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Serum phosphorus is related to left ventricular remodeling independent of renal function in hospitalized patients with chronic kidney disease☆,☆☆

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ABSTRACT

Background: Increasing evidence indicated that phosphorus emerged as an important cardiovascular risk factor in patients with chronic kidney disease (CKD). The fact that serum phosphorus was closely linked to vascular and valvar calcification may account for one important reason. However, left ventricular remodeling may also serve as another potential mechanism of the cardiac toxicity of phosphorus. In the present study, we evaluated the association of serum phosphorus with left ventricular remodeling.
Methods: We investigated consecutive hospitalized patients with pre-dialysis CKD, who did not have symptomatic heart failure or take any phosphorus binder or calcitriol medications. Transthoracic echocardiography was applied to assess their left ventricular remodeling indices, both structural and functional.
Results: The 296 study subjects (mean age 56.4 years) included 169 (57.1%) men, 203 (68.6%) hypertensive patients. In addition to gender, systolic blood pressure, and estimated glomerular filtration rate, serum phosphorus was an independent determinant of left ventricular mass index (LVMI, $P = 0.001$). Similarly, serum phosphorus was also a determinant of left ventricular end diastolic dimension ($P = 0.0003$), but not of relative wall thickness. In multivariate logistic analyses, serum phosphorus was significantly and independently associated with the prevalence of left ventricular hypertrophy (LVH, odds ratio [OR] 2.38 for each 1 mmol/L increase, 95% CI 1.20–4.75, $P = 0.01$). Moreover, the association was only confirmatory in eccentric LVH (OR 3.01, 95% CI 1.43–6.32, $P = 0.003$) but not in concentric LVH (1.38, 95% CI, 0.54–3.49, $P = 0.50$).
Conclusion: Serum phosphorus was significantly and independently associated with LVMI and the prevalence of eccentric LVH in hospitalized patients with CKD.

1. Introduction

It is well established that chronic kidney disease (CKD) carries a high public health burden and cardiovascular diseases (CVD) are the leading causes of death in CKD [1,2]. Indeed, mildly to moderately impaired renal function can convey a high risk of CVD [3]. Even CKD patients are more likely to die of CVD before they reach end stage renal disease [3]. Cardiac structural and functional changes are the most prevalent cardiovascular risks in CKD, accounting for a large number of cardiovascular mortality [4,5]. Cardiac structural and functional changes start in the early stages of CKD and this association strengthens in patients with deteriorated renal function approaching or on dialysis [6,7]. These cardiac changes observed in CKD patients are attributed to not only conventional risk factors but also CKD-related risk factors such as uremic toxins, anemia, mineral metabolism disorders and so on [8].

Recently, serum phosphorus emerged as an important cardiovascular risk factor. Increased serum phosphorus, which is prevalent in CKD patients due to impaired phosphorus excretion, was associated with adverse cardiovascular outcomes in both maintenance hemodialysis [9] and earlier stages of CKD patients [10]. Even serum phosphorus in normal range has been linked with cardiovascular events in coronary disease [11], type 2 diabetes [12], or the incidence of CVD in the community [13,14]. However, the underlying mechanism between phosphorus and CVD has not yet been clarified.

Left ventricular remodeling may be the structural basis of heart failure, arrhythmias and sudden cardiac death, which are the most

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common causes of cardiac death [15]. Although blood pressure still plays a major role in the process inducing left ventricular remodeling in CKD, some other CKD-related factors may also be actively involved in the process. The fact that serum phosphorus is closely linked to vascular and valvar calcification may account for one important reason [16]. However, left ventricular remodeling may also serve as another potential mechanism of the cardiac toxicity of phosphorus. Some studies indicated the significant association between serum phosphorus and left ventricular mass in community-based population [17,18], male stable CVD outpatients [19], and CKD outpatients [20]. However, few studies have characterized the association of serum phosphorus with left ventricular geometry remodeling.

In the present study, we conducted a cross-sectional analysis between serum phosphorus and left ventricular remodeling among hospitalized patients with pre-dialysis CKD, who did not have symptomatic heart failure or take phosphorus binders or calcitriol medications. We characterized the associations of serum phosphorus with left ventricular mass and morphology. Since CKD is closely associated with hypertension and left ventricular remodeling is a well recognized consequence of hypertension, we explored blood pressure and renal function in relation to left ventricular remodeling as compared to serum phosphorus.

2. Method

2.1. Study Population

From January to December 2014, we studied 405 consecutive patients with chronic kidney disease, who were hospitalized in the Department of Nephrology, Xin Hua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine in Shanghai, China. We excluded 109 subjects from the present analysis, because of severe systolic dysfunction with left ventricular ejection fraction less than 50% (n = 19), moderate to severe cardiac valve diseases (n = 17), or taking phosphate binders or calcitriol medication in 2 weeks (n = 42). We also excluded those patients whose data were not complete (n = 19) or whose echocardiographic images were unsatisfied (n = 12). Thus, the total number of patients in the present analysis was 296. They were never treated (n = 257) or did not take any phosphate binders or calcitriol medications for more than 2 weeks (n = 39). The Ethics Committee of Xin Hua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine approved the study protocol.

