Correlation between Gal-3, Klotho, Calcium and Phosphorus Metabolism Indicators and Cardiovascular Complications in Non Dialysis Patients with Chronic Kidney Disease

Zhe Li¹, Jianlong Li²*, Qian Wang¹, Lin Li¹, Yan Gao¹, Chenchen Li¹, Qian Zhang¹, Xing Fan¹

¹Department of Nephrology, Affiliated Hospital of Hebei University, Baoding, 071000, China
²Division of Cardiology, Affiliated Hospital of Hebei University, Baoding, 071000, China
*Corresponding author

Keywords: CKD; Non-dialysis patients; Calcium and phosphorus metabolism; CVD

Abstract: This article explores the correlation between Gal-3, Klotho, calcium and phosphorus metabolism indicators and cardiovascular disease in non dialysis CKD (stage 3-5) patients, summarizes their clinical characteristics, and provides a basis for the prevention and treatment of cardiovascular disease caused by CKD in clinical practice, providing reference for related research. This article selects 100 patients with stage 3-5 CKD who have not received renal replacement therapy. This question involves collecting general data from patients, collecting blood samples from patients, detecting serum calcium, serum phosphorus, Gal-3, and PTH levels at different stages, and calculating the product of calcium and phosphorus. Meanwhile, this study compared the incidence of hypocalcemia, hyperphosphatemia, and hyperparathyroidism at different stages. The research results showed that there was no statistically significant difference in blood calcium levels between CKD3 patients in stages 3 and 4 (P>0.05), but the blood calcium levels of CKD3 patients were significantly lower than those in stages 3 and 4. The difference between the two groups was statistically significant (P<0.05). The calcium and phosphorus products and PTH of patients in different stages gradually increased, but there was no significant difference in ALP levels in different stages (P>0.05). The incidence of hypocalcemia, hyperphosphatemia, high PTH, and calcium phosphate products>55 showed significant differences (P<0.01), and showed an increasing trend with stages, with the lowest in stage 3 and the highest in stage 5. This article analyzes the serum levels of Gal-3, Klotho, and calcium and phosphorus in non dialysis patients with CKD, which has important guiding significance for preventing cardiovascular complications, early intervention, and reducing patient mortality.

1. Introduction

According to statistics, there are 10.8% patients with chronic kidney disease (CKD) in China, and about 100 million people suffer from CKD. Therefore, CKD is a public health problem in
It has a high incidence, complicated etiology and pathology, different clinical manifestations, lingering disease and numerous complications, and eventually develops into end-stage renal disease (ESRD), which is characterized by poor prognosis and high mortality [2]. More and more evidences show that CKD is a common disease with high morbidity and mortality, CVD (CVD complications are the main cause of death [3]. In CKD, due to the compensatory effect of kidney, the obvious disorder of blood calcium and blood phosphorus often occurs when the glomerular filtration rate is low, and the regulatory factors related to calcium and phosphorus metabolism may have changed in the early stage of CKD. The number of deaths caused by CVD accounts for more than 50% of the deaths related to CKD, but conventional CVD risk predictors cannot fully explain the pathogenesis of CKD-related CVD [4]. Because the disorder of calcium and phosphorus metabolism can affect the long-term survival rate and prognosis of CKD patients by affecting cardiovascular system, early warning of calcium and phosphorus metabolism disorder plays an important role.

Abnormal mineral and bone metabolism caused by metabolic disorders such as calcium and phosphorus are the main complications of CKD patients, which will cause bone diseases and multi-system damage, especially the cardiovascular system, leading to high incidence of cardiovascular events, aggravating the illness, increasing the risk of death and increasing the mortality rate of the whole disease [5]. Clinically, especially in the middle and late stages of the disease, patients have different degrees of calcium and phosphorus disorders. Therefore, early detection and diagnosis can provide basis for timely treatment, alleviate clinical symptoms, delay the progress of the disease and reduce the occurrence of death, which is of great significance to CKD patients [6]. Galectin -3 (Gal-3) can promote angiogenesis, change the morphology of vascular endothelial cells, improve microvascular lesions caused by CKD, and can be used as the main index to observe the condition of patients with CKD complicated with chronic kidney disease [7]. Klotho protein is a co-receptor of FGF23, which is mainly expressed in the distal tubule of kidney. This paper mainly analyzes the correlation between Gal-3, Klotho, calcium and phosphorus metabolism levels and cardiovascular complications in CKD non-dialysis patients.

