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Impact of serum FGF23 levels on blood pressure of patients with chronic kidney disease

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Abstract. – OBJECTIVE: To investigate the impact of serum FGF23 levels on blood pressure of patients with chronic kidney disease (CKD).

PATIENTS AND METHODS: 128 patients with chronic kidney disease were selected from February 2013 to January 2016. Using CKD staging method, all the patients were divided into 1 to 5 stages according to the glomerular filtration rate. Enzyme-Linked ImmunoSorbent Assay (ELISA) was used to detect serum FGF23 levels of CKD patients and healthy control subjects. 24 h blood pressure monitoring method was used to monitor the mean arterial pressure of patients. Spearman-related analysis method was used to statistically analyze serum FGF23 level, mean arterial pressure and glomerular filtration rate.

RESULTS: The serum FGF23 levels of CKD patients were significantly higher than those of the healthy control subjects ($p<0.05$). Also, FGF23 expression levels in serum were positively correlated with mean arterial pressure based on the results of the Spearman-related analysis. On the other hand, FGF23 expression levels in serum were negatively correlated with glomerular filtration rate. The FGF23 expression levels in serum of the patients were significantly decreased along with the decrease of mean arterial pressure.

CONCLUSIONS: Serum FGF23 level is positively correlated with mean arterial pressure and negatively correlated with glomerular filtration rate. So, FGF23 has an important clinical significance that can reflect blood pressure and treatment effect of dialysis of CKD patients.

Key Words:
Chronic kidney disease, FGF23, Glomerular filtration rate.

Introduction

Chronic kidney disease is usually developed in patients with glomerular nephritis, nephropyelitis, and lupus nephritis. The glomerular filtration rate is continuously decreased along with the development of disease[1]. It is usually neglected by clinicians because of inconspicuous development of CKD[2-4]. Also, during chronic kidney disease, myocardial hypertrophy can be caused by many factors with the development of the disease. These factors may indirectly induce systemic changes in heart along with altered blood pressure, anemia, inflammation, etc. Furthermore, phosphate metabolic disorder is another prominent risk factor responsible for mortality of patients with CKD[5]. Recently, two phosphorylation regulatory genes including fibroblast growth factor 23 (FGF23) and Klotho gene have been proved to be responsible for cardiac remodeling in CKD patients[6]. In this study, ELISA was used to detect serum FGF23 expression levels during chronic kidney disease and the relationships between FGF23 expression levels and mean arterial pressure, and glomerular filtration rate were analyzed.

Patients and Methods

Inclusion Criteria

(1) The diagnostic standards of CKD described in K/DOQI; (2) the age of enrolled patients and healthy control subjects ≥ 18 years old.

Exclusion Criteria

(1) Nephritis, arterial dissection caused by high blood pressure; (2) Combined with myocardial infarction or aortic aneurysm, aortic dissection, cerebral hemorrhage, stroke, cytoplasmic tumor, thyroid dysfunction and other diseases that affect arterial blood pressure or secondary hypertension; (3) the patients who have undergone surgery, car accident, trauma or infection in other parts recently; (4) the patients with cognitive disorder or mental disorder; (5) the patients did not provide enough clinical serum samples; (6) with alcoholic liver disease, drug-induced hepatic disease and autoimmune liver disease; (7) bleeding and blood coagulation mechanism dysfunction; (8) in-coordination of patients and their families.

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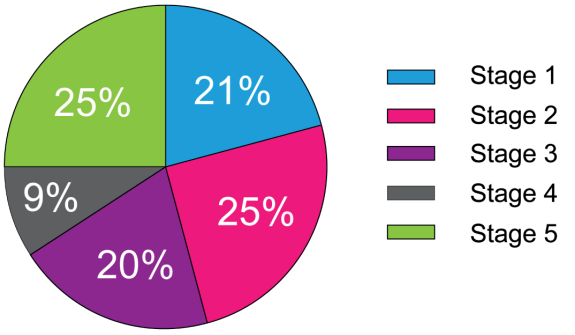

Figure 1. Distribution of clinical stages for the enrolled patients with CKD.