2.2. Anthropometry, Blood Pressure and Blood Sampling

Body mass index was weight in kilograms divided by the height in meters squared. Body surface area was calculated according to the Stevenson's formula in Chinese [21]. Estimated glomerular filtration rate (eGFR) was calculated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) [22], and was staged using K/DOQI classification [23]. Clinic blood pressure was measured by a mercury sphygmomanometer after at least 5 min supine rest and averaged from three readings. Diabetes mellitus was defined as a fasting plasma glucose of at least 7.0 mmol/L or as the use of antidiabetic treatment.

Venous blood sample was obtained in study subjects after an overnight fast. Whole blood hemoglobin and serum creatinine, albumin, glucose, cholesterol, triglyceride, calcium, phosphorus and intact parathyroid hormone (iPTH) were assayed by standard methods at the local laboratories. The serum calcium value was corrected for albumin levels with the use of the following formula: corrected calcium (mg/dl) = serum calcium (mg/dl) + [0.8 × 4.0 − serum albumin (g/dl)].

2.3. Echocardiography

M-mode and 2-dimensional transthoracic echocardiography were performed with the same device using a 2.5-MHz transducer, as recommended by the American Society of Echocardiography (ASE) [24]. Images were taken from the parasternal view in patients lying in the left decubitus position. Left ventricular end diastolic dimension (LVEDd) and posterior wall thickness (PWT) were evaluated by M-mode echocardiography and used to calculate left ventricular mass with Devereux formula [25], which was further divided by body surface area as left ventricular mass index (LVMI) [24]. Left ventricular hypertrophy (LVH) was defined as suggested by the 2007 ESH/ESC guidelines [26], with LVMI greater than 125 g/m^2 in men and 110 g/m^2 in women. Relative wall thickness (RWT) was calculated as the ratio of 2 × PWT/LVEDd. Concentric LVH was defined as RWT greater than 0.45, and eccentric LVH was defined as RWT less than 0.45 in above defined LVH subjects.

Left ventricular ejection fraction (EF), assessed by two-dimensional echocardiography using the modified Simpson's method [24], was used as an index of left ventricular systolic function. Left atrial volume, a reliable index of diastolic function, was assessed by the single-plane modified Simpson's rule in the apical four-chamber view in the frame immediately preceding mitral valve opening. Left atrial volume index (LAVI) was calculated as the left atrial volume divided by body surface area. The peak velocity of early diastolic wave (E') was measured by pulsed-wave tissue Doppler with the sample volume close to the mitral valve annulus in the apical four-chamber view in the lateral wall. Left ventricular diastolic dysfunction (LVDD) was defined as LAVI greater than or equal to 34 ml/m^2 and E' less than 10 cm/s according to the recommendation of ASE [27]. All the echocardiographic measurements were performed by two experienced sonographers who were blinded to clinical details.

2.4. Statistical Methods

We used SAS version 9.13 (SAS institute, Cary, NC) for database management and statistical analyses. Continuous measurements with a skewed distribution were normalized by logarithmic transformation and represented by median and interquartile range. Comparisons of means and proportions relied on the Student t-test and Fisher's exact test, respectively. We first performed stepwise linear regression analyses to identify correlates of left ventricular structural and functional indices (LVMI, LVEDd, RWT, EF, E' and LAVI) with *P*-value set at 0.10 for variables to enter and stay in the model. Then we performed multiple linear and logistic regression analyses to study the association of serum phosphorus with left ventricular structural and functional indices, and with the prevalence of left ventricular hypertrophy and geometry remodeling, before and after subdivision of the study subjects according to serum phosphorus tertile distribution.

3. Results

3.1. Characteristics of the Study Subjects

The 296 study subjects (mean age 56.4 years) included 169 (57.1%) men, 203 (68.6%) hypertensive patients, of whom 171 (58%) took antihypertensive drugs, and 64 (21.6%) diabetic patients. Table 1 shows the characteristics of the study subjects categoried by serum phosphorus in tertiles. Blood pressure and iPTH significantly increased, while serum corrected calcium, hemoglobin, and renal function decreased across increasing tertiles of serum phosphorus ($P \le 0.002$). Among echocardiographic indices, LVMI, LVEDd, RWT and LAVI, and the prevalences of LVH and LVDD significantly increased, while EF decreased across increasing tertiles of serum phosphorus ($P \le 0.004$). The characteristics of the study subjects by CKD stages were shown in Supplemental Table 1.

