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The relation of calcium-phosphorus metabolism-related indexes with cardiac damages

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Abstract. – OBJECTIVE: To observe and analyze the relation of calcium–phosphorus metabolism-related indexes with cardiac damage-related indexes in patients with chronic kidney disease (CKD) and to explore the roles of calcic and phosphor metabolization in cardiac damage and provide references for prevention of cardiovascular events in CKD patients.

PATIENTS AND METHODS: A total of 98 inpatients, from Urology Department, who were not undergoing dialysis treatment and diagnosed with stages 3, 4, and 5 CKD according to K/DOQI guide were recruited. We measured the calcium-phosphorus metabolism-related indexes (including serum calcium (Ca), the serum phosphate (Pi), the intact parathyroid hormone (iPTH), the -collagen-specific sequences (β-CTX), the total N-terminal propeptide of type I procollagen (TPINP), the N-terminal-mid fragment of osteocalcin (N-MID), the cardiac damage-related indexes (including left ventricular end diastolic diameter (LVEDD), the interventricular septal thickness (IVST), the left ventricular posterior wall thickness (LVPWT), the ejection fraction (EF), the blood flow velocity at mitral diastolic late phase (A) and mitral diastolic early phase (E) via echocardiography. Then, we conducted a correlation analysis employing these two types of indexes.

RESULTS: We found an escalating trend in the level of calcium-phosphorus metabolism-related indexes from stage 3 to stage 5 CKD. The difference between stage 3 and 5 is statistically significant ($p < 0.05$) while that between stage 3 and 4 is not ($p > 0.05$). Among 98 CKD patients, the myocardial hypertrophy accounted for 35.9% (n = 36), the diastolic dysfunction accounted for 72.1% (n = 70), and systolic dysfunction accounted for 27.5% (n = 27). Levels of β-CTX, N-MID, TP1NP, Pi, and iPTH are positively associated with the myocardial hypertrophy and yet negatively associated with cardiac systolic (EF) and diastolic function (A/E value).

CONCLUSIONS: Calcium-phosphorus metabolism disorder in the context of kidney dysfunction may contribute to the damages of cardiac structure and functions.

Key Words:
CKD, Calcium-phosphorus metabolism, CVD, iPTH.

Introduction

Recent researches have indicated an extremely high incidence of chronic kidney disease (CKD) complicated by cardiovascular events, which is the chief culprit leading to the death of patients with CKD. Meanwhile, it has also been found that it is less tractable and effective regarding pharmacological intervention for patients with CKD complicated by cardiovascular events than those with non-CKD, which predominantly results from disturbance of calcium and phosphorus in CKD patients[1]. In this article, we aim to discuss relationships of serum calcium, serum phosphate, parathyroid hormone, beta collagen degradation products, TPINP, and N-terminal osteocalcin with indicators of cardiac structure and functions in the context of CKD. We explored the roles of calcic and phosphor metabolization in cardiac damage and provided references for prevention and therapy of patients with CKD complicated by cardiovascular events.

Patients and Methods

Study Sample

In all, 98 inpatients diagnosed with chronic renal failure, who were all examined between July 2013 and July 2014, were identified in the Urology Department of the Central Hospital of Xu Zhou. Estimated glomerular filtration rate (EGFR) of all patients was calculated according to the revised MDRD formula [EGFR (ml/min) = 170 × serum creatinine (mg/dl) – 0.999 × age – 0.176 × blood urea nitrogen (BUN) (mg/dl) – 0.17 × serum albumin (g/dl) + 0.318, ×0.762 for

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female]. Based on the calculated EGFR and CKD stages according to K/DOQI, we divided all participants into three groups: stages 3, 4, and 5 CKD. Subjects include 50 men and 48 women aged 20-69 years. Seven primary diseases were identified, including chronic glomerulonephritis (n = 43), hypertensive nephropathy (n = 18), diabetic nephropathy (n = 22), obstructive nephropathy (n = 5), lupus nephropathy (n = 5), polycystic kidney (n = 2), and HBV-associated nephropathy (n = 3). We excluded subjects consistent with the following conditions: secondary to parathyroid and bone metabolic disease; cardiovascular disease not complicated by CKD.

Methods

First, we took fasting venous blood from participants. Further, iPTH, -CTX, TP1NP, N-MID, serum calcium (Ca), and serum phosphate (Pi) were measured via electrochemiluminescence; hemoglobin (Hb), blood urea nitrogen (BUN), serum creatinine (Cr), and albumin (ALB) were measured by automatic biochemistry analyzer; cardiac echocardiography was performed employing ultrasonic instrument (Philips iE333) to measure indexes of cardiac structure and functions, including left ventricular end diastolic diameter (LVEDD), interventricular septal thickness (IVST), left ventricular posterior wall thickness (LVPWT), ejection fraction (EF), blood flow velocity at mitral diastolic late phase (A) and at mitral diastolic early phase (E), and the A/E ratio.

