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Original Article

Correlation of FGF-23 and OPG with vascular calcification in chronic nephropathy

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Abstract: Objective: To explore the correlation of FGF-23 and OPG with vascular calcification in chronic kidney disease (CKD). Methods: Altogether 154 patients with CKD admitted to Affiliated Hospital of Hebei University of Engineering were selected. Among them, 83 patients with vascular calcification were regarded as the research group (RG). Another 71 patients without vascular calcification were regarded as the control group (CG). The expression of FGF-23 and OPG before operation in RG and CG, the correlation between FGF-23 and OPG in RG, the predictive value of FGF-23 and OPG on vascular calcification, the changes of FGF-23 and OPG expression during treatment, and the risk factors affecting vascular calcification were observed. Results: FGF-23 in RG was higher than that in CG before operation, while OPG was lower than that in CG before operation ($P < 0.05$). FGF-23 was negatively related to OPG before operation in RG ($r = -0.608$, $P < 0.001$). The sensitivity and specificity of FGF-23 for predicting vascular calcification were 74.65% and 83.13%, respectively. OPG had a predictive sensitivity of 66.20% and specificity of 78.31% for vascular calcification. The sensitivity and specificity of FGF-23 combined with OPG for predicting vascular calcification were 84.51% and 83.13%, respectively. FGF-23 in RG was higher than that CG at T0, T1, T2, T3 and T4. FGF-23 was highest at T0, began to decline at T1, and was lowest at T4 ($P < 0.05$). OPG in RG was lower than that CG at T0, T1, T2, T3 and T4. OPG was lowest at T0, began to rise at T1 and was highest at T4 ($P < 0.05$). Blood glucose, blood lipids, FGF-23 and OPG were independent risk factors for vascular calcification ($P < 0.05$). Conclusion: FGF-23 is increased in CKD patients with vascular calcification, while OPG is decreased. Both of them are related to CKD vascular calcification, and may be important observation indicators of vascular calcification in CKD patients.

Keywords: FGF-23, OPG, vascular calcification of chronic kidney disease, correlation

Introduction

Chronic kidney disease (CKD) is a kind of kidney disease commonly found in the clinic [1]. It is the structural and functional damage of the kidney caused by various reasons (kidney damage history > 3 months) [2]. The injuries include chronic glomerulonephritis, latent nephritis, chronic pyelonephritis, diabetic nephropathy, and hypertensive nephropathy [3]. If CKD is not treated promptly and effectively, it will lead to deterioration and progression of the disease, and the course of the disease will be prolonged. CKD patients will develop chronic renal insufficiency and renal failure, eventually inducing uremia [4, 5]. It has a serious effect on the quality of life, endangers people's life and health, and causes serious social and public health problems. According to clinical data, CKD not only has a high incidence rate, but also has a high incidence rate of concomitant cardiovascular diseases, becoming the primary cause of death for CKD patients [6]. Many studies showed that vascular calcification has a close relationship with occurrence of cardiovascular and cerebrovascular events in CKD patients [7]. Vascular calcification in CKD patients can be divided into intimal calcification and medial calcification. The calcification involves the large and middle blood vessels, making these blood vessels harden, narrowing and reducing flexibility, leading to blood vessel blockage and ultimately endangering life [8]. Therefore, how to effectively predict and evaluate vascular calcification is currently a hot topic in clinical research, as well as improving the clinical efficacy and prognosis of CKD.

At present, blood tests are usually used to detect blood lipids for vascular calcification in the clinic, or CT angiography and angiography are further performed. The examination cycle is long and has certain damage to human body [9]. Therefore, it is of great significance for evaluation of vascular calcification to seek a more convenient examination method. Fibroblast growth factor 23 (FGF23) is a hormone-like phosphorus regulating factor [10] secreted by osteocytes and osteoblasts, which regulates phosphate homeostasis and vitamin D metabolism in the kidneys and parathyroid glands. We found through data analysis that FGF-23 is closely related to the progress of CKD [11]. El Din U A A S [12] et al. confirmed that FGF-23 was associated with the changes of blood sugar and blood lipids when studying diabetic nephropathy. Osteoprotegerin (OPG) has the function of inhibiting osteoclast (OC) formation, differentiation, survival and inducing OC apoptosis [13]. Its function is closely related to cytokine kB receptor-activating factor ligand (RANKL) and cytokine kB receptor-activating factor (RANK) [14]. Studies indicated that OPG has a close relationship with osteoporosis in diabetic patients [15], so we estimated that OPG is also related to changes in blood lipids and blood glucose. Therefore, we suspected that FGF23 and OPG have good diagnostic value for vascular calcification in CKD. In order to verify our hypothesis, this experiment will provide new ideas for future clinical practice by exploring the relationship of FGF23 and OPG with vascular calcification in CKD.