3.2. Correlates of Left Ventricular Structural and Functional Indices

In a multiple stepwise regression model, age, gender, body mass index, serum corrected calcium, phosphorus, iPTH, triglyceride, cholesterol, albumin and fasting glucose, blood hemoglobin, eGFR, systolic and diastolic blood pressure, and taking antihypertension drugs were considered as potential correlates of left ventricular structural and functional variables, including LVMI, LVEDd, RWT, EF, E' and LAVI. LVMI was statistically ($P \le 0.01$) and independently associated with both conventional variables as gender (+9.21 g/m^2 higher in men vs. women) and SBP (+3.61 g/m^2 for each 10 mmHg increase), and CKD related factors as eGFR (+2.74 g/m^2 for each 10 ml/min/1.73 m^2 decrease) and serum phosphorus (+12.25 g/m^2 for each 1 mmol/L increase, Table 2). Similarly, LVEDd was also associated (+1.85 mm for each 1 mmol/L increase, $P = 0.0003$), while EF was negatively associated (−1.68%, $P = 0.004$) with serum phosphorus. E' and LAVI might be also associated with serum phosphorus although with less statistical significance ($P = 0.054$ and 0.06, respectively), while RWT had no association with serum phosphorus (Table 2).

In further categorical analysis adjusted for age, gender, BMI, SBP, eGFR and serum triglyceride, LVMI significantly ($P = 0.006$ for trend) increased with 102.4 (95% confidence interval [CI], 96.1–108.6) g/m^2, 107.2 (101.2–113.2) g/m^2 and 115.7 (109.1–122.3) g/m^2 in tertile 1, 2 and 3 of serum phosphorus (Fig. 1A). After similar adjustment but without serum triglyceride, LVEDd also increased ($P = 0.04$ for trend) with 49.2 (95% CI, 48.4–50.0) mm, 49.7 (48.9–50.5) mm and 50.5 (49.6–51.4) mm in tertile 1, 2 and 3 of serum phosphorus (Fig. 1B), while RWT and EF only showed increased or decreased trend but did not reach significance ($P = 0.16$ and 0.13, Fig. 1C and D).

Table 1
Characteristics of the Study Subjects by Tertile Distribution of Serum Phosphorus.

Characteristic	Tertile 1 (n = 98)	Tertile 2 (n = 100)	Tertile 3 (n = 98)	*P*
Phosphorus, mmol/L	1.04 (0.12)	1.35 (0.09)	2.02 (0.56)	<0.0001
Age, years	57.0 (15.1)	56.5 (16.1)	55.6 (15.9)	0.82
Gender, men (%)	59 (60.2%)	50 (50.0%)	60 (61.2%)	0.21
Body mass index, kg/m^2	24.7 (3.8)	25.0 (3.7)	24.2 (4.2)	0.36
Blood pressure, mm Hg				
Systolic	142.2 (22.7)	149.9 (22.4)	161.4 (28.5)	<0.0001
Diastolic	82.8 (11.4)	87.1 (14.2)	89.3 (16.0)	0.005
Serum biochemistry				
Creatinine, μmol/L	99.2 (68.0–164.0)	112.5 (72.0–259.5)	548.3 (179.0–771.0)	<0.0001
Albumin, g/L	33.4 (7.4)	33.2 (6.9)	33.5 (5.8)	0.94
Triglyceride, mmol/L	2.24 (1.56)	2.43 (2.01)	1.85 (2.04)	0.09
Cholesterol, mmol/L	5.71 (2.43)	5.59 (2.70)	4.83 (1.85)	0.02
Fasting glucose, mmol/L	5.60 (1.97)	5.43 (1.30)	5.19 (1.10)	0.17
Corrected calcium, mmol/L	2.28 (0.18)	2.27 (0.11)	2.19 (0.27)	0.002
iPTH, pg/ml	41.7 (27.4–69.1)	45.2 (28.6–82.5)	199.6 (62.0–337.6)	<0.0001
Hemoglobin, g/L	120.1 (23.2)	116.9 (26.2)	91.4 (22.9)	<0.0001
eGFR, ml/min/1.73m^2	66.9 (37.4)	60.6 (39.9)	24.5 (31.2)	<0.0001
DM, n (%)	14 (14.3%)	24 (24.0%)	26 (26.5%)	0.09
Taking antihypertension drugs, n (%)	39 (39.8%)	61 (61.0%)	71 (72.4%)	<0.0001
Echocardiographic indices				
LVMI, g/m^2	94.8 (24.8)	103.7 (33.2)	126.9 (40.6)	<0.0001
LVMI, g/m$^{2.7}$	41.8 (11.3)	46.0 (15.0)	55.1 (17.9)	<0.0001
LVEDd, mm	48.5 (3.6)	49.2 (4.9)	51.7 (5.1)	<0.0001
RWT	0.38 (0.04)	0.40 (0.06)	0.41 (0.06)	0.003
LVH, n (%)	12 (12.2%)	23 (23.0%)	48 (50.0%)	<0.0001
EF, %	67.8 (3.9)	66.6 (4.0)	65.8 (4.8)	0.004
E', cm/s	9.59 (2.82)	9.58 (2.84)	8.85 (2.47)	0.10
LAVI, ml/m^2	24.6 (5.2)	27.1 (7.5)	29.4 (7.9)	<0.0001
LVDD, n (%)	3 (3.1%)	8 (8.7%)	19 (20.2%)	0.0005

Values were presented as mean (standard deviation), median (interquartile range) or number of subjects (%). For definitions of DM, LVH and LVDD, see Methods.
CKD = chronic kidney disease; iPTH = intact parathyroid hormone; eGFR = estimated glomerular filtration rate; LVEDd = left ventricular end diastolic dimension; LVMI = left ventricular mass index; RWT = relative wall thickness; LVH = left ventricular hypertrophy; EF = ejection fraction; E' = The peak velocity of early diastolic wave in tissue Doppler; LAVI = left atrial volume index; LVDD = left ventricular diastolic dysfunction.