Clinical Data

The clinical data of 128 CKD patients including 55 males and 73 females were collected. The age of patients ranged from 28 to 68 years old with an average age of 48.7±2.3 years. The course of disease was from 8 to 8.5 years with a median disease course of 4.5 years. CKD was confirmed by histopathology, laboratory detection and imaging. This study was approved by Ethics Committee of Fuzhou General Hospital.

Enzyme-linked Immunosorbent Assay of Serum FGF23 (ELISA)

FGF43 was detected using ELISA kit (Abcam, Cambridge, MA, USA) according to the manufacturer's instructions. Relevant software was utilized to draw a standard curve, and serum FGF23 level was calculated. If the patients were treated with dialysis therapy, the levels of serum FGF23 before and after dialysis were recorded, respectively.

24 h Ambulatory Blood Pressure Monitoring Method

The non-invasive method was used to indirectly monitor 24 h ambulatory blood pressure and recorded the mean arterial pressure.

Staging Method of CKD[7]

The CKD staging was performed according to the new method established by National Kidney Foundation (Table I).

Statistical Analysis

SPSS19.0 software (Version X; IBM, Armonk, NY, USA) was used for statistical analysis. $p<0.05$ was considered to be statistically significant.

Results

Comparison of Baseline Clinical Data Between Patients and Healthy Control Subjects

Statistical analysis of the age, weight, BMI and other baseline data between 128 CKD patients and 128 healthy control subjects showed no significant statistical difference ($p>0.05$). See Table II.

Staging of Kidney Function of Enrolled Patients

We divided 128 CKD patients into different stages according to methods established by National Kidney Foundation K/DOQI, and there were 27 patients in stage 1, 32 patients in stage 2, 25 patients in stage 3, 12 patients in stage 4 and 32 patients in stage 5. See Table III and Figure 1.

Serum FGF23 Levels of Enrolled Patients and Healthy Control Subjects

The serum FGF23 levels of CKD patients were significantly higher than those of the control subjects ($p<0.05$). See Tables IV and V.

Spearman-Related Analysis

The Spearman-related analysis showed that the serum FGF23 level was positively correlated with mean arterial pressure and negatively correlated with GFR. However, the mean arterial pressure had no significant correlation with GFR ($p>0.05$) (see Table VI, Table VII, Figure 2 and Figure 3).

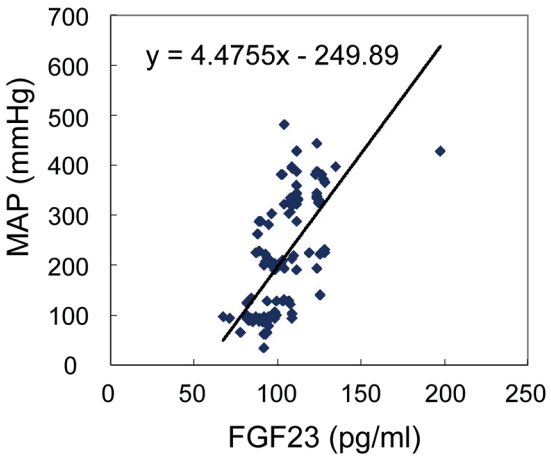

Figure 2. Correlation analysis between FGF23 and MAP: y = 4.4755x - 249.89.

Table I. CKD staging method of national kidney foundation K/DOQI expert group.

Staging	Description	GFR [ml/(min▪1.73 m²)]	Explanation
1	Renal injury index (+) GFR normal	> 90	GFR has no abnormality, and the primary illness was emphasized
2	Renal injury index (+) GFR slightly decreased	60-89	The advancing of CKD was slowed down, and the risk of angiocardiopathy was reduced
3	GFR moderately decreased	30-59	The advancing of CKD was slowed down, and the complications were evaluated and treated
4	GFR severely decreased	15-29	The comprehensive treatment method was adopted to cure complication
5	Kidney failure	<15 or dialysis	Pre-dialysis preparation and dialysis treatment

Table II. Baseline data comparison of enrolled patients ($\bar{x}\pm s$).