Materials and methods

Altogether 154 patients with chronic kidney disease admitted to Affiliated Hospital of Hebei University of Engineering were selected as the research subjects and analyzed prospectively. Among them, 83 patients with vascular calcification were regarded as the research group (RG). The average age was 51.3±6.7. Another 71 patients without vascular calcification were regarded as the control group (CG). The average age was 52.2±7.5. This experiment has been approved by the Ethics Committee. All patients have signed informed consent forms.

Inclusion and exclusion criteria

Inclusion criteria: patients aged 30-70 years; all patients were diagnosed with chronic kidney disease by the examinations of Affiliated Hospital of Hebei University of Engineering; patients in the research group had varying degrees of vascular calcification in imaging examination; all the patients were treated in the Affiliated Hospital of Hebei University of Engineering after being diagnosed; patients had complete case data and agreed to cooperate with the medical staff participating in Affiliated Hospital of Hebei University of Engineering; patients or his immediate family members signed the informed consent form.

Exclusion criteria: patients complicated with other malignant tumors, multiple chronic diseases, other cardiovascular and cerebrovascular diseases, organ dysfunction, drug allergy, mental diseases or physical disabilities, and those who could not take care of themselves; patients with severe inflammation; patients with severe immune deficiency; pregnant or lactating women; patients with autoimmune diseases; patients with abnormal liver function; patients with infectious diseases; patients with an expected survival period of less than 1 month; and patients transferred from another hospital.

Treatment methods

All patients underwent vascular hemodialysis after admission, and were treated with 1.5 mmol/L of bicarbonate dialysate, dialysate of 500 mL/min, blood flow of 230 mL/min, dialysis cycle of 4 h/time, 3 times a week. The patients strictly followed the doctor's advice for 6 consecutive months.

Detection method

Four ml of fasting venous blood was collected before treatment (T0), one month after treatment (T1), two months after treatment (T2), four months after treatment (T3), and six months after treatment (T4). The upper serum was obtained by centrifugation at 10 min (500×g) after 30 min at room temperature. The serum levels of FGF23 (Shanghai Hengfei Biotechnology Co., Ltd., CEA746Ra-1) and OPG (Shanghai Hengfei Biotechnology Co., Ltd., SEA108Po-1) were detected by ELISA. The operation was strictly carried out in a sterile environment according to the kit instructions.

Observation index

Main observation indexes: The expression of FGF-23 and OPG before treatment in the research group and control group was ana-

Table 1. Comparison of general data of two groups of patients [(%)]

	Research group (n = 83)	Control group (n = 71)	t or x^2	P
Age (years)	51.3±6.7	52.2±7.5	0.786	0.433
BMI (KG/cm^2)	23.52±3.05	24.46±4.72	1.488	0.139
Gender			3.520	0.061
Male	69 (83.13)	50 (70.42)		
Female	14 (16.87)	21 (29.58)		
Residence			1.036	0.309
Urban	59 (71.08)	45 (63.38)		
Rural	24 (28.92)	26 (36.62)		
Level of education			0.786	0.887
< high school	41 (49.40)	30 (42.25)		
≥ high school	42 (50.60)	41 (57.75)		
Smoking history			0.538	0.463
Yes	55 (66.27)	43 (60.56)		
No	28 (33.73)	28 (39.44)		
Drinking history			0.629	0.428
Yes	38 (45.78)	28 (39.44)		
No	45 (54.22)	43 (60.56)		
History of hypertension and diabetes			12.740	< 0.001
Yes	52 (37.35)	24 (47.89)		
No	31 (62.65)	47 (52.11)		
Nationality			1.847	0.174
Han	76 (91.57)	60 (84.51)		
Minorities	7 (8.43)	11 (15.49)		
Blood glucose (mmol/l)	9.32±1.02	8.14±1.01	7.189	< 0.001
Blood lipid (mmol/l)	7.36±2.25	5.27±2.13	5.889	< 0.001
Blood phosphorus (mmol/l)	3.45±1.05	2.21±1.02	7.402	< 0.001
CRP (mg/L)	20.34±4.36	12.37±4.23	11.460	< 0.001
Heart rate (beats/minute)	74.43±4.26	65.12±3.32	14.940	< 0.001

