의학석사 학위논문

# Better correlation of pulse wave velocity (PWV) than coronary artery calcium score (CACS) with parameters of mineral bone disturbance in chronic kidney disease (MBD-CKD)

# 만성 콩팥병 환자에서 무기질뼈장애의 지표들과 맥파전도속도의 연관성 분석

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# Abstract

**Introduction:** The coronary artery calcium score (CACS), although frequently used as a hallmark of vascular calcification (VC) in many studies of mineral bone disturbance in chronic kidney disease (MBD-CKD), reflects primarily intimal calcification. However, VC in MBD-CKD occurs largely in the media secondary to osteogenic transformation of vascular smooth muscle cells exposed to the uremic milieu. Hence, we hypothesized that the pulse wave velocity (PWV), which reflects vascular stiffness from medial VC, might correlate with the parameters of MBD-CKD, including fibroblast growth factor 23 (FGF-23), better than does the CACS.

**Methods:** The KNOW-CKD is an ongoing prospective, hospital-based, observational cohort study being conducted in nine major university hospitals across South Korea under the sponsorship of the Korean Center for Disease Control and Prevention. We performed a cross-sectional analysis of the relationship between indicators of VC, such as brachial-ankle PWV (baPWV) and the CACS, and parameters of MBD-CKD using the data from this cohort. The uppermost tertile value of

the mean of the baPWV (MPWV) was regarded as significant arterial stiffness. Severe CAC was defined as a calcium score of ≥100 Agatston units.

**Results:** A total of 753 adult patients were enrolled from August 2011 to November 2011; 58.4% were male, and the median age was 53 years (range, 20– 75 years). The prevalences of hypertension, diabetes, cerebrovascular disease, and coronary heart disease (CHD) were 89.9%, 26.3%, 7.4%, and 5.6%, respectively. In univariate analysis, both the CACS and MPWV were associated with traditional risk factors for atherosclerosis and the parameters of MBD-CKD. However, after binary logistic regression analysis, only traditional risk factors such as age, male gender, diabetes, and CHD were significant risk factors for severe CAC ($p < 0.001$, $p < 0.001$, $p = 0.014$, and $p < 0.001$, respectively). With regard to arterial stiffness, parameters of MBD-CKD, such as estimated GFR (eGFR), random urine protein-to-creatinine ratio (UPCR), and T-score of DEXA for the femur neck, were independent risk factors for significant arterial stiffness ($p = 0.016$, $p = 0.041$, and $p = 0.003$, respectively). We also compared the relationship between log-normalized CACS or MPWV and MBD parameters and assessed the correlation between FGF-23 and

other related parameters. The MPWV showed a stronger relationship with MBD parameters than did the CACS. Furthermore, FGF-23 showed a significant association with other related parameters, such as the serum phosphorus level, corrected calcium, eGFR, UPCR, fractional excretion of phosphorus, and MPWV in the entire study population ($p$ < 0.001, $p$ < 0.001, $p$ < 0.001, $p$ < 0.001, $p$ < 0.001, and $p$ = 0.025, respectively).

**Conclusions:** In this study, we compared the adequacy of the CACS and PWV for assessment of VC in MBD-CKD in a prospective observational CKD cohort. Because the PWV correlated with parameters of MBD-CKD, including FGF-23, better than did the CACS, the PWV rather than the CACS is suggested to be a marker of VC in MBD-CKD.

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**Keywords:** chronic kidney disease, mineral bone disturbance, pulse wave velocity, vascular calcification

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# LIST OF ABBREVIATIONS

BMD bone mineral density

CACS coronary artery calcium (calcification) score

CKD chronic kidney disease

CVD cardiovascular disease

FGF-23 fibroblast growth factor 23

MBD-CKD mineral bone disturbance in chronic kidney disease

PWV pulse wave velocity

VC vascular calcification

# INTRODUCTION

Cardiovascular disease (CVD) is a leading cause of morbidity and mortality in patients with chronic kidney disease (CKD) (Foley, Parfrey *et al*. 1998; Drueke 2000). The last decade has brought an increase in our knowledge of the importance of CVD for patients with CKD. The pathophysiology of CVD in patients with CKD is multifactorial and includes traditional risk factors such as older age, diabetes, hypertension, and hyperlipidemia, and parameters related to CKD such as chronic inflammation, oxidative stress, and abnormal bone and mineral metabolism. Although traditional cardiovascular risk factors are common in the CKD population, many cases of CVD may be related to nontraditional risk factors such as vascular calcification (VC) and arterial stiffness associated with CKD (Blacher, Guerin *et al*. 2001; London 2003).

VC is a major complication in patients with CKD, and there is accumulating evidence that these individuals show a greater burden of VC than the general population (Schwarz, Buzello *et al*. 2000). In patients with CKD, arterial calcification can occur in both the intimal and medial layers. Therefore, clinical

manifestations depend on the location within the arterial wall (Chen and Moe 2012). Intima calcification characterized by calcific plaques or calcified atherosclerosis leads to ischemia or infarction of downstream tissues. On the other hand, medial calcification leads to reduced compliance due to arterial stiffening and produces hemodynamic changes that may result in increased afterload and left ventricular hypertrophy (Chung, Lin *et al.* 2012; Dellegrottaglie, Sands *et al.* 2011). VC associated with mineral bone disturbance in CKD (MBD-CKD) occurs mainly in arterial media, causing vascular stiffness, hypertension, and a lower quality of life with high morbidity and mortality (Amann 2008).

