, chronic inflammation, and vascular calcification [4]. Importantly, an increase in arterial stiffness is associated with a rapid decline in renal function [5] and high incidence of CVD and CV mortality [6, 7].

Calcification is another commonly observed vascular alteration in CKD patients that is broadly divided into the following categories: atherosclerotic intimal calcification, arteriosclerotic medial calcification, cardiac valvular calcification, and calciphylaxis [8]; all of which are poor prognostic factors in CKD patients [9, 10]. Coronary artery calcification (CAC) was recently established as a predictor of CV complications in the general population and is recommended for use in assessing CV risk in asymptomatic adults with intermediate risk [11]. Recent studies have identified CAC as a predictor of CV disease and mortality in CKD patients, suggesting the possibility of a risk prediction tool for CKD [12, 13].

Arterial stiffness can be easily measured by PWV (pulse wave velocity), and recent studies of PWV and CAC in subjects with preserved renal function have demonstrated an association between the two. However, the relationship between PWV and CAC is not well understood in CKD cases where more complex risk factors, such as uremia or altered mineral metabolism, are prevalent. Therefore, we evaluated the association between brachial ankle PWV (baPWV) and CAC in a predialysis CKD cohort of Korean adults.

Patients and Methods

Study Design and Population

This is a cross-sectional study designed to examine the association between baPWV and CAC in CKD patients. Study subjects were participants in the prospective Korean Cohort Study for Outcome in Patients With Chronic Kidney Disease (KNOW-CKD). A detailed protocol of this study was published previously [14]. The study protocol was approved by the Institu-

Fig. 1. Algorithm for selecting study subjects from the KNOW-CKD cohort. baPWV, brachial-ankle pulse wave velocity; CACS, coronary artery calcium score; CAD, coronary artery disease; PAD, peripheral artery disease.

tional Review Board at each participating clinical center in 2011. In brief, KNOW-CKD is a prospective cohort study that enrolled subjects aged 20–75 years with predialysis CKD stage 1–5. Nine nephrology centers at major university hospitals throughout Korea enrolled 2,238 adults with CKD over a 5-year period from 2011–2015. Participating individuals will be monitored for approximately 10 years until death or until end-stage renal disease occurs. In the entire cohort, 1,931 patients who underwent coronary computed tomography (CT) and baPWV were included in the analysis. We excluded 487 patients with missing data regarding our variables of interest. Additionally, we excluded 118 patients with previous history of coronary artery disease or peripheral artery disease. Finally, 1,385 patients were included in the study (Fig. 1).

Clinical and Laboratory Measurements

Data regarding socio-demographic information, medical history, medication use, and health-related behaviors were collected through a self-administered questionnaire, with the assistance of trained staff. Anthropometric data and resting blood pressure (BP) were measured by trained nurses. Blood samples were collected after fasting for at least 10 hours. Random urine samples from midstream collection were used to measure the urine protein to creatinine ratio (PCR). Serum creatinine and 25-(OH)-vit D were measured at the central laboratory. Other biochemical analyses were done at the local laboratory of each participating center. Serum creatinine levels were measured using the isotope dilution mass spectroscopy (IDMS)-traceable method. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [15]: $eGFR = 141 \times \min(\text{serum creatinine}/\kappa, 1)^\alpha \times \max(\text{serum creatinine}/\kappa, 1)^{-1.209} \times 0.993^{\text{age}} \times 1.018$ (if female) $\times 1.159$ (if black), where $\kappa = 0.7$ for females and 0.9 for males, $\alpha = -0.329$ for females and -0.411 for males, min indicates the minimum of serum creatinine/ κ or 1, and max indicates the maximum of serum creatinine/ κ or 1. Hypertension was defined as systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg, or a history of hypertension. Diabetes mellitus was defined as a fasting serum glucose >126 mg/dL or a history of diabetes or anti-diabetic treatment.

baPWV Measurement

baPWV was measured using automated waveform analyzers VP-1000, VP-1000 plus or VP-2000 (OMRON, Kyoto, Japan) according to the manufacturer's protocol. The PWV between the bilateral brachial arteries and the ankle was measured by placing both arms and the ankle in a cuff, to which an oscillometric sensor was implanted. The mean of the right and left baPWV was used to assess arterial stiffness in our analyses.

