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Fibroblast Growth Factor 23, High-Sensitivity Cardiac Troponin, and Left Ventricular Hypertrophy in CKD

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Abstract

Background—Detectable levels of cardiac troponins are common among individuals with chronic kidney disease (CKD), even in the absence of symptomatic cardiovascular disease. Abnormal cardiac troponin values are associated with coronary artery disease (CAD) and left ventricular hypertrophy (LVH), and predict poor clinical outcomes. Elevated levels of fibroblast growth factor 23 (FGF-23) contribute to LVH in CKD. We investigated the association of FGF-23 and hs-cTnI (high-sensitivity cardiac troponin I) and hs-cTnT (high-sensitivity cardiac troponin T) in CKD, and examined the role of LVH in this association.

Study Design—Cross-sectional observational study.

Setting & Participants—153 stable outpatients with non-dialysis-dependent CKD.

Predictor—The primary predictor was FGF-23.

Outcomes—hs-cTnI, hs-cTnT.

Measurements—FGF-23, hs-cTnI, hs-cTnT; LVMI assessed by echocardiography; CAC measured by computed tomography. Left ventricular mass index (LVMI) and coronary artery calcification (CAC) were evaluated as potential mediators of the effect of FGF-23 on hs-cTnI/T.

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Results—Mean age was 64 ± 12 (SD) years, mean estimated glomerular filtration rate (eGFR) was 34 ± 11 mL/min/1.73m², median FGF-23 was 120 (25th–75th percentile, 79–223) RU/mL, median hs-cTnI was 6.5 (25th–75th percentile, 3.5–14.5) pg/mL, and median hs-cTnT was 16.8 (25th–75th percentile, 11.1–33.9) pg/mL. Concentrations of cTnI and cTnT were >99th percentile of a normal population in 42% and 61% of patients, respectively. In unadjusted and multivariable adjusted analyses, hs-cTnI/T were significantly associated with FGF-23. Adjusting for LVMI, but not CAC, weakened the association of FGF-23 and hs-cTnI/T.

Limitations—Vitamin D levels were not measured. Prevalence of CAD may have been underestimated since it was ascertained by self-report.

Conclusions—Minimally elevated cTnI and cTnT, detectable by high-sensitivity assays, are associated with elevated FGF-23 levels in stable outpatients with CKD. FGF-23-associated LVH may contribute to detectable hs-cTnI/T levels observed in non-dialysis-dependent CKD patients.

Keywords

fibroblast growth factor 23; high-sensitivity cardiac troponin; left ventricular hypertrophy; chronic kidney disease

Cardiovascular disease is the most frequent cause of death among patients with chronic kidney disease (CKD).¹ Despite the high prevalence of traditional risk factors for atherosclerosis in CKD, heart failure, arrhythmia, and sudden death comprise a disproportionately greater burden of cardiovascular-related mortality in CKD compared to coronary artery disease (CAD).² Left ventricular hypertrophy (LVH) and LV dysfunction are common non-atherosclerotic mechanisms of cardiovascular injury in CKD.³ Further understanding of the pathogenesis of cardiovascular disease in CKD is needed to define novel strategies for risk reduction.

An elevated level of fibroblast growth factor 23 (FGF-23), a recently discovered hormonal regulator of phosphate metabolism, has come to be understood as a novel risk factor for cardiovascular disease.^{4–6} FGF-23 concentrations increase with decreasing estimated glomerular filtration rate (eGFR), and help to maintain normal phosphate homeostasis in spite of reduced renal mass, by stimulating greater per-nephron phosphate excretion and decreasing 1,25-dihydroxyvitamin D levels.^{7–9} Elevated levels of FGF-23 are independently associated with prevalent and incident LVH, cardiovascular disease events and mortality in CKD and non-CKD populations.^{4–6,10–13} Furthermore, a recent study demonstrated that FGF-23 directly induces LVH,¹³ suggesting that FGF-23 is not simply a biomarker of cardiovascular risk but rather, a novel molecular mediator of cardiac injury.