Several noninvasive imaging techniques have been used to evaluate VC. Computed tomography (CT) imaging techniques are considered to be the gold standard for the evaluation of coronary artery and aortic calcification. In many studies of MBD-CKD, the coronary artery calcium score (CACS) has been used as a hallmark of VC; however, it cannot distinguish intima from medial calcification of arteries and reflects mainly intimal calcification. The pulse wave velocity (PWV) has also been frequently used to assess arterial stiffness, which is related to medial calcification (Guerin, Pannier *et al.* 2008), and

the results of many studies have emphasized the role of arterial stiffness measured by the PWV as an independent cardiovascular risk factor and predictor of all-cause and cardiovascular death in patients with CKD (Blacher, Guerin *et al*. 1999; Blacher, Safar *et al*. 2002; Guerin, Pannier *et al*. 2008).

VC in MBD-CKD occurs largely in the media as a result of osteogenic transformation of vascular smooth muscle cells exposed to the uremic milieu. Hence, we hypothesized that the PWV, which reflects vascular stiffness due to medial calcification, might correlate with parameters of MBD-CKD, including fibroblast growth factor 23 (FGF-23), better than does CACS. Therefore, in this study, we investigated the relationship between the PWV and mineral bone metabolism abnormalities.

# SUBJECTS and METHODS

## 1. Study participants

The KoreaN Cohort Study for Outcome in Patients With Chronic Kidney Disease (KNOW-CKD) is an ongoing prospective, hospital-based, observational cohort study being conducted in nine major university hospitals across South Korea under the sponsorship of the Korean Center for Disease Control and Prevention. A total of 753 adult patients were enrolled from August to November 2011, of which 58.4% were male. Inclusion criteria were an age of 20 to 75 years and established CKD. Patients were excluded if they received chronic dialysis or had undergone organ transplantation. Subjects were also excluded if they were pregnant or diagnosed with cancer, heart failure, cirrhosis, or a single kidney. The protocol was approved by the local ethics committee, and all patients gave written informed consent. This cohort is currently in progress, and the results presented here represent an analysis of baseline data.

## 2. Clinical characteristics

Medical records were reviewed for clinical information and supplemented with a detailed questionnaire. Age, sex, current medications, smoking history (never/former/current), alcohol consumption, and previous medical diagnoses were recorded. Participants also underwent a clinical examination. Blood pressure was measured and body mass index (BMI) was calculated as mass in kilograms divided by height in meters squared.

## 3. Laboratory measurements

Serum markers measured were those related to mineral metabolism, including calcium (Ca), phosphorus (P), alkaline phosphatase, hemoglobin (Hb), creatinine (Cr), albumin, fasting blood sugar, hemoglobin A1c (HbA1c), C-reactive protein (CRP), and lipid profile. Estimated glomerular filtration rate (eGFR) was calculated based on serum Cr using the simplified Modification of Diet in Renal Disease equation. All patients performed a 24-h urine collection for measurements of Cr

clearance, protein, albumin, P, and Ca excretion. Proteinuria was assessed as the random urine protein to Cr ratio (UPCR). Plasma FGF-23 was determined by ELISA. The assay procedure was performed as described by the manufacturer. The absorbance at 450 nm was read.

## 4. Coronary artery calcification scoring

All participants in the current study were examined using multidetector row CT or electron-beam CT for coronary Ca quantification. A Ca threshold of ≥130 HU was used. As described by Agatston, the Ca score was determined by multiplying the area of each calcified lesion by a weighting factor corresponding to the peak pixel intensity of each lesion. The sum of each lesion in all coronary arteries was used for analysis. Severe coronary artery calcification (CAC) was defined as Ca score of ≥100 Agatston units (AU).

## 5. Brachial-ankle pulse wave velocity

The brachial-ankle PWV (baPWV) is used as an arterial

stiffness marker because of its ease of measurement, reproducibility, and proven validity (Yamashina, Tomiyama *et al.* 2002). After a subject had been in the supine position for ≥5 min, blood pressure and baPWV were measured using an automated waveform analyzer (Colin VP-2000/1000; Colin Medical Instruments Corp., Komaki, Japan). Blood pressure was measured in both arms using the blood pressure cuffs of the device, and the higher value was used for further analysis. The mean of the bilaterally measured baPWV was used for analysis. The cohort was divided into three groups according to the mean of the baPWV (MPWV) tertiles, and we regarded the upper third as significant arterial stiffness.

## 6. Bone mineral density

Bone mineral density (BMD) was measured using dual X-ray absorptiometry in the lumbar spine (L-spine), total hip, and femoral neck. The results are expressed as the BMD ($g/cm^2$) and the T-score. T-scores were calculated by taking the difference between the measured BMD and the mean BMD of healthy young adults matched for gender and ethnicity, divided by the standard deviation (SD) of the young adult population.

## 7. Statistical analysis

All data are presented as means ± SD, medians and ranges, or frequencies, as appropriate. For descriptive and analytical purposes, patients were stratified according to the CACS and MPWV (*i.e.*, CACS of <100 AU *versus* CACS of ≥100 AU and MPWV of <1554.5 cm/s *versus* MPWV of ≥1554.5 cm/s). Intergroup comparisons were performed using Student's *t*-test for continuous variables and a $\chi^2$ test for categorical variables. Binary logistic regression analysis was performed on variables with an unadjusted effect, with a *p* value of <0.05 by univariate analysis, to identify risk factors for severe CAC and significant arterial stiffness. The distribution of the CACS was skewed, and some subjects had no calcification. Therefore, the CACS was natural-log-transformed after adding 1. Pearson's correlation coefficient was used to assess (1) the relationship between the CACS or MPWV and CKD-MBD parameters and (2) the relationship between FGF-23 and CKD-MBD parameters, adjusted for age and sex. Statistical analyses were conducted using SPSS version 19 (SPSS, Chicago, IL), and

statistical significance was accepted for $p$ values <0.05.