Table 1. Baseline characteristics in relation to baPWV

Characteristics	Total	baPWV quartiles				p for trend
		1	2	3	4	
N	1,385	346	346	346	347	
PWV, cm/s	1,521.3±333.9	1,179.8±81.5	1,366.4±43.7	1,556.2±72.5	1,981.4±279.5	<0.001
CACS	0.0 (0.0–64.8)	0.0 (0.0–0.7)	0.0 (0.0–9.2)	3.9 (0.0–92)	62.0 (1.3–391.9)	<0.001
CAC	290 (20.9)	22 (6.4)	34 (9.8)	82 (23.7)	152 (43.8)	<0.001
Age, years	52.6±12.3	43.7±11.1	49.7±10.9	55.3±10.4	61.9±8.6	<0.001
Male sex	815 (58.8)	193 (55.8)	209 (60.4)	201 (58.1)	212 (61.1)	0.249
BMI, kg/m ²	24.5±3.5	24.5±3.9	24.4±3.6	24.5±3.3	24.7±3.2	0.371
WHR	0.90±0.07	0.88±0.06	0.89±0.07	0.90±0.06	0.92±0.06	<0.001
Systolic BP, mm Hg	128±16	121±13	126±14	129±15	135±18	<0.001
Diastolic BP, mm Hg	77±11	75±10	78±10	78±12	77±12	0.040
Glucose, mg/dL	110±39	101±30	105±34	111±36	122±50	<0.001
TC, mg/dL	177±38	179±37	179±38	176±39	172±38	0.014
LDL cholesterol, mg/dL	99±31	102±32	101±32	99±30	95±30	0.003
hsCRP, mg/dL	0.6 (0.2–1.7)	0.5 (0.2–1.6)	0.5 (0.2–1.4)	0.7 (0.3–1.7)	0.9 (0.3–2.1)	<0.001
eGFR, mL/min/1.73 m ²	55.7±32.2	72.2±33.9	61.2±33.0	50.2±28.0	39.2±22.8	<0.001
Calcium, mg/dL	9.1±0.5	9.2±0.5	9.2±0.5	9.2±0.5	9.0±0.6	<0.001
Phosphorus, mg/dL	3.7±0.7	3.6±0.6	3.6±0.6	3.7±0.6	3.9±0.8	<0.001
25-(OH)-vit D, ng/mL	17.4±7.4	17.8±7.6	18.4±7.4	17±7.1	16.5±7.2	0.003
Intact PTH, pg/mL	50 (33–82)	41 (28–65)	48 (34–80)	51 (35–88)	61 (43–105)	<0.001
Urine PCR, g/g	0.5 (0.2–1.6)	0.4 (0.1–0.9)	0.4 (0.1–1.1)	0.6 (0.2–1.7)	1.0 (0.3–2.7)	<0.001
Hypertension	1,334 (96.3)	309 (89.3)	337 (97.4)	344 (99.4)	344 (99.1)	<0.001
Diabetes	461 (33.3)	44 (12.7)	69 (19.9)	129 (37.3)	219 (63.1)	<0.001
Dyslipidemia	740 (53.5)	222 (64.2)	190 (54.9)	176 (51.0)	152 (43.8)	<0.001
Current smoker	235 (17.0)	66 (19.1)	56 (16.2)	60 (17.3)	53 (15.3)	0.256

Values for categorical variables are reported as a number (percentage), continuous variables as mean ± standard deviation or median (interquartile range). *p* values are for analysis of variance or Kruskal-Wallis tests for continuous variables and χ^2 tests for categorical variables. PWV, pulse wave velocity; CACS, coronary calcium score; CAC, coronary artery calcification; BMI, body mass index; WHR, waist-hip ratio; BP, blood pressure; TC, total cholesterol; LDL, low-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; eGFR, estimated glomerular filtration rate; PTH, parathyroid hormone; PCR, protein to creatinine ratio.