Cardiac troponin T (cTnT) and I (cTnI) are intracellular proteins that regulate contraction of cardiac myocytes by mediating the interaction between thick and thin filaments within the troponin-tropomyosin complex.¹⁴ Whereas an acute rise in cardiac troponin levels is a diagnostic finding in acute coronary syndromes,¹⁵ cardiac troponin levels above the 99th percentile of a normal population are frequently detectable even in the absence of acute ischemia in patients with LVH and heart failure,^{16–19} and are often detectable in individuals with early CKD without symptomatic heart disease.^{20,21} The mechanism of subclinical myocardial injury that is responsible for abnormal cardiac troponin values in the setting of CKD remains poorly understood.^{14,22} In a cross-sectional study of stable outpatients with non-dialysis-dependent CKD, we tested the hypotheses that elevated FGF-23 is associated with detectable cardiac troponin concentrations, and that presence of LVH mediates a component of this association.

Methods

Study Population

One hundred and fifty three patients with non-dialysis-dependent CKD were recruited from outpatient nephrology clinics at the Massachusetts General Hospital, the University of Maryland School of Medicine, and the Baltimore Veteran's Administration Medical Center from 2006–2007. Eligibility requirements were age ≥ 30 years and sustained reduction (≥ 3 months) of eGFR ≥ 60 mL/min/1.73 m² based on the 4-variable MDRD (Modification of Diet in Renal Disease) Study equation.²³ Exclusion criteria included CKD stage 5 (eGFR < 15 mL/min/1.73 m²), renal replacement therapy (dialysis or kidney transplant), history of coronary artery bypass grafting, or a history of myocardial infarction within 90 days of enrollment. Patients with more severe symptoms than New York Heart Association class 1 heart failure or Canadian Cardiovascular Society class 1 angina were excluded in an effort to recruit a stable population of CKD patients with minimal or no symptoms of heart disease. The study was approved by the Institutional Review Boards of the Massachusetts General Hospital, the University of Maryland School of Medicine, and the Baltimore Veteran's Administration Medical Center. All patients provided written informed consent.

Clinical and Laboratory Data Collection

Vital signs, demographic data, and current medications were collected at enrollment. CAD and other medical history were ascertained by self report. Blood and urine samples from each participant were collected and immediately centrifuged, separated into aliquots, and stored at -80°C for future batched analysis. Serum creatinine, calcium and phosphate were measured with standard commercial assays. As a secondary measure of kidney function, cystatin C concentrations were measured with BN ProSpec® (Siemens Healthcare Diagnostics, www.usa.siemens.com) and cystatin C-based eGFR (eGFR_{cys}) was calculated using the nonstandardized CKD-EPI (CKD Epidemiology Collaboration) equation.²⁴ Intact parathyroid hormone (PTH) concentrations were measured with the Roche Elecsys assay (Roche, www.roche.com). FGF-23 concentrations were measured in duplicate with a 2-site ELISA assay that detects 2 epitopes in the carboxyl-terminal portion of FGF-23 (CV $< 5\%$; Immutopics, immutopicsintl.com).

Serum cTnI was measured by a prototype high-sensitivity assay (Dimension Vista® 1500, Siemens Healthcare Diagnostics). Serum cTnT was measured using a commercial high-sensitivity assay (Elecsys® 2012, Roche Diagnostics, www.roche.com). Guidelines state optimal sensitivity of cardiac troponin assays is achieved when the diagnostic cut-point exceeds the 99th percentile of a normal reference population.²⁵ The manufacturer provided reference values for high-sensitivity assays, defined by the 99th percentile of high-sensitivity cardiac troponin I (hs-cTnI) (n=288, 122 males [42%], age range 18–59 years) and high-sensitivity cardiac troponin T (hs-cTnT) (n=616, 309 males [50.2%] age range 20–71 years) levels in healthy participants. For hs-cTnI, the reported 99th percentile cutoff is 9 pg/mL (10% CV at 3 pg/mL); for hs-cTnT, the 99th percentile cutoff is 14 pg/mL (10% CV at 13 pg/mL). Although cTnI/T and FGF-23 levels were measured from a single serum sample only, recent reports suggest that troponins and FGF-23 do not readily fluctuate in individuals over time.^{26–28}

Cardiac Imaging

All participants underwent two-dimensional transthoracic echocardiograms which were interpreted by a single reviewer at the University of Maryland who was blinded to the participants' clinical data. Left ventricular mass index (LVMI) was calculated with the modified American Society of Echocardiography equation indexed to height^{2.71}. LVH was defined as LVMI > 50 g/m^{2.71} for men and > 47 g/m^{2.71} for women.¹⁰