# RESULTS

## 1. Baseline characteristics

The demographics and clinical characteristics of the patients are shown in Table 1. The mean age was 52.2 ± 12.6 years (53, 20- 75 years), and male subjects comprised 58.4%. Most of the patients had hypertension, 26% had diabetes, and 36.8% were obese (BMI of ≥25 kg/$m^2$). Glomerulonephritis was the main cause of CKD (32.2%), and polycystic kidney disease was the next most common (28%). On the basis of the CKD classification proposed by the National Kidney Foundation (Kidney Disease Outcomes Quality Initiative), approximately 62% of patients were in stage 3 or 4. Serum laboratory values, including renal function, lipid profiles, and serum markers of mineral metabolism and inflammation are presented in Table 2. The mean serum Cr and eGFR levels were 1.9 ± 1.3 mg/dL and 49.0 ± 30.2 mL/min/1.73 $m^2$, respectively. The BMD, CACS, and MPWV are shown in Table 3. The mean CACS and MPWV were 153.2 ± 491.9 AU (0, 0- 6343 AU) and 1507.17 ± 349.38 cm/s (1427.3, 951.5- 4632.5 cm/s), respectively.

Table 1. Characteristics of the study participants (n = 753).

| | Mean ± SD or frequency |
|---|---|
| Age (y) | 52.2 ± 12.6 y (53, 20- 75 y) |
| Gender (male, %) | 58.4 |
| BMI (kg/m$^2$) | 24.1 ± 3.3 |
| Comorbidity (%) | |
| HTN | 89.9 |
| DM | 26.3 |
| CHD | 5.6 |
| CVA | 7.4 |
| PAD | 1.8 |
| Obesity (BMI ≥25 kg/m$^2$, %) | 36.8 |
| Cause of CKD (%) | |
| GN | 32.2 |
| DMN | 17.2 |
| HTN and non-GN | 16.2 |
| PKD | 28 |
| Others | 6.4 |
| Smoking history (%) | |
| Never or ex-smoker | 84.3 |
| Current smoker | 15.7 |

| | |
|---|---|
| CKD classification (%) | |
| Stage 1 | 11.3 |
| Stage 2 | 18.0 |
| Stage 3 | 39.5 |
| Stage 4 | 22.4 |
| Stage 5 | 8.8 |
| Medications (%) | |
| Antihypertensive drugs | 96.2 |
| Lipid-lowering drugs | 40.8 |
| Vitamin D* | 8.3 |
| Calcimimetics | 6.6 |
| Ca-based P binder | 2.4 |

BMI, body mass index; HTN, hypertension; DM, diabetes mellitus; CHD, coronary heart disease; CVA, cerebrovascular accident; PAD, peripheral arterial disease; CKD, chronic kidney disease; GN, glomerulonephritis; DMN, diabetic nephropathy; PKD, polycystic kidney disease.

*Includes vitamin D, active vitamin D, and vitamin D analogue.

Table 2. Biochemical characteristics of the study population (n = 753).

| | Mean ± SD |
|---|---|
| Hb (g/dL) | 12.8 ± 1.9 |
| Albumin (g/dL) | 4.2 ± 0.4 |
| CRP (mg/dL) | 0.2 ± 0.5 |
| FBS (mg/dL) | 107 ± 39 |
| HbA1c (%) | 6.4 ± 1.4 |
| Creatinine (mg/dL) | 1.9 ± 1.3 |
| eGFR (mL/min/1.73 $m^2$) | 49.0 ± 30.2 |
| TC (mg/dL) | 176 ± 38 |
| TG (mg/dL) | 151 ± 95 |
| HDL-C (mg/dL) | 52 ± 17 |
| LDL-C (mg/dL) | 98 ± 31 |
| Uric acid (mg/dL) | 7.1 ± 2.1 |
| P (mg/dL) | 3.7 ± 0.7 |
| c-Ca × P | 33.1 ± 6.2 |
| ALP (IU/L) | 88.2 ± 64.3 |
| UPCR (mg/mg) | 1.37 ± 1.93 |
| $FEPO_4$ (%) | 20.9 ± 31.0 |
| FGF-23 (RU/mL) | 29.0 ± 41.1 |

Hb, hemoglobin; CRP, C-reactive protein; FBS, fasting blood sugar; eGFR, estimated GFR; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; P, phosphate; c-Ca × P, corrected calcium and phosphorus product; ALP, alkaline phosphatase; UPCR, random urine protein to creatinine ratio; $FEPO_4$, fractional excretion of phosphate; FGF-23, fibroblast growth factor 23.

Table 3. BMD, CACS, and PWV.

| | Mean ± SD |
|---|---|
| DEXA (T-score) | |
| L-spine | -0.14 ± 1.49 |
| Total hip | 0.25 ± 1.31 |
| Femoral neck | -0.25 ± 1.38 |
| CACS (AU) | 153.2 ± 491.9 |
| MPWV (cm/s) | 1507.17 ± 349.38 |

CACS, coronary artery calcification score; AU, Agatston units; MPWV, mean of brachial-ankle pulse wave velocity.