Groups	Cases	Age (year)	BMI (kg/m²)	Operation time (min)	Blood loss volume (ml)	MAP (mmHg)
CKD group	128	44.5±12.7	20.7±1.2	192.3±27.4	178.3±22.9	118.3±12.4
Healthy control group	128	51.6±10.8	21.2±1.3	-	-	76.5±10.9
t-value	-	0.33	1.29	0.83	0.39	21.43
p-value	-	0.47	0.22	0.28	0.39	0.02

Impact of Blood Dialysis Treatment on Serum FGF23 Level and Mean Arterial Pressure

Among all the patients, 32 patients in stage 5 were treated with hemodialysis treatment. We recorded serum FGF23 levels and mean arterial pressure before and after the hemodialysis treatment. The results showed that FGF23 and MAP were significantly lower after hemodialysis treatment than those before treatment, (p<0.05). See Table VIII for details.

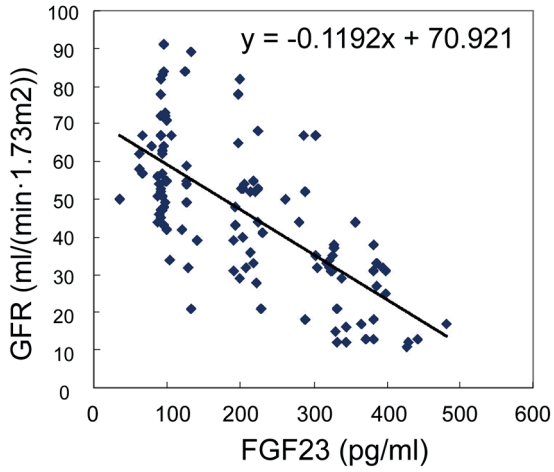

Figure 3. Correlation analysis between FGF23 and GFR: y = -0.1192x + 70.921.

Table III. Kidney function staging of enrolled patients.

Stage 1	Stage 2	Stage 3	Stage 4	Stage 5
27	32	25	12	32

Table IV. Comparison of serum FGF23 level between enrolled patients and healthy control subjects.

Groups	Cases	FGF23 (pg/ml)
CKD group	128	337.4±67.3
Healthy control group	128	12.46±7.48
t-value	-	51.27
p-value	-	<0.001

Discussion

Fibroblast growth factor 23 (FGF23) is a protein with a molecular weight of 32kDa. The main role of FGF23 is to regulate phosphate and inhibit the conversion of 25-hydroxyvitamin D to its active form 1,25-dihydroxyvitamin D by increasing urinary phosphorus excretion. The decreased of blood 1,25-dihy-

Table V. Comparison of serum FGF23 and other biochemical indexes in enrolled patients of different CKD stage.

Groups	Cases	FGF23 (pg/ml)	Cr (μmol/L)	Ca2+ (mmol/L)	P3- (mmol/L)	CRP (mg/L)	1,25-(OH)2-VitD3 (pmol/l)	PTH (pg/L)	BUN (mmol/L)
1	27	89.7±12.5	187.4±21.7	1.81±0.18	2.78±0.49	4.38±0.28	31.27±2.7	291.4±10.5	5.2±0.3
2	32	112.3±11.8	204.3±35.4	1.94±0.16	2.51±0.36	9.58±0.33	28.27±1.9	387.5±12.7	7.9±0.5
3	25	187.6±19.5	265.4±38.7	2.01±0.24	1.97±0.27	10.25±0.92	21.23±2.6	401.7±11.5	8.4±0.8
4	12	203.4±21.3	339.5±29.5	2.29±0.21	1.87±0.58	14.29±1.32	18.36±3.1	466.4±19.3	10.8±2.4
5	32	317.5±21.7	827.6±88.3	2.67±0.28	1.82±0.49	18.38±2.48	14.27±4.5	489.5±28.7	18.6±1.5
F	0.27	29.4	28.3	30.5	31.4	21.5	20.8	22.8	27.1
p	0.33	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Table VI. Spearman-related analysis results (r).