Statistical Analysis

SPSS 19.0 software (SPSS Inc., Chicago, IL, USA) was employed to perform all the statistical analyses. Measurement data were given as mean ± standard deviation. Comparison of indexes between groups was carried out using one-way analysis of variance. Correlations were estimated via Pearson's correlation analysis. All reported probabilities were two-sided with $p < 0.05$ and considered statistically significant.

Results

General Characteristics

The detailed information of 98 participants such as age, gender, indexes of renal function, and calcium-phosphorus metabolism were given in Table I.

The statistical results indicated an escalating trend in levels of serum phosphate (Pi), intact parathyroid hormone (iPTH), β-collagen-specific sequences (β-CTX), total N-terminal propeptide of type I procollagen (TPINP), and N-terminal-mid fragment of osteocalcin (N-MID) from stage 3 to stage 5 CKD. The stage 5 is the highest level. The difference between stages 3 and 5 is statistically significant ($p < 0.05$) while that one between stages 3 and 4 is not significant ($p > 0.05$).

Results of Cardiac Indexes

Results from echocardiography showed that the myocardial hypertrophy accounted for 35.9%

Table I. General clinical data and indexes of calcium–phosphorus metabolism of 108 participants.

	CKD3 (n = 37)	CKD4 (n = 24)	CKD5 (n = 37)
Age (year)	56 ± 2.79	51.06 ± 3.02	51.30 ± 2.47
Gender (male/female)	16/21	12/12	22/15
HP (mmHg)	147.76 ± 2.42	144.12 ± 2.27	156.1 ± 3.17
DP (mmHg)	85.38 ± 1.61	85.13 ± 1.47	87.57 ± 1.75
Hb (g/l)	113.61 ± 4.48	98.3 ± 2.45[b]	84.9 ± 3.69[bc]
ALB (g/l)	34.04 ± 0.79	35.57 ± 1.11	35.44 ± 0.77
BUN (mmol/l)	14.50 ± 1.17	21.22 ± 1.05[a]	30.97 ± 2.12[ac]
CR (μmmol/l)	147.36 ± 5.43	289.46 ± 10.01[a]	804.97 ± 56.47[ac]
eGFR (ml/min)	43.03 ± 1.62	19.61 ± 0.97[a]	7.33 ± 0.52[ac]
iPTH (pg/ml)	108.91 ± 21.17	161.02 ± 18.62[ac]	337.06 ± 57.45[ac]
Ca (mmol/l)	2.19 ± 0.02	2.13 ± 0.08	2.146 ± 0.29
Pi (mmol/l)	1.39 ± 0.05	1.47 ± 0.02	2.03 ± 0.09[ac]
β-CTX (pg/ml)	1257.57 ± 113.33	1676.41 ± 144.04	2606.36 ± 204.69[ac]
TP1NP (ng/ml)	63.61 ± 7.73	114.13 ± 16.36[a]	283.12 ± 50.42[ac]
N-MID (ng/ml)	36.88 ± 5.15	62.91 ± 6.15	134.4 ± 15.2[ac]

Compared with stage 3 CKD, $p^a < 0.01$, $p^b < 0.05$; compared with stage 4 CKD, $p^c < 0.01$.

Table II. Cardiac abnormality rate according to different CKD stages.

	CKD stage 3	CKD stage 4	CKD stage 5	Total
Systolic dysfunction	5/37 (13.5%)	7/24(29.1%)	15/37 (40.5%)	27/98 (27.5%)
Diastolic dysfunction	17/37 (45.9%)	20/24 (83.3%)	33/37(89.1%)	70/98 (72.1%)
Myocardial hypertrophy	8/37 (21.6%)	9/24 (37.5%)	19/37 (51.3%)	36/98 (35.7%)

Compared with stage 3 CKD, $p^a < 0.01$, $p^b < 0.05$; compared with stage 4 CKD, $p^c < 0.01$.

Table III. Results from echocardiography according to different CKD stages.