## 2. Comparison of patients with and without severe CAC

As mentioned above, we defined severe CAC as a Ca score of ≥100 AU. A total of 697 patients had CACS data, and were divided according to the CACS. The differences between patients with and without severe CAC are listed in Table 4. Patients with severe CAC were more likely to be older males and have more comorbidities. They also had a higher mean pulse pressure; higher levels of serum P, Cr, uric acid, HbA1c, and UPCR; and lower levels of Hb, eGFR, and T-scores of DEXA for the total hip and femoral neck. Patients with severe CAC showed lower levels of total cholesterol and low-density lipoprotein cholesterol, which may have been related to most having been administered lipid-lowering drugs (66%). There were no differences in the fractional excretion of phosphate ($FEPO_4$) and FGF-23 between the two groups. The MPWV was significantly increased in patients with severe CAC. After binary logistic regression analysis, serum P and traditional risk factors such as age, male gender, diabetes, and coronary heart disease (CHD) were significant risk factors for severe CAC (Table 5).

Table 4. Comparison of patients with and without severe CAC (n = 697).

| | CACS <100 AU (n = 550) | CACS ≥100 AU (n = 147) | *p* value |
|---|---|---|---|
| Age (y) | 49.6 ± 12.3 | 61.2 ± 8.8 | <0.001 |
| Male (%) | 53.3 | 76.2 | <0.001 |
| Obesity (%) | 35.2 | 42.1 | 0.130 |
| HTN (%) | 87.8 | 95.9 | 0.005 |
| DM (%) | 19.0 | 55.5 | <0.001 |
| CHD (%) | 1.3 | 19.9 | <0.001 |
| CVD (%) | 6.0 | 12.3 | 0.010 |
| PAD (%) | 1.3 | 4.1 | 0.025 |
| Lipid-lowering D (%) | 33.8 | 66.0 | <0.001 |
| Vitamin D (%) | 8.0 | 8.8 | <0.740 |
| Hb (mg/dL) | 12.8 ± 1.9 | 12.4 ± 1.8 | 0.011 |
| P (mg/dL) | 3.7 ± 0.7 | 3.8 ± 0.7 | 0.025 |
| c-Ca × P | 32.8 ± 6.3 | 33.9 ± 5.7 | 0.051 |
| Cr (mg/dL) | 1.8 ± 1.3 | 2.2 ± 1.2 | 0.001 |
| eGFR(mL/min/1.73 $m^2$) | 51.8 ± 31.5 | 38.1 ± 22.7 | <0.001 |
| TC (mg/dL) | 178 ± 37 | 165 ± 37 | <0.001 |
| TG (mg/dL) | 147 ± 88 | 167 ± 123 | 0.028 |

| | | | |
|---|---|---|---|
| HDL−C (mg/dL) | 53 ± 17 | 46 ± 14 | <0.001 |
| LDL−C (mg/dL) | 100 ± 31 | 90 ± 27 | 0.001 |
| Uric acid (mg/dL) | 6.9 ± 2.1 | 7.6 ± 2.0 | <0.001 |
| CRP (mg/dL) | 0.2 ± 0.4 | 0.3 ± 0.6 | 0.211 |
| HbA1c (%) | 6.2 ± 1.3 | 7.1 ± 1.7 | <0.001 |
| UPCR (mg/mg) | 1.24 ± 1.68 | 1.89 ± 2.64 | 0.015 |
| $FEPO_4$ (%) | 20.13 ± 32.60 | 24.27 ± 26.45 | 0.190 |
| FGF−23 (RU/mL) | 28.2 ± 43.0 | 29.1 ± 23.6 | 0.810 |
| DEXA (T−score) | | | |
| L−spine | −0.18 ± 1.47 | 0.09 ± 1.57 | 0.053 |
| Total hip | 0.30 ± 1.32 | 0.04 ± 1.25 | 0.049 |
| Femoral neck | −0.17 ± 1.39 | −0.57 ± 1.28 | 0.002 |
| MPWV (cm/s) | 1443.2 ± 276.9 | 1779.3 ± 474.6 | <0.001 |

Lipid−lowering D, lipid−lowering drug.

Table 5. Binary logistic regression of risk factors for severe CAC.

| Factors | *p* value | OR | 95% CI |
|---|---|---|---|
| Age | <0.001 | 1.090 | 1.061- 1.121 |
| Male | <0.001 | 2.921 | 1.600- 5.333 |
| DM | 0.006 | 2.206 | 1.259- 3.867 |
| CHD | <0.001 | 10.244 | 3.690- 28.442 |
| Serum P | 0.036 | 1.515 | 1.028- 2.231 |

## 3. Comparison between patients with and without significant arterial stiffness

A total of 630 subjects in the current study underwent measurement of bilateral baPWV. The mean bilateral baPWV values were divided into tertiles, and we regarded the upper third as significant arterial stiffness. Patients with significant arterial stiffness were more likely to be older and have more comorbidities, with the exception of peripheral arterial disease (Table 6). They also had a higher mean pulse pressure; higher levels of serum P, Cr, uric acid, CRP, HbA1c, UPCR, and FGF-23; and lower levels of Hb, eGFR, and T-scores of DEXA for L-spine, total hip, and femoral neck. There were no differences in $FEPO_4$ between the two groups. The CACS was noticeably

increased in patients with significant arterial stiffness. With regard to arterial stiffness, as well as age and diabetes, parameters of mineral bone metabolism such as eGFR, UPCR, and T-scores for the femoral neck were also independent risk factors for significant arterial stiffness (Table 7).