Coronary Artery Calcium Score (CACS) Measurement

Electrocardiography-gated multislice computed tomography scans of the thorax were performed using a standard protocol. Quantitative CACS was calculated as described by Agatston et al. [16] We defined the presence of CAC as CACS >100, which also differentiates between mild and moderate-to-severe coronary artery disease [17–19].

Statistical Analysis

Participants were divided into four groups according to baPWV quartile. Continuous variables were expressed as mean ± standard deviation or median and interquartile range. Continuous variables were compared between two groups with a *t* test or the Mann-Whitney U test, and continuous variables were compared between the four groups with analysis of variance or the Kruskal-Wallis test. Categorical variables were expressed as percentages, and comparisons between the patient groups were performed with the χ^2 test.

To evaluate the associations between serum baPWV categories and CACS, we used a Tobit regression model for natural log (CACS + 1). We estimated ratios and 95% confidence intervals (CIs) for CACS + 1 comparing the higher baPWV categories with the lowest baPWV category. We further used logistic regression analysis to estimate the odds ratio (OR) and confidence interval (CI) for the presence of CAC in higher baPWV categories compared with the lowest baPWV category. We then conducted sensitivity analyses using CAC with different cutoff values (CACS >0, CACS >200, and CACS >400). Statistical analyses were performed with Stata Version 15.0 (StataCorp LP, College Station, TX, USA).

Table 2. Multivariate-adjusted CACS ratios according to baPWV

baPWV quartile	Model 1		Model 2		Model 3	
	Ratios (95% CI)	<i>p</i>	Ratios (95% CI)	<i>p</i>	Ratios (95% CI)	<i>p</i>
1	Reference		Reference		Reference	
2	1.29 (0.67–2.50)	0.448	1.11 (0.59–2.09)	0.740	1.11 (0.59–2.08)	0.745
3	3.91 (1.99–7.68)	<0.001	2.08 (1.08–4.01)	0.029	2.03 (1.05–3.92)	0.034
4	11.76 (5.8–23.84)	<0.001	3.44 (1.66–7.14)	0.001	3.03 (1.59–6.87)	0.001

Model 1: Adjusted for age and sex. Model 2: Adjusted for model 1 + WHR, systolic blood pressure, diabetes, eGFR, LDL cholesterol, hsCRP, urine protein to creatinine ratio, and current smoking. Model 3: Adjusted for model 2 + calcium, phosphorus, 25-OH-vit D, and intact PTH. CACS, coronary artery calcium score; CI, confidence interval; WHR, waist-hip ratio; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; PTH, parathyroid hormone.

Table 3. Multivariate-adjusted ORs (95% CI) for CAC according to baPWV

baPWV quartile	Model 1		Model 2		Model 3	
	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>
1	reference		reference		reference	
2	0.99 (0.55–1.78)	0.962	0.87 (0.47–1.61)	0.664	0.87 (0.47–1.61)	0.652
3	2.15 (1.25–3.68)	0.005	1.56 (0.88–2.75)	0.128	1.55 (0.88–2.75)	0.131
4	3.64 (2.12–6.26)	<0.001	1.99 (1.10–3.60)	0.024	1.98 (1.09–3.60)	0.025

Model 1: Adjusted for age and sex. Model 2: Adjusted for model 1 + WHR, systolic blood pressure, diabetes, eGFR, LDL cholesterol, hsCRP, urine protein to creatinine ratio, and current smoking. Model 3: Adjusted for model 2 + calcium, phosphorus, 25-OH-vit D, and intact PTH. OR, odds ratio; CAC, coronary artery calcification; CI, confidence interval; WHR, waist-hip ratio; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; PTH, parathyroid hormone.