3.3. Association between Serum Phosphorus and LVH and LVDD

After adjustment for age, gender, BMI, logistic regression analyses demonstrated that serum phosphorus as a continuous variable was significantly associated with the prevalence of LVH (odds ratio [OR] 6.09 for each 1 mmol/L increase, 95% CI 3.28–11.32, $P < 0.0001$) and LVDD (4.29, 95% CI 2.00–9.18, $P = 0.0002$; Table 3). With further adjustment for SBP, the associations remained statistically significant (OR 3.94 and 3.10, 95% CI 2.06–7.52 and 1.39–6.94, $P < 0.0001$ and $P = 0.005$; Table 3). However, with additional adjustment for eGFR, and additional adjustment for triglyceride for LVH, the association with LVH still existed (OR 2.38, 95% CI 1.20–4.75, $P = 0.01$), whereas the association with LVDD did not reach significance (1.97, 95% CI 0.85–4.57, $P = 0.11$, Table 3). With further adjustment for serum corrected calcium and iPTH, the association of serum phosphorus with LVH still remained unaltered (OR 2.57, 95% CI 1.14–5.80, $P = 0.02$). In categorical analysis, the association of serum phosphorus and LVH was confirmatory mainly in tertile 3 vs. 1 of serum phosphorus (OR 2.52, 95% CI 1.17–5.98, $P = 0.02$; Table 3).

As compared with serum phosphorus, SBP was significantly associated with the prevalence of both LVH (OR 1.46 for each 10 mmHg increase, 95% CI 1.25–1.70, $P < 0.0001$) and LVDD (1.24, 95% CI

Table 2
Determinants of left ventricular structure and function.

	LVMI (g/m^2)		LVEDd (mm)		RWT		EF (%)		E' (cm/s)		LAVI (ml/m^2)	
Variables	β (SE)	*P*	β (SE)	*P*	β (SE)	*P*	β (SE)	*P*	β (SE)	*P*	β (SE)	*P*
Age (+10 years)	--	--	--	--	--	--	--	--	−0.57 (0.11)	<0.0001	1.04 (0.30)	0.0006
Men (vs. women)	9.21 (3.61)	0.01	−2.93 (0.46)	<0.0001	--	--	--	--	--	--	−3.30 (0.85)	0.0001
Body mass index (+1 kg/m^2)	--	--	0.23 (0.06)	0.0002	0.002 (0.001)	0.052	−0.15 (0.07)	0.03	−0.14 (0.04)	0.0007	−0.21 (0.11)	0.046
SBP (+10 mmHg)	3.61 (0.73)	<0.0001	0.20 (0.10)	0.04	0.005 (0.001)	0.0003	--	--	--	--	0.36 (0.18)	0.04
eGFR (−10 ml/min/1.73 m^2)	2.74 (0.53)	<0.0001	0.28 (0.06)	<0.0001	0.002 (0.001)	0.04	−0.15 (0.08)	0.06	--	--	0.45 (0.13)	0.0007
Serum Phosphorus (+1 mmol/L)	12.25 (3.83)	0.001	1.85 (0.50)	0.0003	--	--	−1.68 (0.58)	0.004	−0.61 (0.31)	0.054	1.79 (0.95)	0.06
Serum Triglyceride (+1 mmol/L)	1.88 (1.13)	0.096	--	--	--	--	--	--	--	--	--	--

In these stepwise multiple linear regressions, age, gender, body mass index, serum corrected calcium, phosphorus, intact PTH, triglyceride, cholesterol and albumin, fasting blood glucose, hemoglobin, estimated glomerular filtration rate from the CKD-EPI formula, systolic and diastolic blood pressure, and taking antihypertension drugs were considered as potential determinants, with *P* value set at 0.10 to enter and stay in the models. Only significant determinants were presented.
β = estimated parameter; SE = standard error; LVMI = left ventricular mass index; LVEDd = left ventricular end diastolic dimension; EF = ejection function; E' = The peak velocity of early diastolic wave in tissue Doppler; LAVI = left atrial volume index, SBP = systolic blood pressure; eGFR = estimated glomerular filtration rate from the CKD-EPI formula.