Table 6. Comparison of patients with and without significant arterial stiffness (n = 630).

| | MPWV <1554.5 cm/s (n = 421) | MPWV ≥1554.5 cm/s (n = 209) | *p* value |
|---|---|---|---|
| Age (y) | 46.7 ± 11.2 | 60.4 ± 9.7 | <0.001 |
| Male (%) | 56.5 | 59.3 | 0.549 |
| Obesity (%) | 37.4 | 33.5 | 0.339 |
| HTN (%) | 87.4 | 94.7 | 0.004 |
| DM (%) | 13.6 | 51.0 | <0.001 |
| CHD (%) | 2.1 | 10.1 | <0.001 |
| CVD (%) | 4.8 | 13.0 | <0.001 |
| PAD (%) | 1.7 | 2.4 | 0.528 |
| Lipid-lowering D (%) | 31.8 | 51.7 | <0.001 |
| Vitamin D (%) | 7.1 | 10.0 | 0.206 |
| Hb (mg/dL) | 13.2 ± 1.9 | 11.9 ± 1.8 | <0.001 |

| | | | |
|---|---|---|---|
| P (mg/dL) | 3.6 ± 0.6 | 3.9 ± 0.7 | <0.001 |
| c−Ca × P | 32.4 ± 5.9 | 34.7 ± 6.4 | <0.001 |
| Cr (mg/dL) | 1.7 ± 1.1 | 2.4 ± 1.5 | <0.001 |
| eGFR (mL/min/1.73 $m^2$) | 57.1 ± 32.3 | 35.9 ± 21.4 | <0.001 |
| TC (mg/dL) | 179 ± 37 | 173 ± 38 | 0.087 |
| TG (mg/dL) | 146 ± 92 | 162 ± 109 | 0.067 |
| HDL−C (mg/dL) | 54 ± 17 | 49 ± 18 | 0.003 |
| LDL−C (mg/dL) | 101 ± 31 | 95 ± 28 | 0.031 |
| Uric acid (mg/dL) | 6.8 ± 2.1 | 7.4 ± 2.0 | 0.001 |
| CRP (mg/dL) | 0.2 ± 0.4 | 0.3 ± 0.7 | 0.033 |
| HbA1c (%) | 6.0 ± 1.3 | 7.0 ± 1.4 | <0.001 |
| UPCR (mg/mg) | 1.08 ± 1.40 | 1.99 ± 2.31 | <0.001 |
| $FEPO_4$ (%) | 18.94 ± 34.15 | 23.09 ± 25.30 | 0.158 |
| FGF−23 (RU/mL) | 26.6 ± 40.6 | 34.4 ± 47.6 | 0.035 |
| DEXA (T−score) | | | |
| L−spine | −0.05 ± 1.37 | −0.42 ± 1.60 | 0.003 |
| Total hip | 0.53 ± 1.25 | −0.29 ± 1.28 | <0.001 |
| Femoral neck | 0.20 ± 1.28 | −0.87 ± 1.22 | <0.001 |
| CACS (AU) | 70.8 ± 326.7 | 295.6 ± 708.6 | <0.001 |

Table 7. Binary logistic regression of risk factors for significant arterial stiffness.

| Factors | *p* value | OR | 95% CI |
|---|---|---|---|
| Age | <0.001 | 1.095 | 1.066- 1.126 |
| DM | <0.001 | 3.208 | 1.789- 5.751 |
| eGFR | 0.013 | 0.986 | 0.975- 0.997 |
| UPCR | 0.040 | 1.174 | 1.007- 1.368 |
| DEXA (FN) | 0.003 | 0.713 | 0.571- 0.890 |

DEXA (FN), T-score of DEXA for femoral neck.

## 4. Correlation between CACS or MPWV and CKD-MBD parameters

Table 8 shows the correlation between the log-normalized CACS or MPWV and CKD-MBD parameters in both the total study population and the two subgroups of patients divided according to diabetes status After adjusting for age and sex, the CACS was associated with pulse pressure, uric acid, and UPCR in the whole study population. However, no significant correlation was found between the CACS and related parameters in the two subgroups. Meanwhile, the MPWV was associated with pulse pressure, serum P, corrected Ca, UPCR, FGF-23, and T-scores of DEXA for the femoral neck in all

study patients; these associations were also found in both subgroups. Compared with the CACS, the MPWV showed a stronger relationship with MBD-CKD parameters.

## 5. Correlation between FGF-23 and CKD-MBD parameters

As presented in Table 9, we also investigated the relationship of plasma FGF-23 with MBD-CKD parameters in both the total study population and the two subgroups of patients divided according to diabetes status. After adjusting for age and sex, FGF-23 was positively associated with pulse pressure, uric acid, serum P, UPCR, $FEPO_4$, and MPWV and negatively correlated with corrected Ca, high-density lipoprotein cholesterol, and eGFR in the entire study population. In the subgroup analysis, FGF-23 showed a significant relationship with uric acid, serum P, eGFR, and $FEPO_4$ in the non-diabetes group and with serum P, corrected Ca, eGFR, and UPCR in the diabetes group. The correlation between FGF-23 and MPWV was significant in the whole study population, but not in either of the subgroups.