All participants underwent cardiac computed tomography scans to assess coronary artery calcification (CAC). Examinations were performed on a 64-slice scanner (Sensations 64 [Siemens Medical Solutions, www.medical.siemens.com] at the Massachusetts General Hospital; Brilliance 64 [Philips Healthcare, www.healthcare.philips.com] at the University of Maryland) using standard protocols. A single blinded observer at the University of Maryland quantified calcifications with dedicated scoring software (Brilliance Workspace, Philips Healthcare) using the method of Agatston et al.²⁹ A positive test was defined as CAC $\geq$ 100 Agatston units (U).

Statistical Analyses

Clinical characteristics were assessed with standard descriptive statistics. We defined abnormal cTnI/T concentrations as values $>$ 99th percentile of a healthy population. We used Spearman correlation coefficients to examine the univariate predictors of hs- cTnI/T concentrations. Additionally, we determined the prevalence of LVH among those with FGF-23 levels below the median and both hs-cTnI and hs-cTnT below the 99th percentile of normal versus those with FGF-23 levels above the median and both hs-cTnI and hs-cTnT above the 99th percentile of normal.

Next, we performed multivariable linear regression analyses to investigate the independent association between FGF-23 and hs-cTnI/T. All variables were examined on a continuous scale, and FGF-23, hs-cTnI, hs-cTnT, PTH, and CAC were natural log transformed (Ln) to approximate a normal distribution. Separate regression analyses were performed for hs-cTnI and hs-cTnT as the dependent variables. In all models, we included FGF-23 as the primary predictor and adjusted for age, sex, systolic blood pressure (SBP), diabetes, eGFR, serum phosphate, PTH, and history of CAD. We tested whether eGFR or SBP modified the association between FGF-23 and hs- cTnI/T. We substituted eGFR_{cys} for eGFR calculated by the MDRD Study equation in a sensitivity analysis and examined multivariable models with the inclusion of active vitamin D use as a covariate. Finally, we repeated the main adjusted analyses in the subgroup of participants without a history of self-reported CAD to further investigate the relationship between FGF-23 and cTnI/T independent of known CAD.

In order to determine whether LVMI or CAC, a marker of CAD, mediated the relationship between FGF-23 and hs- cTnI/T, these variables were separately added to the adjusted models expressed as both continuous and categorical variables (presence or absence of LVH and CAC score $<$ or $\geq$ 100 U). Based on our hypothesis that the association of FGF-23 and hs-cTnI/T is mediated by LVH independent of CAD, we expected that the addition of LVMI to the model, but not CAC, would weaken the association between FGF-23 and hs-cTnI/T. Two-sided *P*-values $<$ 0.05 were considered statistically significant. All statistical analyses were performed using JMP Pro 9 statistical software (www.jmp.com).

Results

Patient Characteristics

Mean eGFR in the entire study population was 34 ± 11 mL/min/1.73m², 15% had a known history of prevalent CAD, and 13% were taking active vitamin D. Median hs-cTnI was 6.5 (25th–75th percentile, 3.5–14.5) pg/mL, and median hs-cTnT was 16.8 (25th–75th percentile, 11.1–33.9) pg/mL. Median FGF-23 was 120 (25th–75th percentile, 79–223) RU/mL, which is greater than levels observed in healthy individuals.^{12,30} Table 1 summarizes clinical data for the 153 participants stratified by FGF-23 below and above the median. Those with higher FGF-23 had a significantly lower eGFR, higher hs-cTnI and hs-cTnT, and greater likelihood of active vitamin D use (*P* $<$ 0.05 for all). Concentrations of cTnI and cTnT

were > 99th percentile of a normal population in 42% and 61% of the study population, respectively, and those with higher FGF-23 were more likely to have abnormal hs-cTnI/T levels ($P<0.05$ for both). Differences in cardiac imaging data among subgroups dichotomized by median FGF-23 were not statistically significant.