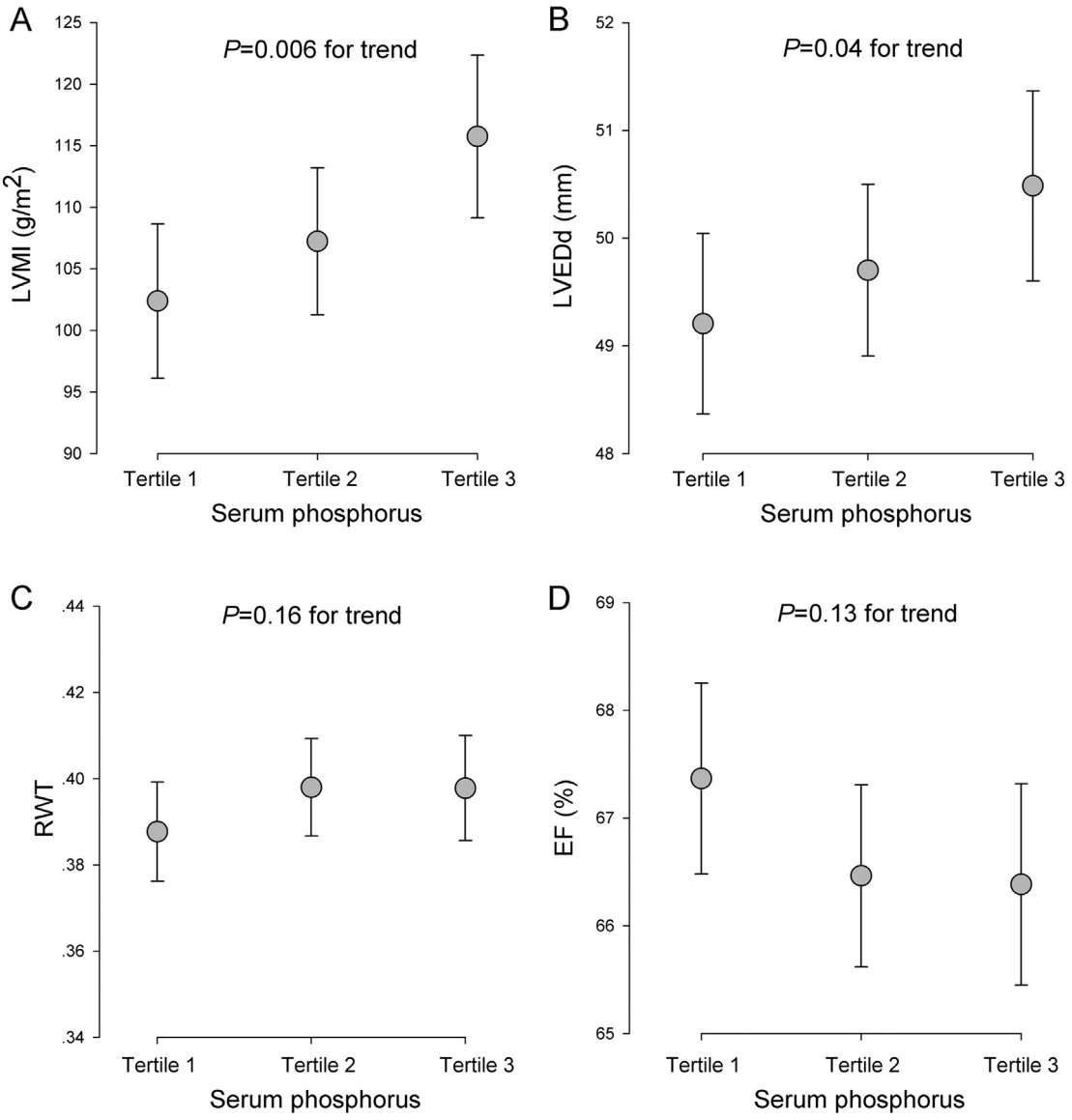

Fig. 1. Left ventricular structural and functional indices according to the tertile distribution of serum phosphorus. Symbols represent mean, adjusted for age, gender, body mass index, SBP, and eGFR, and with additionally adjusted for serum triglyceride for LVMI. Vertical lines denote 95% confidential interval. Serum phosphorus tertile 1, 2, and 3 were 0.55–1.19, 1.20–1.50 and 1.51–4.05 mmol/L, respectively. *P* values for trend were given. SBP = systolic blood pressure; eGFR = estimated glomerular filtration rate from the CKD-EPI formula; LVMI = left ventricular mass index; LVEDd = left ventricular end diastolic dimension; RWT = relative wall thickness; EF = ejection fraction;

1.03–1.49, $P = 0.02$) with similar full adjustment, and eGFR was significantly associated with the prevalence of both LVH (1.18 for each 10 ml/min/1.73 m^2 decrease, 95% CI 1.01–1.38, $P = 0.04$) and LVDD (1.27, 95% CI 1.03–1.58, $P = 0.02$; Table 3).