Table 8. Correlations between CACS or MPWV and CKD-MBD parameters (adjusted by age and gender; subgroup analysis).

| Parameters | Total population (n=753) | | DM (-) (n=540) | | DM (+) (n=193) | |
|---|---|---|---|---|---|---|
| | ln (CACS+1) R ($p$-value) | MPWV R ($p$-value) | ln (CACS+1) R ($p$-value) | MPWV R ($p$-value) | ln (CACS+1) R ($p$-value) | MPWV R ($p$-value) |
| Pulse pr | 0.256 (0.001) | 0.406 (<0.001) | 0.087 (0.420) | 0.521 (<0.001) | 0.253 (0.034) | 0.313 (0.008) |
| DEXA (FN) | -0.109 (0.169) | -0.270 (0.001) | -0.122 (0.256) | -0.385 (<0.001) | -0.057 (0.639) | -0.254 (0.033) |
| Uric acid | 0.160 (0.043) | 0.006 (0.939) | 0.047 (0.665) | 0.178 (0.094) | 0.171 (0.154) | -0.170 (0.157) |
| P | 0.147 (0.062) | 0.192 (0.014) | 0.091 (0.399) | 0.115 (0.283) | 0.038 (0.752) | 0.175 (0.144) |
| c-Ca x P | 0.154 (<0.001) | 0.194 (<0.001) | 0.094 (0.047) | 0.099 (0.037) | 0.071 (0.374) | 0.194 (0.014) |
| ALP | -0.017 (0.831) | 0.043 (0.585) | 0.064 (0.553) | 0.064 (0.550) | 0.013 (0.913) | 0.184 (0.125) |
| HDL-C | -0.086 (0.276) | 0.085 (0.285) | 0.093 (0.389) | 0.271 (0.010) | -0.137 (0.256) | 0.060 (0.619) |
| CRP | -0.026 (0.739) | 0.080 (0.309) | -0.060 (0.578) | 0.101 (0.348) | -0.026 (0.831) | 0.063 (0.602) |
| eGFR | -0.034 (0.664) | -0.144 (0.068) | 0.178 (0.095) | 0.022 (0.841) | -0.169 (0.159) | -0.297 (0.012) |
| UPCR | 0.184 (0.019) | 0.362 (<0.001) | 0.147 (0.169) | 0.193 (0.070) | 0.068 (0.573) | 0.404 (<0.001) |
| FGF-23 | 0.060 (0.447) | 0.176 (0.025) | -0.045 (0.678) | 0.038 (0.721) | -0.004 (0.976) | 0.171 (0.153) |
| $FEPO_4$ | -0.005 (0.951) | 0.098 (0.213) | 0.078 (0.469) | 0.108 (0.316) | -0.148 (0.217) | 0.073 (0.544) |
| ln (CACS+1) | - | 0.257 (0.001) | - | 0.092 (0.391) | - | 0.244 (0.040) |
| MPWV | 0.257 (0.001) | - | 0.092 (0.391) | - | 0.244 (0.040) | - |

Table 9. Correlations between FGF-23 and CKD-MBD parameters (adjusted by age and gender; subgroup analysis).

| Parameters | Total population (n=753) | | DM (-) (n=540) | | DM (+) (n=193) | |
|---|---|---|---|---|---|---|
| | R | *p*-value | R | *p*-value | R | *p*-value |
| Pulse pr | 0.244 | 0.002 | 0.154 | 0.151 | 0.233 | 0.051 |
| DEXA (FN) | -0.045 | 0.568 | 0.113 | 0.290 | -0.076 | 0.529 |
| Uric acid | 0.183 | 0.020 | 0.390 | <0.001 | 0.083 | 0.492 |
| P | 0.566 | <0.001 | 0.310 | 0.003 | 0.615 | <0.001 |
| c-Ca x P | 0.257 | <0.001 | 0.155 | 0.017 | 0.375 | <0.001 |
| ALP | 0.014 | 0.864 | 0.050 | 0.639 | 0.061 | 0.616 |
| HDL-C | -0.205 | 0.009 | -0.100 | 0.349 | -0.203 | 0.089 |
| eGFR | -0.317 | <0.001 | -0.252 | 0.017 | -0.358 | 0.002 |
| UPCR | 0.306 | <0.001 | 0.022 | 0.838 | 0.311 | 0.008 |
| $FEPO_4$ | 0.249 | 0.001 | 0.244 | 0.021 | 0.216 | 0.071 |
| ln (CACS+1) | 0.060 | 0.447 | 0.045 | 0.678 | -0.004 | 0.976 |
| MPWV | 0.176 | 0.025 | 0.038 | 0.721 | 0.171 | 0.153 |

# DISCUSSION

In this study, we compared the adequacy of the CACS and PWV in terms of assessment of the correlation between arterial calcification and MBD-CKD parameters in a prospective observational CKD cohort. Using univariate and multivariate logistic regression analyses, we identified that the risk factors for severe CAC were mainly traditional risk factors for atherosclerosis. On the other hand, independent risk factors for significant arterial stiffness were eGFR, UPCR, and T-score of DEXA for the femoral neck, as well as age and diabetes after multivariate regression analysis. We also compared the relationship between the log-normalized CACS or MPWV and MBD parameters and assessed the correlation between FGF-23, which is considered to be a new risk factor for MBD-CKD, and other related parameters. The MPWV showed a stronger relationship with MBD parameters than did the CACS. Furthermore, FGF-23 showed a significant association with the other related parameters, such as serum P, corrected Ca, eGFR, UPCR, $FEPO_4$, and MPWV, in the entire study population.