	CKD3 (n = 37)	CKD4 (n = 24)	CKD5 (n = 37)
IVST (mm)	10.38 ± 0.02	10.35± 0.18	11.04 ± 0.22[b]
LVPWT (mm)	9.38 ± 0.14	9.74 ± 1.96	10.26 ± 0.23[a]
LVDd (mm)	51.53 ± 1.15	53.45 ± 1.86	53.73 ± 0.94
A/E	1.09 + 0.04	1.15 + 0.09	1.33 + 0.06
EF (%)	60.2 ± 1.45	55.4 ± 1.36	48.5 ± 1.08[b]

Compared with stage 3 CKD, $p^a < 0.01$, $p^b < 0.05$.

(n = 36), the diastolic dysfunction accounted for 72.1% (n = 70), and systolic dysfunction accounted for 27.5% (n = 27). Data in Table II suggested that systolic and diastolic dysfunction, and myocardial hypertrophy has occurred from stage 3 in CKD patients. Furthermore, the prevalence of cardiac structural and functional abnormality is significantly elevated as the renal dysfunction continues deteriorating.

We conclude (Table III) that left ventricular end diastolic diameter (LVEDD), interventricular septal thickness (IVST), and ejection fraction (EF) significantly increased in patients with stage 5 CKD. Compared with stage 3 CKD, the difference reached statistical significance ($p < 0.05$), but failed compared to stage 4 CKD ($p > 0.05$). The ratio between blood flow velocity at mitral diastolic late phase (A) and mitral diastolic early phase (E) was suggestive of the presence of diastolic dysfunction in stage 3 CKD.

The Relation of Calcium-Phosphorus Metabolism-Related Indexes with Cardiac Damages

Results of analysis for correlation between calcium-phosphorus metabolism- and cardiac damage-related indexes suggested that levels of β-CTX, N-MID, TP1NP, Pi, iPTH, HPandDP were positively associated with the myocardial hypertrophy and yet negatively associated with cardiac systolic (EF) and diastolic function (A/E value) (Table IV).

Discussion

The kidney is the most important organ responsible for regulating minerals. As the kidney dysfunction continued worsening, the decreased activity of 1-α hydroxylase resulted in decreased production of 1,25-dihydroxy vitamin D3 and decreased intestinal absorption of calcium and phosphates, thereby decreasing serum calcium. The hypocalcemia would, in turn, stimulate cells in parathyroid gland for PTH synthesis and secretion via cell calcium receptor (CaR). PTH can promote release of calcium and phosphorus from bones, promote calcium reabsorption and inhibit phosphorus reabsorption in renal tubule, thus elevating serum calcium and decreasing serum phosphorus. If the kidney dysfunction kept worsening, renal tubular reabsorption dysfunction would eventually lead to hyperphosphatemia, high parathyroid hormone levels, soft-tissue and vascular calcification, and increase in cardiovascular events. TP1NP level, as a reliable marker of osteogenesis, is indicative of speed of collagen synthesis. β-CTX, which indicates the speed of bone resorption, is a specific marker for degradation of type I collagen. The level of β-CTX would significantly elevate in the context of kidney failure[2]. N-MID, which is synthesized and secreted by osteoblast, is majorly responsible for maintaining normal speed of bone mineralization and suppressing formation of abnormal hydroxyapatite crystals and inhibiting the speed of

Table IV. Analysis for correlation between calcium–phosphorus metabolism- and cardiac damage-related indexes.

	β-CTX		TP1NP		N-MID		iPTH		P		Ca	
	r	p	r	p	r	p	r	p	r	p	r	p
HP	0.247	0.02	0.258	0.01	0.286	<0.01	0.164	0.02	0.217	0.04	0.163	<0.01
DP	0.179	0.04	0.133	0.2	0.353	<0.01	0.165	0.12	0.366	<0.01	0.157	<0.01
IVST	0.288	<0.01	0.384	<0.01	0.380	<0.01	0.292	<0.01	0.52	0.63	0.520	0.62
LVPWT	0.287	<0.01	0.395	<0.01	0.317	<0.01	0.210	0.05	0.174	0.04	0.136	0.1
LVDd	0.320	<0.01	0.086	0.42	0.269	0.09	0.197	0.04	0.238	0.04	0.290	<0.01
A/E	−0.217	0.03	−0.087	0.77	−0.27	0.23	−0.325	<0.01	−0.271	0.04	0.133	<0.01
EF	−0.282	0.64	−0.251	0.16	−0.349	0.01	−0.367	<0.01	−0.283	<0.01	0.281	0.01

growth cartilage mineralization. N-MID is a biochemical index of bone turnover. It is mainly excreted by kidney and would increasingly arise as renal clearance declined[3]. Liu et al[1] found a close relationship between the indexes above and incidence of cardiovascular disease. it has also been suggested that it is less tractable and effective in terms of pharmacological intervention for patients with CKD complicated by cardiovascular events than those with non-CKD, which predominantly results from disturbance of calcium and phosphorus in CKD patients.