Results

The baseline characteristics of study participants classified by baPWV quartiles are summarized in Table 1. CAC was more prevalent among the higher baPWV groups (6.4, 9.8, 23.7, and 43.8% for the 1st to 4th baPWV quartiles, respectively, $p < 0.001$). Overall, the higher was the baPWV quartile, the worse was the cardiometabolic profile. For example, patients with higher baPWV were older and had a higher waist-hip ratio, higher systolic BP, lower eGFR, and higher intact parathyroid hormone. Likewise, patients who were male and had diabetes had higher prevalence in the higher baPWV quartiles.

In Tobit regression analysis, high baPWV was associated with higher CACS after multivariate adjustment. The CACS ratio comparing the highest baPWV quartile with the lowest quartile was 3.03 (95% CI, 1.59–6.87) in the fully adjusted model 3 (Table 2).

Similarly, high baPWV was significantly associated with CAC after adjusting for traditional and non-traditional CV risk factors in multivariate logistic analysis. As shown in Table 3, the OR for CAC in the highest baPWV quartile compared with the lowest quartile was 1.98 (95% CI, 1.09–3.60) in the fully adjusted model 3.

For our study, we defined CAC as CACS >100, but the associations between baPWV and CAC with different cutoffs were also evaluated in sensitivity analysis (Table 4). Compared with the lowest baPWV quartile patients, the highest quartile patients had a CAC OR of 2.55

Table 4. Multivariate-adjusted ORs (95% CI) for CAC with different cutoffs

baPWV quartile	CACS >0		CACS >200		CACS >400	
	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>
1	reference		reference		reference	
2	1.09 (0.74–1.61)	0.647	0.81 (0.38–1.72)	0.583	0.77 (0.29–2.05)	0.600
3	1.30 (0.87–1.94)	0.206	1.37 (0.69–2.73)	0.364	1.57 (0.67–3.71)	0.300
4	1.65 (1.02–2.65)	0.040	2.13 (1.06–4.29)	0.034	2.55 (1.08–6.04)	0.033

Adjusted for age, sex, WHR, systolic blood pressure, diabetes, eGFR, LDL cholesterol, hsCRP, urine protein to creatinine ratio, current smoking, calcium, phosphorus, 25-OH-vit D, and intact PTH. OR, odds ratio; CAC, coronary artery calcification; CACS, coronary artery calcium score; CI, confidence interval; WHR, waist-hip ratio; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; PTH, parathyroid hormone.

(95% CI, 1.08–6.04; $p < 0.001$) when CAC was defined as CACS >400. The results were similar when CAC was defined as CACS >0 or CACS >200. In further sensitivity analysis, the association between baPWV and CAC was similar across clinically relevant subgroups. There were no significant interactions by sex (female vs. male, p for interaction = 0.110), age (<50 vs. ≥50 years, p for interaction = 0.115), BMI (<23.5 vs. ≥23.5 kg/m², p for interaction = 0.816), diabetes (no vs. yes, p for interaction = 0.595), eGFR (<45 vs. ≥45 ml/min/1.72 m², p for interaction = 0.457), proteinuria (<1.0 vs. ≥1.0 g/day, p for interaction = 0.295), or hsCRP (<1.0 vs. ≥1.0 mg/dL, p for interaction = 0.278).

Discussion

In this study, we found that high baPWV was associated with CAC in predialysis CKD patients, and that this relationship was independent of traditional and non-traditional CV risk factors. Furthermore, this association was preserved with different CAC cutoff values and was consistent across different subgroup analyses.

These results are similar to those of previous studies of patients with preserved renal function. Torii et al. analyzed randomly selected Japanese men ($n = 986$) aged 40–79 years and they showed that elevated baPWV was associated with higher CAC prevalence in the general population [20]. They found that the optimal baPWV cutoff level to detect CAC was 1,612 cm/s. Similarly, in an international study of 1,131 healthy middle-aged men, baPWV was cross-sectionally associated with CAC, and the odds for developing CAC increased by 19% per every 100-cm/s increase in baPWV [21]. The largest study in this regard was the study by Cainzos-Achirica et al. In a single-center study of young and middle-aged Korean patients ($n = 15,185$), baPWV was independently associated with CAC presence and severity in asymptomatic adults [22]. We also found that the addition of baPWV to traditional risk factors significantly improved CAC diagnosis. Furthermore, another study by our research group found that high baPWV was also associated with CAC progression [23].