Arterial calcification in patients with CKD has two clinical effects: atherosclerosis and arteriosclerosis. Atherosclerotic

calcification represents the prototypic lesion described by Virchow (Virchow 1989). It is characterized by fibro-fatty plaque formation and can lead to myocardial infarction from stenosis and acute thrombus formation, or may result in ischemia in both the coronary and peripheral arteries. Clinically, arterial calcification can be detected through a number of techniques, including plain radiography, echocardiography, ultrasonography, and CT. Of these, CT imaging is considered to be the gold standard for the evaluation of arterial calcification, and it allows reproducible quantification of coronary artery and aortic calcification. Therefore, it serves as an excellent research end-point. Through many studies, the CACS has represented a strong relationship with traditional risk factors of atherosclerosis and is now considered to be a marker of the atherosclerotic plaque burden (Koukoulaki, Papachristou *et al.* 2012). It has also been shown to be a predictor of the incidence of myocardial infarction and death from CVD in patients with CKD as well as in the general population (Budoff and Gul 2008; Matsuoka, Iseki *et al.* 2004; Ramakrishna, Miller *et al.* 2007; Chang, Nabi *et al.* 2009). In agreement with data published previously, our results suggest that traditional risk factors for atherosclerosis, such as age, male gender, diabetes, and history

of previous CHD, increased the risk of severe CAC significantly. However, after analysis, we did not detect a relationship between severe CAC and MBD-CKD parameters, with the exception of the serum P level, in this cohort. It is possible that the CT imaging techniques did not permit differentiation of medial from intima calcification. Thus, CACS reflected mainly the intima calcification of arteries, which is characterized by atheromatous plaques.

Arteriosclerosis, which is characterized by medial or circumferential calcification of arteries, leads to thickening of the medial layer of elastic arteries. This clinically manifests as an increased PWV, elevated pulse pressure, and left ventricular hypertrophy (Moe 2006). Medial calcification in patients with CKD is associated with abnormal mineral metabolism characterized by hyperphosphatemia, hypocalcemia, hyperparathyroidism, and vitamin D deficiency. Other biochemical abnormalities classically associated with CKD, namely inflammation and oxidative stress, also play a critical role in the calcification process. These important stimuli enhance de-differentiation or transformation of vascular smooth muscle cells into an osteoblast/chondrocytic phenotype. Next, these cells lay down collagen and noncollagenous proteins

(extracellular matrix) in the intima or media and then mineralize the matrix through the secretion of matrix vesicles or through apoptosis (Moe, O'Neill *et al*. 2002). P and Ca increase the mineralizing potential of these matrix vesicles (Chen, O'Neill *et al*. 2008; Shroff, McNair *et al*. 2008). This mechanism may explain why vascular calcification is increased in CKD, in which disturbances of mineral metabolism are common, and why there may be a relationship between bone mineralization and arterial calcification (Barreto, Barreto Fde *et al*. 2008).

Arterial stiffness related to medial calcification can be measured by the PWV at the systemic, regional, or local level. Measurement of the carotid–femoral PWV is generally considered to be the gold standard. However, the baPWV is widely used to assess arterial stiffness in practice due to its time efficiency and technical simplicity. Tthe baPWV is well correlated with the carotid–femoral PWV in the general population (Tanaka, Munakata *et al*. 2009) and is a strong predictor of cardiovascular outcomes in patients undergoing hemodialysis (Kato, Takita *et al*. 2012). Therefore, we used the baPWV as an indicator of arterial stiffness in our study. Our data analysis showed that the correlation between the MPWV and CKD–MBD parameters is stronger than that of the CACS.

Age and gender-adjusted MPWV showed positive relationships with pulse pressure, serum P, UPCR, and FGF-23 and negative relationships with corrected Ca and T-scores of DEXA for the femoral neck. These associations were also found in the two subgroups of patients divided according to diabetes status. The CACS was correlated with pulse pressure, uric acid, and UPCR; however, no significant associations between the CACS and MBD-related parameters in both subgroups were found. Various PWV thresholds are used to indicate clinically significant arterial stiffness, so we stratified subjects according to MPWV tertiles and regarded the upper third as significant arterial stiffness. Similar to previous studies, we found that bone mineral abnormalities as indicated by eGFR, UPCR, and T-scores of the femoral neck significantly increased the risk of arterial stiffness.

FGF-23 is a recently discovered regulator of phosphate and mineral metabolism. Its main physiological function is the regulation of phosphate homeostasis by directly increasing urinary phosphate excretion and indirectly decreasing active intestinal phosphate absorption. In patients with CKD, FGF-23 levels are inversely related to eGFR and increased even in the early stage (Ix, Shlipak *et al.* 2010). Recent data indicate that

circulating FGF-23 may be a sensitive early marker of disordered bone mineral metabolism (Isakova, Wahl *et al.* 2011) and could be a surrogate marker of cardiovascular outcomes in patients with CKD (Gutierrez, Mannstadt *et al.* 2008; Isakova, Xie *et al.* 2011). In this CKD cohort, we also elucidated the relationship between FGF-23 and MBD-CKD parameters such as pulse pressure, serum P, corrected Ca, eGFR, UPCR, $FEPO_4$, and MPWV. Of these markers of abnormalities in mineral bone metabolism, serum P, corrected Ca, eGFR, and UPCR were strongly correlated with FGF-23 in the whole study population, and after subgroup analysis, these relationships were maintained. However, none of the T-scores of DEXA or CACS showed an association with FGF-23. Other observational studies in patients with CKD regarding the relationship between circulating FGF-23 levels and BMD have yielded inconsistent results (Manghat, Fraser *et al.* 2010; Desjardins, Liabeuf *et al.* 2012).