lyzed. The correlation between FGF-23 and OPG in the research group was studied. The predictive value of FGF-23 and OPG for vascular calcification was explored.

Secondary observation indexed: The change of FGF-23 and OPG expression during treatment was explored. Risk factors affecting vascular calcification were observed.

Statistical method

SPSS 22.0 was applied to analyze the data. The counting data were expressed as (rate), and chi-square test was applied for pair-wise comparison. The measurement data were expressed as (mean ± standard deviation). The independent sample t test was applied for comparison among multiple groups. The comparison among multiple time points used repeated measurement analysis of variance and Bonferroni back testing. The diagnostic value was analyzed by ROC curve. Pearson correlation coefficient was applied for correlation analysis. $P < 0.05$, indicated the difference was statistically significant.

Results

General data comparison

There was no difference in age, BMI, residence, sex, education level, smoking history, drinking history and nationality between the two groups ($P > 0.05$). Hypertension, diabetes history, blood glucose, blood lipids, blood phosphorus, CRP and heart rate had statistical differences ($P < 0.05$) as shown in **Table 1**.

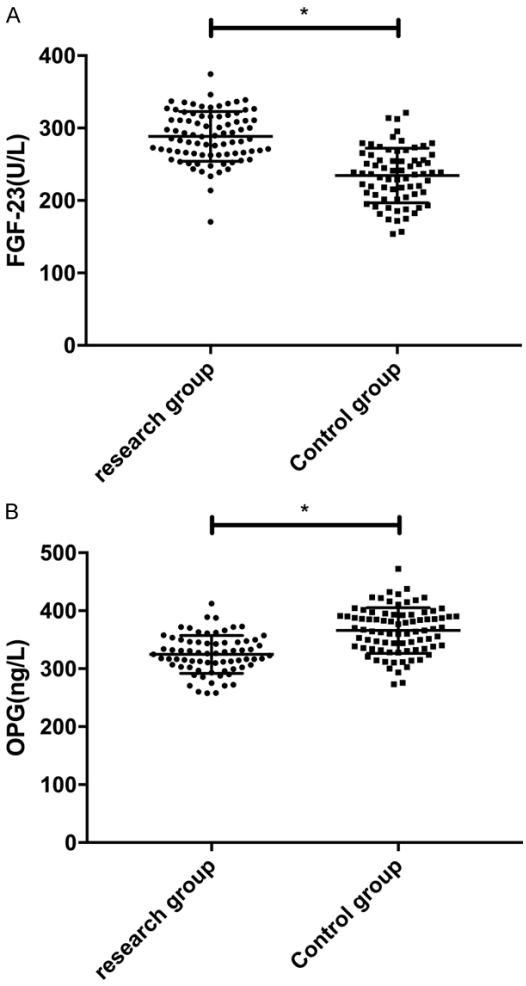

Figure 1. Expression of FGF-23 and OPG before treatment in RG and CG. A. Compared with CG before treatment, the concentration of FGF-23 in RG was higher, * indicates that P < 0.05; B. Compared with CG before treatment, the OPG concentration in RG was lower, * indicates that P < 0.05.

Expression of FGF-23 and OPG before treatment in the research group and control group

After examination, it was found that FGF-23 in the research group was significantly higher than that in the control group before treatment (P < 0.05). OPG in the research group was significantly lower than that in the control group before treatment (P < 0.05). See **Figure 1**.

Correlation between FGF-23 and OPG in research group

Pearson correlation coefficient analysis showed that FGF-23 was negatively correlated with OPG before treatment in the RG (r = -0.608, P < 0.001). See **Figure 2**.