Several studies have evaluated the association between arterial stiffness and CAC in CKD patients. Haydar et al. analyzed 55 hemodialysis patients [24] and found that aortic PWV correlated with total CAC after correcting for age, dialysis duration, and time-averaged C-reactive protein. In another study of 104 predialysis patients by Toussaint et al., carotid-femoral PWV (cfPWV) correlated with coronary calcium score and calcium volume [25]. Interestingly, in a study of 132 hemodialysis patients by Di Iorio et al., multivariate analyses revealed that CAC progression was associated with a significant increase

in cfPWV [26]. However, previous studies of CKD patients are very small and do not take into account important risk factors such as sex, obesity, renal function, or phosphorus level. To the best of our knowledge, this is the only large-scale study of CKD patients that has identified a relationship between arterial stiffness and CAC after adjusting for various risk factors.

There are several candidate mechanisms underlying the association between arterial stiffness and CAC. First, arterial stiffness is not independent of vascular calcification and may be a physiologic expression of arteriosclerosis that is an outcome of medial and intimal calcification [27]. In CAC cases, both intimal and medial calcifications are observed [28], although intimal calcification is more common than vascular calcification in CKD cases where medial calcification is more prevalent [29]. Second, arterial stiffness can induce atherosclerosis directly. Intimal calcification is an important finding as atherosclerosis progresses and atherosclerotic plaques form [30, 31]. Arterial wall shear stress, endothelial dysfunction, and alterations in the extracellular matrix, such as elastin fragmentation or collagen deposition combined with high arterial stiffness, are suggested mechanisms underlying atherogenesis [32]. Third, arterial stiffness and vascular calcification share risk factors including age, sex, blood pressure, diabetes, inflammation, and chronic kidney disease, which are the basis for linking arterial stiffness to vascular calcification [30, 32]. We have controlled for these risk factors to look for independent relationships between the two, but it is also possible that there are residual or unmeasured confounders.

As mentioned above, recent studies have found that subclinical atherosclerosis detected as CAC is a predictor of CVD and high CV mortality in CKD patients as well as in the general population [12, 13]. However, coronary calcium scoring requires high costs, skilled expertise, and risk of radiation exposure. In contrast, PWV measurement is relatively simple, cost effective, and does not require a separate expert to read the results. Furthermore, baPWV does not require the inguinal area to be exposed or special training to take measurements compared with cfPWV [33, 34]. In this regard, this study offers clinical implications for increased significance of baPWV as a CV risk stratification tool in CKD patients.

Our results should be interpreted with caution due to a few limitations. First, this study is cross-sectional in design. We cannot define a causal relationship between arterial stiffness and CAC. Second, some information that might improve our analysis was not available, such as physical activity and markers of insulin resistance. Despite these limitations, the relatively large number of study subjects from different centers, our well-structured research design, and our inclusion of various risk factors in CKD are strengths of this study.

In conclusion, increased arterial stiffness measured by high baPWV was associated with CAC in a predialysis CKD cohort of Korean adults. These results remained significant after adjusting for various traditional and non-traditional CV risk factors and after using different cutoff values for CAC or different subgroup rearrangements. However, this cross-sectional study alone cannot elucidate a specific underlying mechanism for this association. Further research is warranted to determine the exact mechanism by which arterial stiffness leads to the development of CAC and CVD in CKD patients. Longitudinal studies may help determine the role of arterial stiffness in the development or progression of CAC in CKD.

Disclosure Statement

No conflict of interest to declare.

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Author Contributions

Young Youl Hyun: Drafting the article, analysis and interpretation of data, revising the article and final approval of the article.

Hyang Kim, Kook-Hwan Oh, Curie Ahn, Sue K. Park, Dong Wan Chae, Seung Hyeok Han, Yong-Soo Kim, Sung Woo Lee, Chang Seong Kim: Analysis and interpretation of data, revising the article and final approval of the article.

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