This study had several limitations. First, it was an observational cross-sectional analysis. Therefore, it was impossible to assess the adequacy of the PWV or CACS as predictors of progression of CKD-MBD and cardiovascular outcomes. Second, our PWV cut-off value was lower than

those in previous studies. Because no appropriate cut-off point of the PWV was present in the CKD population, we divided patients into tertiles of MPWV and regarded the upper third as significant arterial stiffness. Third, we did not include representative indicators of MBD-CKD, such as intact parathyroid hormone, 25-hydroxy vitamin D, and 1,25-dihydroxy vitamin D, in this analysis because we measured these parameters using various methods; as a result, there was a deviation between methods. However, a strength of this study is that it involved a well-designed multicenter CKD cohort. To date, this is to our knowledge the largest comparison of the relationship between PWV or CACS and mineral bone abnormalities in pre-dialysis patients with CKD.

In conclusion, we compared the adequacy of the PWV and CACS for assessment of vascular calcification related to mineral bone disturbances in patients with CKD. As expected, the PWV showed a strong correlation with mineral bone abnormalities. These findings suggest that the PWV is superior to the CACS as an indicator of VC associated with MBD-CKD.

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# 국문 초록

**서론:** 만성 콩팥병 환자의 무기질뼈장애에 대한 여러 연구에서 관상동맥 석회화 정도는 혈관 석회화에 대한 지표로 사용되어 왔지만, 이는 주로 혈관내막의 석회화를 반영한다. 그러나 무기질뼈장애가 동반된 만성 콩팥병 환자의 혈관 석회화는 대부분 요독에 노출된 혈관 평활근세포의 뼈형성 형질전환에 의해 유발된다. 따라서, 혈관중막의 석회화에 의한 동맥 경직도를 반영하는 맥파전도속도가 관상동맥 석회화 정도보다 섬유모세포 성장인자를 포함한 무기질뼈장애의 여러 지표들과 더 밀접한 연관성을 보일 것으로 생각된다.

**방법:** KNOW-CKD는 현재 진행중인, 병원 기반의 전향적 관찰 연구로서 한국 질병관리본부의 후원을 받고 있으며, 국내 9개 대학병원이 참여하고 있다. 본 연구는, 이 코호트 자료를 바탕으로 혈관 석회화를 반영하는 맥파전도속도 및 관상동맥 석회화 정도와 무기질뼈장애의 지표들 사이의 관련성에 대해 단면조사를 시행하였다. 양쪽에서 상완동맥과 족부동맥사이의 맥파전도속도를 측정하였고, 그 평균값을 삼등분하여 상위 1/3에 해당하는 경우, 유의한 동맥 경직이 있다고 판단하였다. 또한, 관상동맥혈관의 석회화 값이

100AU 이상인 경우 중증의 혈관 석회화가 있다고 판단하였다.

**결과:** 2011년 8월부터 11월까지 총 753명의 환자가 연구에 참여하였으며, 남자는 58.4%였고, 중앙 연령은 53세(범위, 20−75세)였다. 전체 환자에서 고혈압, 당뇨, 뇌혈관질환, 관상동맥질환의 유병률은 각각 89.9%, 26.3%, 7.4%, 5.6% 였다. 단변량분석에서 관상동맥 석회화 정도 및 맥파전도속도는 모두 전형적인 죽상경화증의 위험 인자들 및 무기질뼈장애를 나타내는 지표들과 관련성을 보였다. 그러나 이분형 로지스틱 회귀분석 결과, 나이, 남성, 당뇨 및 관상동맥질환 등 전형적인 죽상경화증의 위험인자만 혈관 석회화에 대한 위험성을 높였다 ($p<0.001$, $p<0.001$, $p=0.014$, $p<0.001$). 동맥 경직도 측면에서는 사구체여과율, 임의뇨단백 크레아티닌 비율, 대퇴경부의 T 점수가 동맥 경직에 대한 위험인자가 되었다 ($p=0.016$, $p=0.041$, $p=0.003$). 또한, 무기질뼈장애 지표들과 관상동맥혈관 석회화 정도 및 맥파전도속도의 관련성을 서로 비교하였고, 섬유모세포 성장인자와 다른 무기질뼈장애 지표들과의 연관성에 대해서도 조사하였다. 그 결과 맥파전도속도가 관상동맥혈관 석회화보다 무기질뼈장애의 지표들과 더 밀접한 관련성을 보였고, 섬유모세포 성장인자 역시 혈청 인, 칼슘, 사구체여과율, 임의뇨단백 크레아티닌 비율, 분획성인산염 배설 및 맥파전도속도와 상관성을 나타내었다 ($p<0.001$, $p<0.001$, $p<0.001$, $p<0.001$, $p<0.001$, $p=0.025$).

**결론:** 본 연구는, 무기질뼈장애가 동반된 만성 콩팥병 환자의 혈관 석회화 평가 시 관상동맥혈관 석회화 정도와 맥파전도속도 중 어느 것이 더 적합한지를 비교한 연구이다. 분석 결과, 맥파전도속도는 관상동맥혈관 석회화 보다 섬유모세포 성장인자를 포함한 무기질뼈장애의 지표들과 더 밀접한 관련성을 보였다. 그러므로, 맥파전도속도가 무기질뼈장애가 동반된 만성 콩팥병 환자에서 혈관의 석회화를 평가하는 데 더 적합할 것으로 생각된다.

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**주요어:** 만성 콩팥병, 맥파전도속도, 무기질뼈장애, 혈관 석회화
**학 번:** 2011 – 21888