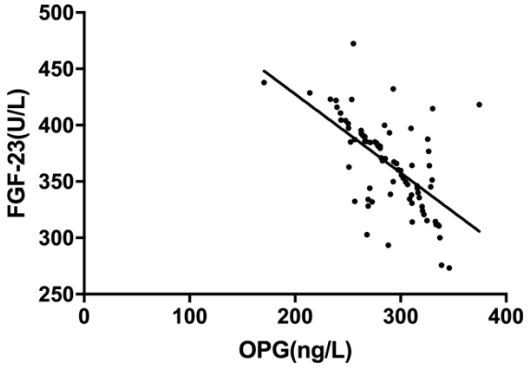

Figure 2. Correlation analysis of FGF-23 and OPG in RG. Pearson correlation coefficient analysis showed that FGF-23 and OPG in the RG showed negative correlation before treatment (r = -0.608, P < 0.001).

Predictive value of FGF-23 and OPG for vascular calcification

ROC curve analysis showed that FGF-23 had a predictive sensitivity of 74.65% and specificity of 83.13%. OPG had a predictive sensitivity of 66.20% and specificity of 78.31%. However, Logistic regression analysis was used to calculate the combined detection formula: LOG (P) = 21.997+-0.041× FGF-23+-0.033× OPG. The prediction sensitivity and specificity of the formula were 84.51% and 83.13%, respectively. See **Figure 3** and **Table 2**.

Changes of FGF-23 and OPG expression during treatment

FGF-23 in RG was higher than that CG at T0, T1, T2, T3 and T4. FGF-23 was highest at T0, began to decline at T1, and was lowest at T4 (P < 0.05). The OPG of RG was lower than that CG at T0, T1, T2, T3 and T4. The OPG of research group was lowest at T0, began to rise at T1, and was highest at T4 (P < 0.05). See **Figure 4**.

Risk factors affecting vascular calcification

Taking **Table 1** as the single factor analysis result, the indicators with differences among them were included in the assignment (See **Table 3** for assignment), and then Logistic regression was carried out. The results (see **Table 4**) showed that blood glucose, blood lipids, FGF-23 and OPG were independent risk

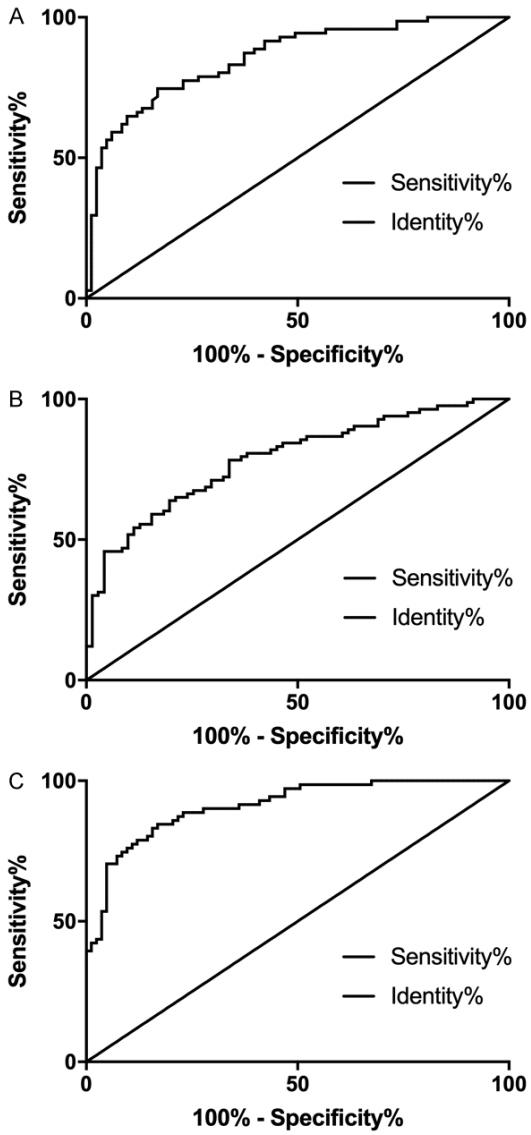

Figure 3. Predictive value of FGF-23 for vascular calcification. A. ROC curve of FGF-23 for predicting vascular calcification. B. ROC curve of OPG for predicting vascular calcification. C. ROC curve of FGF-23 combined with OPG for predicting vascular calcification.

factors affecting vascular calcification in patients with chronic kidney disease ($P < 0.05$).