2. Materials and methods

2.1. Clinical data

This study selected 100 patients from CKD stages 3 to 5 who did not receive renal replacement therapy according to the K/DOQI guidelines for CKD clinical staging, and all signed informed consent forms for this study. Among them, there are 50 male patients and 50 female patients, aged 30-85 years, with an average age of 38.7 years.

Inclusion criteria: ① Age>18 years old; ② Meets the definition criteria and staging of CKD in the 2012 Kidney disease improving global out homes (KDIGO), and none of them have entered dialysis.

Exclusion criteria: ① Sudden deterioration of renal function, severe acidosis, severe damage to liver function, malignant tumors, primary hyperparathyroidism, heart failure, etc.; ② Those who have recently taken drugs that affect glomerular filtration rate, such as kidney protection and detoxification; ③ Those who have taken calcium or phosphorus binders or other similar substances in the past month. Those who have one of the above situations shall not be considered as research subjects.
2.2. Research method

This article collects general data from patients, collects blood samples from patients, detects serum calcium, serum phosphorus, Gal-3, and PTH levels of patients at different periods, and calculates the product of calcium and phosphorus. At the same time, the incidence of hypocalcemia, hyperphosphatemia and high PTH in each period was compared. Make a unified form, collect general clinical data of patients such as name, contact number, sex, age, body weight, basic etiology, complications, therapeutic drugs, etc., and take fasting venous blood samples from patients. The biochemical indicators are mainly serum calcium, serum phosphorus, alkaline phosphatase (ALP), PTH, serum creatinine (Scr), etc., and finally make a unified arrangement. IPTH, β-CTX, TP1NP, N-MID, blood calcium and blood phosphorus were measured by electrochemiluminescence of fasting venous blood, and hemoglobin (Hb), urea nitrogen (BUN) and serum creatinine (Cr) were measured by automatic biochemical analyzer.

2.3. Statistical treatment

SPSS26.0 statistical software was used for data analysis, with measurement data expressed as mean ± standard deviation (x ± s). Independent sample t-test was used for inter group comparison, and counting data comparison was performed using χ² Inspection; The correlation analysis was conducted using linear regression analysis, and on this basis, multiple linear regression analysis was performed. P<0.05 indicates a statistically significant difference.

3. Results

There was no significant difference in blood calcium levels between stage 3 and stage 4 (P > 0.05), but the blood calcium level of patients with CKD5 was significantly lower than that of patients with CKD3 and CKD4, and the difference between groups was statistically significant (P < 0.05). The levels of serum phosphorus, calcium-phosphorus product and PTH all increased with the progress of staging, and the differences between groups were statistically significant (P < 0.01), but there was no statistical difference in ALP levels in each stage (P > 0.05), as shown in Table 1.

<table>
<thead>
<tr>
<th>CKD staging</th>
<th>n</th>
<th>Blood calcium (mmol/L)</th>
<th>Blood phosphorus (mmol/L)</th>
<th>PTH(pg/ml)</th>
<th>Gal-3 (ng/ml)</th>
<th>ALP(U/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 3</td>
<td>42</td>
<td>2.22±0.21</td>
<td>1.21±0.22</td>
<td>39.69±3.29</td>
<td>11.8±2.3</td>
<td>32.11±10.99</td>
</tr>
<tr>
<td>Phase 4</td>
<td>38</td>
<td>2.17±0.35</td>
<td>1.29±0.33</td>
<td>64.88±66.21*</td>
<td>13.5±3.1</td>
<td>40.25±15.01*</td>
</tr>
<tr>
<td>Phase 5</td>
<td>30</td>
<td>2.04±0.22*</td>
<td>0.83±0.56*</td>
<td>221.11±169.22**</td>
<td>15.7±2.5</td>
<td>50.48±22.01*</td>
</tr>
</tbody>
</table>

Note: Compared with CKD3 phase, * P<0.01; Compared with CKD4 phase, # P<0.01

The incidence of hypocalcemia, hyperphosphatemia, hyperphosphatemia, and calcium phosphorus product>55 showed an increasing trend with stage, with the lowest in stage 3 and the highest in stage 5, and the difference was statistically significant (P<0.05), as shown in Table 2.