Univariate and Stratified Analyses

Both hs-cTnI and hs-cTnT were significantly correlated with FGF-23 ($r=0.28$ [$P=0.001$] and $r=0.34$ [$P<0.001$], respectively; Figure 1). With the exception of higher SBP (for hs-cTnI, $r=0.18$, $P=0.03$; for hs-cTnT, $r=0.16$, $P=0.05$), detectable hs-cTnI/T were not consistently associated with most traditional cardiovascular risk factors, including smoking, diabetes, obesity, and cholesterol levels. Both hs-cTnI and hs-cTnT were correlated with eGFR ($r=-0.16$ [$P=0.05$] and $r=-0.32$ [$P<0.001$], respectively), but neither correlated with phosphate, calcium, or PTH.

Median hs-cTnT was significantly greater in those with CAC score ≥ 100 U versus those with scores < 100 (21.7 pg/mL versus 14.6 pg/mL, respectively; $P=0.009$). Median concentrations of both hs-cTnI and hs-cTnT were higher among those with LVH compared to those without (for hs-cTnT, 28.7 pg/mL versus 15.6 pg/mL; for hs-cTnI, 17.9 pg/mL versus 4.9 pg/mL; $P<0.001$ for each). No participants with FGF-23 levels below the median and both hs-cTnI and hs-cTnT below the 99th percentile of normal had LVH. In contrast, among those with FGF-23 levels above the median and both hs-cTnI and hs-cTnT above the 99th percentile of normal, the prevalence of LVH was 35% compared with 21% in the overall study population.

Multivariable Analyses

The significant unadjusted association between FGF-23 and hs-cTnI/T was unchanged with adjustment for demographic characteristics, eGFR and other CKD-specific risk factors (Table 2). In the full models neither PTH nor serum phosphate was associated with either hs-cTnI or hs-cTnT.

Adjusting for eGFR_{cys} in place of eGFR calculated by the MDRD Study equation and adjusting for active vitamin D use yielded consistent results. Although hs-cTnI/T were higher among participants with lower eGFR and higher SBP, neither eGFR nor SBP modified the association between FGF-23 and hs-cTnI/T (P for interaction > 0.05 for each). Additionally, even among individuals with no known history of CAD, FGF-23 was significantly associated with hs-cTnI ($\beta=0.33$, $P=0.003$) and hs-cTnT ($\beta=0.24$, $P<0.001$) in fully adjusted multivariable models.

Effect Mediation

Adjusting for CAC had no significant effect on the association between FGF-23 and both hs-cTnI and hs-cTnT (Table 2). In contrast, the addition of presence of LVH or LVMI, expressed as a continuous variable, to the multivariable model weakened the association between FGF-23 and both hs-cTnI and hs-cTnT.

Discussion

In this cross-sectional study of 153 participants with non-dialysis-dependent CKD without symptomatic cardiovascular disease, higher FGF-23 levels were independently associated with detectable cTnI and cTnT concentrations measured by high-sensitivity assays. The association between FGF-23 and cTnI/T was independent of traditional CAD risk factors and was unchanged after adjusting for CAC, suggesting that the relationship was not mediated by atherosclerosis. In contrast, the strength of association between FGF-23 and

cTnI/T was partially attenuated by adjusting for LVMI and presence of LVH. This suggests that the relationship between FGF-23 and cTnI/T levels may be partially mediated by LVH. Our recent report, in which elevated FGF-23 levels predicted new-onset LVH in a prospective study of non-dialysis-dependent CKD patients and directly induced LVH in animal models,¹³ supports our hypothesis that FGF-23-mediated LVH contributes to the high rates of detectable cTnI/T levels in asymptomatic CKD patients.

Observational studies have consistently reported that increased cTnT predicts cardiovascular disease and mortality in asymptomatic CKD and dialysis-dependent patients.^{31–39} Whether detectable cTnI/T levels in asymptomatic patients with CKD are caused by subclinical coronary ischemia,^{36,40,41} structural and functional LV abnormalities,^{38,42,43} or a combination of both remains unresolved. Myocardial strain caused by LVH may alter cardiac myocyte permeability leading to cTnI/T release, and increased oxygen demand by the hypertrophic LV coupled with diminished coronary reserve may result in subclinical ischemia with or without macrovascular CAD.²² Our finding that traditional atherosclerosis risk factors did not consistently correlate with either hs-cTnI or hs-cTnT suggests that atherosclerosis was not an important determinant of detectable cTnI/T levels in this study.