Discussion

Vascular calcification is a frequent clinical complication in CKD patients [16]. Research results showed that vascular calcification usually induces cardiovascular diseases and aggravates the patient's condition [17], which has important clinical significance in the prognosis. The clinical occurrence of vascular calcification is mostly focused on cardiovascular disease [18], while the diagnostic method is mostly imaging examination [19]. Viskovic K [20] and Halasz C L [21] applied imaging diagnostic methods in CKD research, but there are still some prognostic risk factors. In order to find a new diagnostic method, this study explored the correlation of non-cardiovascular factors FGF-23 and OPG with vascular calcification in chronic kidney disease, and provided a new idea for clinical diagnosis of vascular calcification in CKD patients.

The experimental results indicated that FGF-23 in CKD patients with vascular calcification is significantly higher than that in CKD patients before treatment. The expression level of OPG was significantly lower than that of CKD patients. This result suggested that FGF-23 and OPG acted on the process of vascular calcification in CKD patients. According to previous studies, FGF-23 was considered to be a urinary phosphate-related protein hormone, which was regulated by blood phosphorus level, blood calcium level and serum PTH level [22]. It was produced by extrarenal tissues and acted on the kidney. FGF-23 could increase phosphate excretion, inhibit 1-α-hydroxylase, reduce its ability to activate vitamin D and subsequently impair calcium absorption [23]. Previous studies have proved that vitamin D deficiency can cause diabetes [24]. Therefore, it was concluded that vitamin D deficiency can cause a significant increase in blood glucose, which is one of the therapeutic factors for vascular calcification. We speculated that the increase in FGF-23 causes vitamin D deficiency, which leads to an increase in blood glucose and finally vascular calcification. It was also found that some scholars pointed out that in mice fed with high fat, inflammation became a powerful factor driving the production of FGF-23 through stimulation [25]. However, vascular blockage and necrosis caused by vascular calcification could cause serious inflammatory reactions [26]. Therefore, it was speculated that inflammatory reactions may also cause the elevation of FGF-23, leading to vascular calcification. Diabetes not only led to metabolic disorders of fat, protein and sugar, but also affected the bone metabolic process. Some studies showed that vascular calcification is not only related to the imbalance of calcium and phosphorus metabolism, but also closely

Table 2. Predictive value of FGF-23 and OPG for vascular calcification

	FGF-23	OPG	FGF-23 combined with OPG
Cut-off	256.100	334.00	0.504
AUC	0.856	0.787	0.911
Std. Error	0.030	0.036	0.023
95% CI	0.797~0.915	0.716~0.858	0.867~0.955
Sensitivity (%)	74.65	66.20	84.51
Specificity (%)	83.13	78.31	83.13
P	< 0.001	< 0.001	< 0.001