<table>
<thead>
<tr>
<th>CKD staging</th>
<th>n</th>
<th>Hypocalcemia</th>
<th>Hyperphosphatemia</th>
<th>High PTH</th>
<th>Calcium-phosphorus product &gt; 55</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 3</td>
<td>42</td>
<td>14.1±(9/42)</td>
<td>18.1±(11/42)</td>
<td>5.4±(4/42)</td>
<td>2.2±(1/42)</td>
</tr>
<tr>
<td>Phase 4</td>
<td>38</td>
<td>22.2±(10/38)</td>
<td>55.3±(24/38)**</td>
<td>22.1±(8/38)*</td>
<td>21.9±(12/38)</td>
</tr>
<tr>
<td>Phase 5</td>
<td>30</td>
<td>49.2±(16/30)**##</td>
<td>75.2±(20/30)**##</td>
<td>29.8±(7/30)*</td>
<td>61.8±(19/30)#</td>
</tr>
</tbody>
</table>

Note: Compared with CKD3 phase, * P<0.05, ** P<0.01; Compared with CKD4 phase, # P<0.005, ##
Statistical analysis was conducted using PTH as the dependent variable and blood calcium, blood phosphorus, calcium phosphorus product, ALP, GFR, etc. as independent variables. The results showed that PTH levels were positively correlated with blood phosphorus (r=0.518, P<0.01) and calcium phosphorus product (r=0.469, P<0.01), and negatively correlated with GFR (r=-0.551, P<0.01) and blood calcium (r=-0.407, P<0.01); There is no correlation with ALP. Further, with PTH as the dependent variable and gender, age, blood calcium, blood phosphorus, GFR, and calcium phosphorus product as independent variables, multiple linear regression analysis was conducted. Only three indicators of blood calcium, blood phosphorus, and GFR entered the regression equation, with a multiple correlation coefficient of r=0.581. It indicates that blood calcium, blood phosphorus, and glomerular filtration rate are independently correlated with PTH (P<0.05) and are independent influencing factors, as shown in Table 3.

Table 3: Multiple linear regression analysis of PTH

<table>
<thead>
<tr>
<th>Variable</th>
<th>Regression coefficient</th>
<th>Standard error</th>
<th>Standard regression coefficient</th>
<th>t value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant term</td>
<td>29.221</td>
<td>88.889</td>
<td>-</td>
<td>3.821</td>
<td>0.000</td>
</tr>
<tr>
<td>Blood calcium</td>
<td>-0.201</td>
<td>0.581</td>
<td>0.394</td>
<td>2.355</td>
<td>0.033</td>
</tr>
<tr>
<td>Blood phosphorus</td>
<td>0.163</td>
<td>1.507</td>
<td>0.335</td>
<td>3.721</td>
<td>0.022</td>
</tr>
<tr>
<td>GFR</td>
<td>-0.825</td>
<td>0.373</td>
<td>0.261</td>
<td>1.703</td>
<td>0.041</td>
</tr>
</tbody>
</table>

4. Discussion

The kidney is the most important mineral regulating organ. With the decline of renal function, the renal tubular reabsorption dysfunction eventually leads to hyperphosphatemia, hyperparathyroidism, calcification of soft tissues and blood vessels, and increased cardiovascular events. Metabolic disorders such as calcium and phosphorus, renal osteodystrophy and vascular calcification in CKD patients are the three main manifestations of abnormal mineral-bone metabolism [8]. Among them, the metabolic disorder of minerals such as calcium and phosphorus is the basis and key to its occurrence. With the progress of renal function, the degree of disorder gradually rises. Most CKD patients have CVD before entering the end stage, and left ventricular hypertrophy is the most common. Some studies have shown that left ventricular hypertrophy is closely related to the prognosis of CRF and is an important index to predict the risk of death in CRF patients. From the pathological changes of myocardial tissue, the changes of myocardial structure in uremia include myocardial hypertrophy, fibrosis, thickening of arterial and arteriolar walls in ventricular wall. In CKD, renal function decreases, and the filtration rate of phosphorus in glomerulus decreases. The disorder of 25- hydroxylation of vitamin D3 is the reason for the disorder of calcium and phosphorus metabolism. Hypocalcemia stimulates the secretion of parathyroid hormone to promote the excretion of phosphorus by renal tubules and correct hyperphosphatemia, which is an important compensatory mechanism of the body.