New data from large observational studies in the general population also indicate that non-atherosclerotic factors may be the primary cause of chronically detectable cTnI/T concentrations.^{18,19} In asymptomatic individuals with and without cardiovascular disease, hs-cTnT was significantly associated with cardiovascular death and heart failure but not with myocardial infarction.¹⁸ While similar outcome studies in CKD are lacking, one recent study found that cTnT was not closely related to CAD, despite a 33% prevalence of CAD in this CKD population.⁴⁴ In our cohort, cTnI/T were elevated above the 99th percentile cut-point even in patients without a history of CAD (58% for cTnT; 35% for cTnI). We acknowledge that ascertainment of CAD by self-report may underestimate true CAD prevalence in our study, and that individuals with undiagnosed CAD could contribute to the high rate of detectable hs-cTnI/T. However, median hs-cTnT was above the 99th percentile cut-point even in those with CAC < 100 U, who were unlikely to have significant asymptomatic CAD, and the highest hs-cTnT and hs-cTnI levels were observed among patients with LVH.

A limitation of our cross-sectional study is that a causal mechanism linking FGF-23, LVH and detectable cTnI/T cannot be inferred. However, our data add to growing evidence that FGF-23 plays a central role in cardiac injury among those with CKD, and are consistent with the results of animal studies of FGF-23 and LVH.¹³ While our data conflict with a study that found neither FGF-23 nor LVMI was associated with cTnT; that study was performed in a hemodialysis population in which cTnT concentrations were not measured by high-sensitivity assays.⁴⁵ In contrast, our results validate two recent studies in which hs-cTnT was independently associated with FGF-23 in an analogous cohort of non-dialysis-dependent patients²¹ and in those undergoing hemodialysis.⁴⁶ The inclusion of cardiac imaging in the present study extends these results by allowing analysis of the relationship between these biomarkers and cardiac morphology. Another limitation is absence of vitamin D levels, since low levels have been associated with elevated cTnT and FGF-23 levels, and deficiency may contribute to LVH and cardiovascular disease.^{47–49} Further studies are needed to determine if routine measurement of hs-cTnI/T and FGF-23 levels may promote early identification of CKD patients at high risk for cardiovascular disease events, and whether interventions that lower FGF-23 levels will also reduce cTnI/T levels in CKD patients.

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Figure 1.

Scatter plots of high sensitivity (A) cardiac troponin I (hs-cTnI) and (B) cardiac troponin T (hs-cTnT) versus fibroblast growth factor 23 (FGF-23) in patients with chronic kidney disease. Red lines indicate best-fit regression lines derived from the least mean square method. The regression equations were $\ln(\text{hs-cTnI}) = 0.45 + 0.32 \cdot \ln(\text{FGF-23})$ and $\ln(\text{hs-cTnT}) = 1.38 + 0.31 \cdot \ln(\text{FGF-23})$, with P values of $P=0.003$ and $P<0.001$, respectively.

Table 1

Demographic and clinical data stratified by median FGF-23

Variable	FGF-23 ≤ 120 RU/mL (n=77)	FGF-23 > 120 RU/mL (n=76)	P
Age, y	63 ± 11	64 ± 12	0.7
Male sex	75	62	0.07
White	64	59	0.6
eGFR, mL/min/1.73m ²	39 ± 10	28 ± 10	<0.001
Blood pressure			
Systolic, mm Hg	132 ± 16	137 ± 24	0.2
Diastolic, mm Hg	75 ± 11	76 ± 12	0.9
Body Mass Index, kg/m ²	30.9 ± 5.7	30.0 ± 7.2	0.4
CAD History	14	16	0.8
Active vitamin D use	6	20	0.01
Traditional atherosclerotic risk factors			
Hypertension	92	93	0.8
Cholesterol, mg/dL	185 ± 46	170 ± 41	0.03
Diabetes mellitus	49	46	0.7
Current tobacco use	9	21	0.04
Laboratory values			
Serum phosphate, mg/dL	3.7 ± 0.7	3.8 ± 0.8	0.8
Serum calcium, mg/dL	9.2 ± 0.6	9.1 ± 0.7	0.5
PTH, pg/mL	67 [47–114]	76 [48–108]	0.4
Cardiac Biomarkers			
hs-cTnI, pg/mL	5.3 [3.3–10.3]	10.4 [3.9–25.4]	0.01
hs-cTnT, pg/mL	14.4 [9.6–24.6]	21.3 [13.6–45.4]	<0.001
Individuals with abnormal cTnI *	30	53	0.007
Individuals with abnormal cTnT *	51	71	0.009
Cardiac Imaging			
CAC Agatston score, U	67 [0–294]	101 [3–323]	0.6
CAC ≥ 100 U	44	51	0.4
LVMI, g/m ^{2.71}	39.8 ± 10.8	41.7 ± 14.1	0.4
LVH **			
Males	17	20	0.8
Females	11	31	0.09
LVEF, %	58 ± 5	58 ± 6	0.5