CKD is often complicated by cardiovascular events, which has been the chief culprit leading to death of patients with CKD and impart great influences on patients' life and survival quality. The majority of CKD patients were suffered from a cardiovascular disease (left ventricular hypertrophy as the most common type) before the disease becomes advanced. Some line of evidence suggested a close relationship between left ventricular hypertrophy and (chronic renal failure, CRF) prognosis. Therefore, left ventricular hypertrophy becomes an important index for predicting mortality risk. Regerding changes in myocardial tissue pathology structure, remodeling of the myocardium in uremia includes myocardial hypertrophy, fibrosis (type I collagen deposition), wall thickening of the ventricular artery, and small artery[4]. Our results indicated that the myocardial hypertrophy accounted for 35.9% (n = 36), the diastolic dysfunction accounted for 72.1% (n = 70), and systolic dysfunction accounted for 27.5% (n = 27). Levels of β-CTX, N-MID, TP1NP, Pi, and iPTH are positively associated with the myocardial hypertrophy and yet negatively associated with cardiac systolic (EF) and diastolic function (A/E value) (Tables II-IV).

Among risk factors predicting mortality of cardiovascular events, angiosteosis is an independent risk factor for cardiovascular and all-cause mortality in CKD patients and is superior to other traditional predicting factors[5]. Researches were suggestive of a close association between angiosteosis and calcium-phosphorus metabolism disorders and hyperparathyroidism. Angiostenosis is categorized into microvascular and macrovascular sclerosis. Microvascular sclerosis is referred to as impairments of tiny vessels nurturing large vessels and myocardium, which would lead to malnutrition of large vessels. Vascular impairment accompanied by sclerosis resulting from calcium and phosphate deposition in vascular wall resulted in reduced compliance; meanwhile, luminal stenosis of large vessels caused by intimal fibrosis leads to increased peripheral resistance, elevated blood pressure, increased cardiac workload, and, eventually, left ventricular hypertrophy[6,7]. Myocardial oxygen consumption caused by myocardial hypertrophy and subendocardial ischemia caused by impairments of tiny vessels nurturing myocardium would eventually give rise to cardiac dysfunction.

Hyperphosphatemia, as an independent risk factor for high mortality in cardiovascular disease, is closely linked with pathophysiologic process (such as myocardial hypertrophy, fibrosis, and vascular calcification) in CKD patients. The potential mechanisms by which hyperphosphatemia contributed to vascular smooth muscle cells (VSMCs) calcification include stimulation of osteogenic/chondrogenic differentiation, vesicle release, apoptosis, loss of inhibitors, extracellular matrix degradation, and oxidative stress response induced by mitochondrial membrane potential change[8]. PTH is a cardiac toxin derived from chronic kidney failure, whose excessive rise could induce myocardial hypertrophy, activating fibroblast and myocardial interstitial fibrosis, which would eventually increase cardiac non-vascular interstitial volume[9]. Moreover, PTH can also induce

disturbance of carbohydrate and lipid metabolism, exacerbate anemia, or promote inflammation, all of which would indirectly contribute to exacerbated myocardial hypoxia and metabolic disorders, resulting in extensive myocardial damage and compensatory hypertrophy and cardiac dysfunction[10]. Consistent PTH arising can promote calcium-phosphate deposition in myocardium, resulting in myocardial and cardiac valve calcification, which would eventually facilitate structural and functional changes in the cardiovascular system for patients with uremia. Evidence revealed that osteocyte is involved in carbohydrate and lipid metabolism, which may potentially affect cardiovascular system and subsequent deadly incident. Of note, osteocalcin (OC) can stimulate adiponectin expression, improve insulin resistance and glucose intolerance, and promote angiosclerosis[11]. Researches for β-CTX and cardiovascular disease are relatively inadequate. Lerchbaum et al[12,13] observed a U-shaped association of OC and β-CTX with fatal events in a large cohort of men at high cardiovascular risk. In other words, high and low β-CTX levels can increase risk of cardiovascular disease. Research in female suggested an independent association of high β-CTX level with all-cause and cardiovascular mortality.

Conclusions

In total, it's the multiple factors and links that underlie the incidence of CKD complicated by cardiovascular damage. Further studies warrant for elucidating the underlying mechanisms. The accumulation of a large number of clinical experience is necessary for taking control of incidence of CKD complicated by cardiovascular disease and achieving effective pharmaceutical intervention.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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