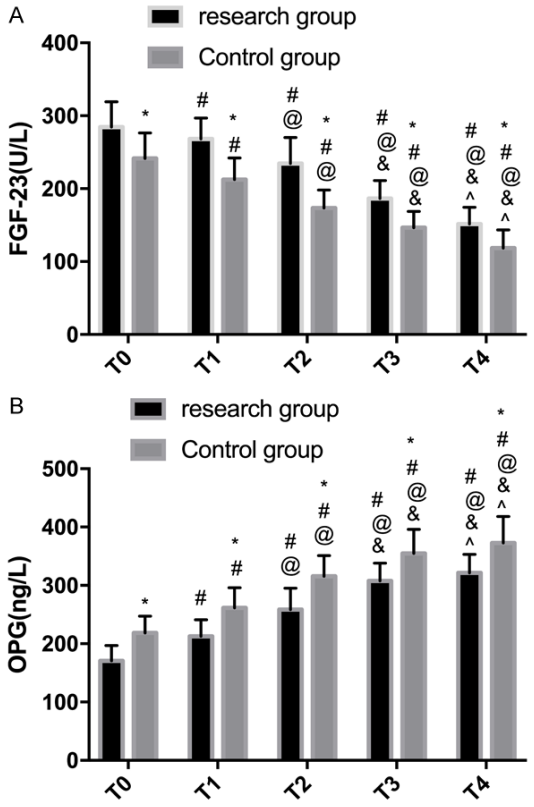

Figure 4. Changes of FGF-23 and OPG during treatment. A. Changes of FGF-23 during treatment. B. Changes of OPG during treatment. * indicates that compared with the research group at the same time, $P < 0.05$; # indicates that compared with the same group at T0, $P < 0.05$; @ indicates that intra-group comparison at T1, $P < 0.05$; & indicates that intra-group comparison at T2, $P < 0.05$; ^ indicates that intra-group comparison at T3, $P < 0.05$.

related to ossification of vascular structure [27]. Osteoporosis was mostly related to reduction of OPG level [28]. Therefore, we speculated that reduction of OPG level leads to abnormal bone metabolism in patients and further leads to vascular calcification in patients. Since we did not carry out this experiment here, we cannot confirm whether our conjecture is correct. We will supplement this study with the mechanism experiments of vascular calcification with FGF-23 and OPG. Subsequently, we further studied the correlation between FGF-23 and OPG in CKD patients with vascular calcification. The results showed that FGF-23 and OPG were negatively correlated in CKD patients with vascular calcification before treatment. This result indicated that FGF-23 is increased and OPG is decreased in CKD patients with vascular calcification. Further experiments found that FGF-23 combined with OPG had better predictive value for vascular calcification. Compared with traditional diagnostic methods such as blood test and image diagnosis, FGF-23 combined with OPG is more convenient in predicting vascular calcification and can be used as an observation index of CKD vascular calcification and is widely used in clinic. In the study, we also observed the expression changes of FGF-23 and OPG before treatment, the 1st, 2nd, 4th and 6th month of treatment. The expression of FGF-23 in CKD patients with vascular calcification was the highest before treatment, while the expression of OPG increased as the treatment time went by. This result further showed that FGF-23 and OPG are closely related to vascular calcification, and also supports our above experimental results. Finally, we analyzed the risk factors affecting vascular calcification. The results showed that blood sugar, blood lipids, FGF-23, and OPG are independent risk factors affecting vascular calcification in patients with chronic kidney disease. It was further confirmed that FGF-23 and OPG are closely related to vascular calcification.

However, this study still has some deficiencies. First, the conclusion of this study has not been fully confirmed. In the subsequent experiments, we will carry out the conclusion

Table 3. Assignment table

Factor	Assignment
Blood glucose	The data conformed to continuous variables and were analyzed using original data.
Blood liquid	The data conformed to continuous variables and were analyzed using original data.
Blood phosphorus	The data conformed to continuous variables and were analyzed using original data.
CRP	The data conformed to continuous variables and were analyzed using original data.
Heart rate	The data conformed to continuous variables and were analyzed using original data.
FGF-23	The data conformed to continuous variables and were analyzed using original data.
OPG	The data conformed to continuous variables and were analyzed using original data.
History of hypertension and diabetes	No = 0; Yes = 1

Table 4. Logistic regression analysis

	S.E.	β	Wald x^2	P	OR	95% CI
Blood glucose	0.721	0.324	5.622	0.007	2.015	1.621~2.642
Blood liquid	1.262	0.342	8.623	0.001	3.452	2.623~4.323
FGF-23	2.056	0.472	20.162	0.000	7.623	4.623~9.623
OPG	0.842	0.321	7.623	0.000	2.428	1.623~3.642

confirmation by basic experiments. Second, there was no follow-up in this experiment, and the prognosis of patients with vascular calcification by FGF-23 and OPG was unclear. We will extend the follow-up time in the follow-up experiment to clarify the prognosis. Finally, there may be other indicators that affect vascular calcification in the analysis of related factors, which need further analysis and exploration.

To sum up, FGF-23 is increased in CKD patients with vascular calcification, while OPG is decreased. Both of them are closely related to CKD vascular calcification, and may be important observation indicators of vascular calcification in CKD patients.

Disclosure of conflict of interest

None.

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