Note: Values for continuous variables are expressed as mean ± standard deviation or median [25th–75th percentile]; values for categorical variables given as percentage. Conversion factors for units: eGFR in mL/min/1.73m² to mL/s/1.73m², ×0.01667; cholesterol in mg/dL to mmol/L, ×0.02586; phosphate in mg/dL to mmol/L, ×0.3229; calcium in mg/dL to mmol/L, ×0.2495. No conversion necessary for PTH in pg/mL and ng/L.

Abbreviations: FGF-23, fibroblast growth factor 23; eGFR, estimated glomerular filtration rate; CAD, coronary artery disease; PTH, parathyroid hormone; hs-cTnI, high-sensitivity cardiac troponin I; hs-cTnT, high-sensitivity cardiac troponin T; CAC, coronary artery calcification; LVMI, left ventricular mass index; LVH, left ventricular hypertrophy; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index.

* abnormal defined as individuals with hs-cTn values > 99th percentile of a normal population

** positive test defined by LVMI > 50 g/m^{2.71} for males and > 47 g/m^{2.71} for females

Table 2

Unadjusted and adjusted associations of ln(FGF-23) with ln(hs-cTnI/T) concentrations

	Difference in ln(hs-cTnI) per 1-RU/mL increase in ln(FGF-23)		Difference ln(hs-cTnT) per 1-RU/mL increase in ln(FGF-23)	
	β (95%CI)	<i>P</i>	β (95%CI)	<i>P</i>
Unadjusted	0.32 (0.11 – 0.54)	0.003	0.31 (0.16 – 0.46)	<0.001
Model 1 ^a	0.33 (0.11 – 0.54)	0.003	0.24 (0.10 – 0.38)	<0.001
Model 1 + ln(CAC) ^b	0.36 (0.13 – 0.59)	0.002	0.22 (0.08 – 0.35)	0.002
Model 1 + CAC ^c	0.33 (0.11 – 0.54)	0.003	0.24 (0.10 – 0.38)	<0.001
Model 1 + LVMI ^d	0.20 (–0.02 – 0.42)	0.07	0.20 (0.05 – 0.34)	0.008
Model 1 + LVH ^e	0.23 (0.01 – 0.45)	0.04	0.18 (0.04 – 0.32)	0.01

^aModel 1: ln(FGF-23) (in RU/mL) adjusted for age (years), sex, SBP (mmHg), diabetes, eGFR (mL/min/1.73m²), serum phosphate (mg/dL), ln(PTH) (in pg/mL), and history of CAD.

^bAddition of ln(CAC) (in U) to Model 1.

^cAddition of CAC to Model 1; positive test defined by CAC ≥ 100 U.

^dAddition of LVMI (g/m^{2.71}) to Model 1.

^eAddition of LVH to Model 1; positive test defined by LVMI > 50 g/m^{2.71} for males and > 47 g/m^{2.71} for females.

Note: hs-cTnI/T concentrations measured in pg/mL. β is the regression coefficient (amount of change in the response variable for each unit-change in the explanatory variable).

Abbreviations: hs-cTnI, high-sensitivity cardiac troponin I; hs-cTnT, high-sensitivity cardiac troponin T; FGF-23, fibroblast growth factor 23; CAC, coronary artery calcification; LVMI, left ventricular mass index; LVH, left ventricular hypertrophy; SBP, systolic blood pressure; eGFR, estimated glomerular filtration rate; PTH, parathyroid hormone; CAD, coronary artery disease; CI, confidence interval.