Index	Gender	Age	Disease course (month)	MAP (mmHg)	GFR (ml/[min▪1.73m^2])	Hb (g/L)	ALB (g/L)	Cr (μmol/L)	BUN (mmol/L)	BMI (kg/m^2)
FGF23										
r	0.02	0.35	0.17	4.5	-0.12	0.24	0.15	0.06	0.38	0.14
p	>0.05	>0.05	<0.05	<0.05	<0.05	>0.05	>0.05	>0.05	>0.05	>0.05

Index	Ca^{2+} (mmol/L)	P3-(mmol/L)	CRP (mg/L)	1,25-(OH) 2-VitD3 (pmol/l)	PTH (pg/L)
FGF23					
r	0.35	0.17	0.16	0.28	0.24
p	<0.05	<0.05	>0.05	>0.05	>0.05

Table VII. Multi-variable linear return analysis.

Variables	β	SE	β′	*t*	*p*	(95% CI) Upper limit	(95% CI) Lower limit
MAP	0.531	0.14	0.764	20.412	<0.05	0.26	0.81
GFR	0.581	0.10	0.642	10.652	<0.05	0.39	0.78
Ca2+	0.768	0.08	0.871	0.981	>0.05	0.61	0.92
P3-	0.872	0.02	0.382	0.782	>0.05	0.58	0.97

Table VIII. Impact of hemodialysis treatment on serum FGF23 and mean arterial pressure.

	Cases	Before dialysis	After dialysis	*t*-value	*p*-value
FGF23	32	437.8±87.3	192.3±24.3	19.27	0.002
MAP		124.3±22.1	89.2±12.5	18.32	0.003

droxyvitamin D can lead to the increased absorption of phosphorus in the gastrointestinal tract, which in turn cause secondary hyperparathyroidism. Therefore, the normal levels of FGF23 have an important function in maintaining the normal function of endocritic axis in human body. Moreover, it's also helpful in maintaining mineralization of healthy bones and calcium-phosphorus metabolism. However, the above balance was disturbed in CKD patients. As kidney filtration function was significantly decreased in CKD patients, the serum FGF23 level was increased, leading to the increased secretion of phosphate, which in turn caused electrolyte disturbance in CKD patients. The disturbed electrolyte balance can lead to high blood pressure as observed in the present study. Previous studies also showed that the high serum FGF23 levels had a certain correlation with the occurrence of angiocardiopathy, including ischemic heart disease, stroke, heart failure, atrial fibrillation, etc. The phosphate/vitamin D axis malfunction was conside-

red as one of important step for the development of CKD, which is responsible for angiocardiopathy. It's also found that high phosphate levels in serum might lead to the significantly increased mortality rate of CKD patients[2,3]. We further found that FGF23 was correlated with the all-cause mortality of end-stage kidney disease patients, especially for the patients in in CKD2-4-stage[4-7]. In the cross-sectional study, we found that the increase in mortality rate of CKD patients had a certain correlation with the development of angiocardiopathy[8,9]. Our study also showed that, the mean arterial pressure of long-stage CKD patients was significantly increased ($p<0.05$), and the increased level of blood pressure was positively correlated with the level of FGF23. So, FGF23 can be considered as one of indexes to indicate the possibility of angiocardiopathy in kidney failure, which will improve the diagnosis and treatment. Previous studies[10-12] discussed the effect of FGF23 on high blood pressure, heart failure and arrhythmia by animal experiments. It has been found that the role of FGF23 in promoting cardiovascular disease is essentially through the activation of the renin-angiotensin-aldosterone system, which promotes the reabsorption of sodium in the distal renal tubules, leading to high blood pressure, further causing cardiac hypertrophy and arrhythmia[13-15]. Also, FGF23 could regulate the balance between body phosphate and vitamin D to a certain extent. However, it might indirectly stimulate the occurrence of angiocardiopathy in CKD patients[16-20]. We also noticed that FGF23 was correlated with MAP and GER. Also, the mean arterial pressure and serum FGF23 levels in-patient with kidney failure were significantly improved after dialysis treatment.

Conclusions

Early CKD should be actively prevented and symptomatic treatment should also be applied. Patients with end-stage CKD should be treated with dialysis, which can significantly improve the patients' living quality and prevent angiocardiopathy.

Conflict of Interest

The Authors declare that they have no conflict of interest.

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