3.4. Association between Serum Phosphorus and Left Ventricular Geometry Remodeling

The association of serum phosphorus with left ventricular geometry remodeling was also investigated. The prevalence of concentric and eccentric LVH was 6.1%, 5.0%, 19.4% and 6.1%, 18.0%, 29.6% in tertile 1, 2, 3 of serum phosphorus, respectively, which suggested that eccentric LVH was more prevalent across increasing tertiles of serum phosphorus (Fig. 2). Indeed, serum phosphorus was significantly associated with the prevalence of only eccentric LVH (OR 3.01 for each 1 mmol/L increase, 95% CI 1.43–6.32, $P = 0.003$) but not with concentric LVH (1.38, 95% CI, 0.54–3.49, $P = 0.50$; Fig. 3) with adjustment for age, gender, BMI, SBP, eGFR and serum triglyceride. With further adjustment for serum corrected calcium and iPTH, the association with eccentric LVH remained unaltered (OR 2.97, 95% CI, 1.25–7.05, $P = 0.01$). The categorical analysis was also confirmatory mainly in tertile 3 vs. 1 of serum phosphorus.

As compared with serum phosphorus, SBP was significantly associated with the prevalence of both concentric (OR 1.59 for each 10 mmHg increase, 95% CI 1.31–1.93, $P < 0.0001$) and eccentric LVH (1.28, 95% CI 1.10–1.48, $P = 0.001$) with similar adjustment, whereas eGFR was significantly associated with the prevalence of concentric (1.38 for each 10 ml/min/1.73 m^2 decrease, 95% CI 1.10–1.74, $P = 0.005$) but not with eccentric LVH (1.11, 95% CI 0.99–1.25, $P = 0.09$; Fig. 3).

Sensitivity analysis showed that the associations of serum phosphorus with LVH and eccentric LVH remained unaltered in hypertensive chronic kidney disease patients (data not shown). LVMI was calculated by dividing left ventricular mass by height in meters to the power of 2.7

Table 3
Association of LVH and LVDD with serum phosphorus, SBP and eGFR.

	LVH*		LVH†		LVH‡	
	OR (95% CI)	*P value*	OR (95% CI)	*P*	OR (95% CI)	*P*
Serum Phosphorus						
Phosphorus (+1 mmol/L)	6.09 (3.28–11.32)	<0.0001	3.94 (2.06–7.52)	<0.0001	2.38 (1.20–4.75)	0.01
Tertile 2 vs. 1	2.17 (1.01–4.68)	0.047	1.85 (0.82–4.17)	0.14	2.11 (0.82–5.41)	0.12
Tertile 3 vs. 1	7.00 (3.39–14.45)	<0.0001	4.52 (2.06–9.93)	0.0002	2.52 (1.17–5.98)	0.02
SBP (+10 mmHg)	1.53 (1.35–1.73)	<0.0001	1.41 (1.23–1.60)§	<0.0001	1.46 (1.25–1.70)	<0.0001
eGFR (−10 ml/min/1.73 m^2)	1.33 (1.21–1.46)	<0.0001	1.24 (1.13–1.37)	<0.0001	1.18 (1.01–1.38)	0.04
	LVDD*		LVDD†		LVDD‡	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Serum Phosphorus						
Phosphorus (+1 mmol/L)	4.29 (2.00–9.18)	0.0002	3.10 (1.39–6.94)	0.005	1.97 (0.85–4.57)	0.11
Tertile 2 vs. 1	2.58 (0.62–10.68)	0.19	2.21 (0.51–9.51)	0.28	1.86 (0.42–8.37)	0.41
Tertile 3 vs. 1	9.65 (2.57–36.18)	0.0008	6.25 (1.57–24.93)	0.009	3.28 (0.74–14.47)	0.11
SBP (+10 mmHg)	1.42 (1.20–1.64)	<0.0001	1.26 (1.06–1.51)§	0.01	1.24 (1.03–1.49)	0.02
eGFR (−10 ml/min/1.73 m^2)	1.46 (1.19–1.79)	0.0002	1.36 (1.11–1.66)	0.01	1.27 (1.03–1.58)	0.02

LVH = left ventricular hypertrophy; LVDD = left ventricular diastolic dysfunction; SBP = systolic blood pressure; eGFR = estimated glomerular filtration rate from the CKD-EPI formula; OR = odds ratio; CI = confidential interval.
* indicates model 1 adjusted for demographic variables including age, gender and body mass index.
† indicates model 2 further adjusted for SBP.
‡ indicates model 3 fully adjusted for demographic variables, SBP, eGFR, serum phosphorus, and for LVH with additionally adjusted for serum triglyceride.
§ further adjusted for eGFR in model 2. For definitions of LVH and LVDD, see Methods.

with 52 g/$m^{2.7}$ in men or 47 g/$m^{2.7}$ in women as a cutoff point for LVH definition also followed a similar pattern (data not shown).

4. Discussion

In this study, we found that serum phosphorus was significantly and independently associated with LVMI and the prevalence of LVH in hospitalized patients with CKD. To the best of our knowledge, our study was the first to demonstrate this association mainly due to the eccentric left ventricular remodeling. As compared, both SBP and eGFR were associated with LVMI and the prevalence of LVH, with SBP associated with both concentric and eccentric LVH, whereas eGFR, excluded the effect of serum phosphorus, associated with only concentric LVH.