At the third stage, the serum calcium and phosphorus levels of patients are still at normal level, but the PTH level is slightly increased, which may be due to the compensation mechanism in the body. Studies have shown that when the glomerular filtration rate is less than 60ml/min and the blood calcium and phosphorus levels are close to normal, the overall level of PTH has increased, and when the glomerular filtration rate drops to less than 30ml/min, all patients basically suffer from hypocalcemia and hyperphosphatemia [9]. In CKD3 stage, the levels of blood calcium, blood phosphorus and calcium-phosphorus product of patients are basically close to normal, but the level of PTH has started to increase slightly, and the incidence of various situations has generally
increased with the progress of stages. This shows that when most patients have not had abnormal calcium and phosphorus levels in CKD3, the disorder of calcium and phosphorus metabolism already exists. Although it is not shown in the data, the internal environment of the body has begun to change. When the disease progressed to the fifth stage, the patient had entered the stage of renal failure, and the filtration function was very poor. The blood phosphorus level in the patient increased significantly, showing high phosphorus, and the blood calcium level decreased significantly. The patient showed various clinical manifestations of hypocalemia, and PTH also increased significantly to regulate calcium and phosphorus levels. In the biochemical mechanism, PTH indirectly increases Ca2+ absorbed by intestine by activating vitamin D3. When blood Ca2+ increases, blood phosphorus decreases, which can further adjust the level of calcium and phosphorus metabolism. However, the increase of plasma Ca2+ concentration will hinder PTH secretion, while the decrease of plasma Ca2+ concentration will stimulate PTH secretion. In addition to blood Ca2+ concentration, blood phosphorus and blood magnesium concentrations also affect PTH secretion, which can be said to promote and influence each other. Vascular sclerosis includes micro-vessels and macro-vessels. The former refers to the micro-vessels that nourish the macro-vessels and myocardium, and its damage can make the macro-vessels malnourished, and the deposition of calcium and phosphorus on the vascular wall will harden, which will reduce their compliance. At the same time, the intima and fibrous tissue of large blood vessels proliferate, the peripheral resistance of lumen stenosis increases, blood pressure increases, and the heart load increases, which eventually leads to left ventricular hypertrophy.

Because PTH-related protein receptors are widely found in many tissues and organs of the body, almost all organs can be the target organs of PTH, which can cause or aggravate the functional damage of multiple systems including cardiovascular, nervous, skeletal, endocrine and immune systems [10]. All these show the importance of PTH to the body, and clinically, with the progress of CKD, especially in the late stage, most patients will have abnormal PTH metabolism. Cardiac hypertrophy leads to the increase of myocardial oxygen consumption, coupled with the damage of small blood vessels that nourish myocardium, and subendocardial myocardial ischemia eventually leads to cardiac insufficiency. Hyperphosphatemia is closely related to pathophysiological processes such as myocardial hypertrophy, fibrosis, calcification of blood vessels and valves in CKD patients, and is an independent risk factor for high mortality of cardiovascular disease. With the progress of the disease, the degree of disorder is further aggravated, and hyperphosphatemia and hyperphthemia make the body of CKD patients in a high-risk state, which not only aggravates the clinical symptoms of CKD patients, affects their progress in CKD, but also seriously affects their quality of life, and more importantly, reduces the survival rate of patients and accelerates their death. PTH is a cardiotoxin of chronic renal failure. Excessive PTH activates fibroblasts and starts myocardial interstitial fibrosis. Continued increase of PTH can promote calcium and phosphorus deposition in myocardium, leading to calcification of myocardium and heart valves, and ultimately promote structural and functional changes of cardiovascular system in uremia patients. Early intervention should be carried out in CKD patients to restore the calcium and phosphorus levels to normal levels, reduce the occurrence of subsequent complications, and make patients have a good prognosis.

5. Conclusions

Hypocalcemia and hyperphosphatemia are common complications for CKD patients, and they interact with each other. Hypocalcemia can stimulate parathyroid hormone secretion, and then promote renal tubular phosphorus excretion and correct hyperphosphatemia, which is the adaptive compensation mechanism of the body. When hyperphosphatemia occurs, it may lead to hypocalcemia, increase parathyroid hormone secretion, cause secondary hyperparathyroidism, and
then aggravate hypocalcemia and hyperphosphatemia, forming a vicious circle. Early monitoring is helpful to take effective preventive measures, delay the progress of vascular calcification and reduce the occurrence of cardiovascular events. Treatment should be given when CKD patients are in the third stage, so as to correct the disorder of calcium and phosphorus metabolism, reduce the occurrence of complications and reduce the mortality of patients.

Acknowledgements

Baoding City Science and Technology Plan Project (No.2241ZF302).

References