We confirmed some previous studies which explored the association between serum phosphorus and left ventricular mass in community population [17,18], male stable CVD patients [19] and CKD patients [20]. In a community-based study, serum phosphorus within a normal range was positively associated with greater left ventricular mass independent of hypertension, although the magnitude of the association was modest (10.2 g in men and 7.1 g in women increases without body surface area correction for each 1 mmol/L increment in serum phosphorus [1 mmol/L = 3.1 mg/dl]) [17]. In another community-dwelling study with young adults (mean age 25 years), serum phosphorus 5 years earlier was also associated with LVMI (7.1 g/m^2 for each 1 mmol/L increment in serum phosphorus) and the prevalence of LVH, with the significance mainly presented in the fifth quintile phosphorus levels (>4.0 mg/dl) [18]. In a study with stable CVD outpatients, higher serum phosphorus was associated with greater LVMI in men (4.5 g/m^2 increase for each 1 mmol/L increment in serum phosphorus), but not in women [19]. The association between serum phosphorus and left ventricular mass was greatly strengthened in CKD outpatients with

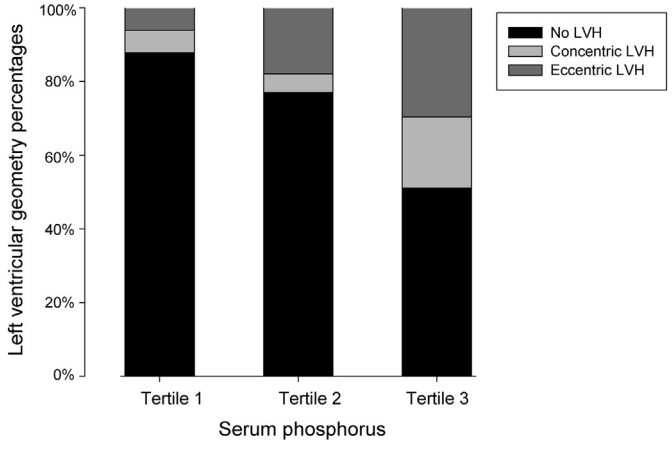

Fig. 2. Association of left ventricular geometry percentage with tertile distribution of serum phosphorus. For definitions of concentric and eccentric LVH, see Methods. LVH = left ventricular hypertrophy.

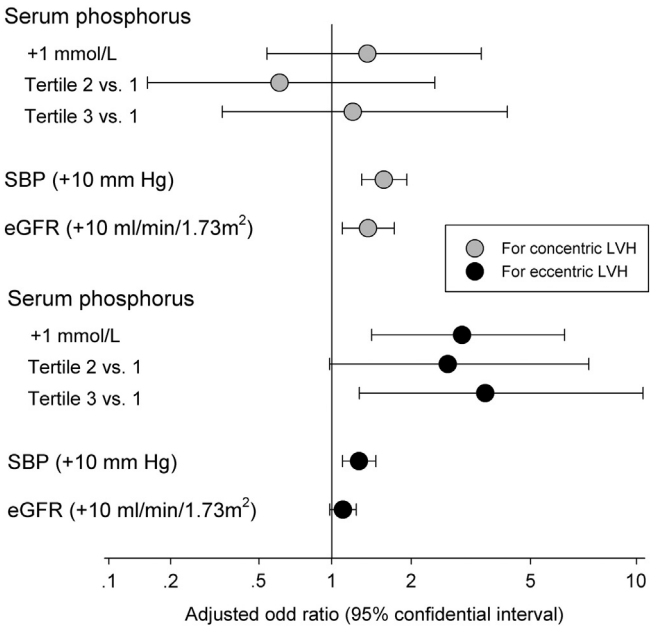

Fig. 3. Association of left ventricular geometry remodeling with serum phosphorus analyzed by multivariate logistic regression. Symbols represent odds ratio adjusted for age, gender, body mass index, SBP, and eGFR, and with additionally adjusted for serum triglyceride for LVMI. Horizontal lines denote 95% confidential interval. For definitions of concentric and eccentric LVH, see Methods. SBP = systolic blood pressure; LVH = left ventricular hypertrophy; eGFR = estimated glomerular filtration rate from the CKD-EPI formula.

stage 2 to stage 4 using cardiac magnetic resonance (16.7 g/m^2 increase for each 1 mmol/L increment in serum phosphorus) [20]. Our data (12.3 g/m^2 for each 1 mmol/L increment in serum phosphorus) also suggested a more close association of serum phosphorus with left ventricular mass in CKD. However, these abovementioned studies did not further explore serum phosphorus in relation to the left ventricular geometry remodeling, although one study referred to this possibility of serum phosphorus in relation to eccentric remodeling in the discussion [17].

Our study was cross-sectional, and hence could not draw any causal conclusion on the relationship between serum phosphorus and left ventricular mass in CKD patients. However, some lines of evidence might suggest for a possible causal link. First, it is widely accepted that serum phosphorus is associated with a higher risk of cardiac death [9,10,28]. In view that increased left ventricular mass is the structural basis of heart failure, arrhythmias and many other serious cardiac diseases, we might carefully speculate that higher serum phosphorus resulting in increased left ventricular mass may be one of the mechanisms that contribute to the independent prediction of serum phosphorus for adverse cardiac outcomes.

Second, it is well known that serum phosphorus is closely linked to vascular calcification [16] and arterial stiffness [29]. Due to decreased vascular compliance, serum phosphorus may indirectly increase left ventricular workload, which in turn may increase left ventricular mass. In our study, we did not assess the measurements of arterial stiffness such as pulse wave velocity. However, using an easily practical measurement pulse pressure, we still can see the increased pulse pressure with the increasing serum phosphorus (59.4, 62.8, 72.1 mmHg in tertile 1, 2, and 3, $P = 0.0001$), which may suggest decreased vascular compliance, especially in the part of aorta.

Third, data from experimental uremia also suggested a causal role of phosphorus [30–32]. High dietary phosphorus and resultant higher serum phosphorus promoted left ventricular mass increase and cardiac fibrosis in two strains of subtotally nephrectomized rat model [30,31]. In another mice model with chronic renal failure, multiple regression analysis suggested that serum phosphorus, but not fibroblast growth factor-23 (FGF23), was independently correlated with left ventricular mass [32]. Furthermore, the phosphorus binder sevelamer treatment improved aortic stiffness and diastolic dysfunction and secondarily prevented LVH [32].

Nonetheless, whether serum phosphorus directly or indirectly influences left ventricular geometry remodeling needs further investigation. Generally, concentric LVH is considered as long-term increased afterload such as hypertension, whereas eccentric LVH may result from increased preload such as volume overload [33]. However, we did not assess the fluid balance, such as measurement of inferior vena cava collapse with 2-dimentional echocardiography. Since left ventricular eccentric remodeling may predict a worse cardiovascular prognosis [34,35], and serum phosphorus levels may be modifiable, the causality of this association needs to be explored in both mechanistic studies and randomized controlled trials.

Despite a clear association between serum phosphorus and left ventricular mass being observed, it is noteworthy that blood pressure and renal function are still undoubtedly two major determinants for left ventricular mass in CKD. In abovementioned CKD outpatients using cardiac magnetic resonance study, serum phosphorus only accounted for 5% of the variance of left ventricular mass in a multi-variable regression model which explained 30% of the variation in LVMI [20]. In our study, the number for serum phosphorus was 4% in a multi-variable regression model which explained 34% of the variation in LVMI ($P < 0.0001$). However, SBP and eGFR accounted for major variances in this model (17% and 11%, respectively).

In our study that precluded the subjects whose EF were less than 50%, we did not detect solid associations between serum phosphorus and left ventricular systolic and diastolic function. One of the reasons is that due to resting echocardiography we only employed rather than combining with stress echocardiography, which uses exercise or pharmacological challenge to assess cardiac functional reserve. It is well established that only assessing the resting cardiac function may miss some important messages about real cardiac function. When a heart begins to fail, compensatory mechanisms are activated that maintain the resting cardiac performance within as normal a range as possible. The case is similar to the association between renal dysfunction and cardiac structural and function change, in which despite a clear association between renal dysfunction and LVH, no association between renal function and cardiac systolic or diastolic function was demonstrated [6].

Our study should be interpreted within the context of its strengths and limitations. First, our study was performed in CKD who did not take any phosphorus binders or calcitriol medications, and were accounted for other components of mineral metabolism (serum calcium and iPTH). In addition, we simultaneously compared serum phosphorus with blood pressure and renal function in relation to left ventricular remodeling in hospitalized patients with CKD. Finally, one study regarding the effect of phosphate binder treatment on left ventricular mass in CKD patients did not reach the expected results [36]. The only association of serum phosphorus with eccentric LVH found in our study may have some suggestions to future randomized controlled trials about phosphorus binders improving left ventricular mass. However, in addition to the cross-sectional design, several other limitations are noteworthy. First, our study subjects were consecutive hospitalized patients instead of randomly selected CKD population, which made it careful to extend our conclusions to all CKD population. In addition, we utilized echocardiography rather than cardiac magnetic resonance for assessment of cardiac structure and function. Although the former is a readily available technique, the latter may be a more accurate and reproducible measurement. Finally, some studies demonstrated that the phosphaturic hormone FGF-23 was associated with LVH in CKD [37,38] and even demonstrated a causal role in rodents model [38], but failed to be replicated by other studies [32,39,40]. Since FGF-23 was not measured in our study, and hence does not allow addressing the relative contributions of phosphorus and FGF-23 or the interaction of serum phosphorus with FGF-23.

In conclusion, serum phosphorus was significantly and independently associated with LVMI and the prevalence of eccentric LVH in hospitalized patients with CKD. These results suggest that serum phosphorus might be a mediator for left ventricular eccentric remodeling in CKD. Our finding should be replicated in other clinical and epidemiological studies. More importantly, further experimental investigation should be performed to delineate whether changes in serum phosphorus by diet control or phosphorus combiners would cause relevant changes in left ventricular geometry remodeling, and further convey benefits for cardiac morbidity and mortality in CKD.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2016.06.181.

Conflicts of interest

The authors report no relationships that could be construed as a conflict of interest.

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