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Original Article

Changes and significance of serum FGF21 in children with primary nephrotic syndrome and chronic renal failure

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Abstract: Objective: The aim of the study was to investigate the changes and significance of serum fibroblast growth factor 21 (FGF21) in children with primary nephrotic syndrome (PNS) and chronic renal failure. Methods: Pediatric patients with active PNS and normal renal function (the nephrotic syndrome group), pediatric patients with chronic renal failure (the renal failure group), and children who had healthy physical examinations (the control group) were included. The serum levels of FGF21, total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL-C), and low-density lipoprotein (LDL-C) were measured by enzyme-linked immunosorbent assay (ELISA), and the serum albumin and 24 h urine protein were measured in the PNS group. Results: Compared with the normal control group, the level of serum FGF21 in the PNS group and the renal failure group increased significantly ($P < 0.05$). The TC, TG, HDL-C, and LDL-C levels increased significantly in the PNS group ($P < 0.05$). The levels of TG and HDL-C increased significantly in the renal failure group ($P < 0.05$). The levels of TC, HDL-C, and LDL-C in the renal failure group were lower than those in the PNS group ($P < 0.05$). There was no significant difference in TG level between the two groups ($P > 0.05$). Conclusion: The level of serum FGF21 may be correlated with the occurrence and development of nephrosis in children. The higher the level of serum FGF21, the more serious the renal injury.

Keywords: Primary nephrotic syndrome, fibroblast growth factor 21, serum lipid, renal failure, children/kids

Introduction

Chronic kidney disease (CKD) is a common chronic disease. According to oversea statistics, about 2% of patients with CKD will develop chronic renal failure. In the last century, more than two million children had nephrotic diseases in China. The incidence of nephrotic syndrome was also higher in children with renal disease. The annual incidence was 2-7 in every 100,000 children, and the morbidity was 1.2-1.6/10,000 [1]. Because of the insidious onset and slow development of the disease in children, some pediatric patients may develop chronic renal failure. In some cases of the steroid hormone-resistance type of the primary nephrotic syndrome (PNS), with the development of the disease, renal failure can be caused by the impairment of renal function. Some patients with a nephrotic syndrome develop hyperlipidemia. The abnormal metabolism of the serum lipids in these patients can accelerate the progress of the nephrotic syndrome.

In 2000, Japanese researchers Nishimura et al. [2] first detected the transcription product fibroblast growth factor 21 (FGF21) gene in mouse embryonic tissue. The protein of mouse FGF21 consists of 210 amino acids with a typical signal peptide composed of 30 amino acids at the amino-terminal. The human FGF21 protein is a peptide composed of 181 amino acids with the N-terminal containing a signal peptide sequence composed of 28 amino acids [3].

In recent years, studies on FGF21 and CKD have shown that FGF21 can prevent lipotoxicity and early renal injury induced by diabetes.

Zhang et al. [4] established the lipotoxic mouse model and Type 1 diabetic mouse model, respectively. It was found that FGF21 could prevent lipotoxicity and early apoptosis of renal cells, together with the hypertrophy and renal dysfunction induced by diabetes. In the FGF21-KO mice, it was found that lipotoxicity and diabetes might cause serious renal damage. By intraperitoneal injection of FGF21, lipotoxicity and renal damage could be significantly reduced [5]. Stein et al. [6] also suggested that serum FGF21 might be correlated with renal excretion in patients with long-term hemodialysis. Lee et al. [7] studied 1,136 patients with Type 2 diabetes in China and carried out follow-up examinations for four years. It was found that the elevated level of serum FGF21 could be used as a biomarker to predict the progress of renal diseases, especially for early diabetic nephropathy. It was suggested that FGF21 was expressed in the kidney [5]. With the progress of CKD, the level of FGF21 increased gradually, suggesting that FGF21 could be a sensitive biological index to predict the progress of CKD. At present, FGF21 has been studied more in Type 2 diabetes, diabetic nephropathy, cardiovascular disease, nonalcoholic fatty liver, and other diseases in adults, but less in children. The level and significance of serum FGF21 in pediatric patients with PNS and chronic renal failure remain unclear. We hypothesized that FGF21 might be correlated with lipid metabolism disorder in children with PNS and with the progression of CKD.

Research subjects and methods

Research subjects

The renal disease group: From March 2016 to February 2017, 22 male and four female pediatric patients with PNS admitted to the First Affiliated Hospital of Jinan University were enrolled in the PNS group. The average age of these patients was 5.90±3.68 years. Five male and six female pediatric patients with chronic renal failure were enrolled in the renal failure group. The average age of these patients was 11.26±2.89 years. The primary renal failure diseases were as follows: three cases of PNS, three cases of ANCA-related vasculitis, one case of hemolytic uremia, one case of systemic lupus erythematosus nephritis, one case of congenital nephrotic syndrome, one case of congenital urinary tract malformation and one case of unknown etiology. In the renal failure group, four cases were treated with peritoneal dialysis and seven cases with hemodialysis. This study was conducted with approval from the Ethics Committee of the First Affiliated Hospital of Jinan University (No: 2017-017). All the guardians gave consent to conduct the study and signed informed consent.

For the control group, 14 males and six females who had undergone physical examination in the outpatient department of our hospital were enrolled. The average age of these patients was 6.84±3.62 years. There was no significant difference in gender, age, or body weight between children in the control group and those in the PNS group. Thus, the data were comparable. There was no abnormality in the detection of hepatic and renal function, no history of primary and secondary kidney diseases, other metabolic diseases, or family history.

The inclusion criteria for the primary nephrotic syndrome: (1) Age < 18 years old. Unlimited for males and females. (2) The diagnostic criteria for PNS: 1. Large amount of proteinuria (urine protein+++ - ++++), three times a week with the 24 h urine protein ≥ 50 mg/kg, the urine protein/creatinine ration (mg/mg) ≥ 2.0; 2. Hypoalbuminemia (serum albumin < 25 g/L); 3. Hyperlipidemia (serum cholesterol > 5.7 mmol/L); 4. Different degrees of edema.

The exclusion criteria for the primary nephrotic syndrome: Congenital nephrotic syndrome; Secondary nephrotic syndrome, including the acute glomerulonephritis, systemic lupus erythematosus nephritis, Henoch-Schönlein purpura nephritis, hepatitis B virus-related nephritis, drug-induced nephritis, Alport syndrome and other nephrotic syndromes secondary to systemic diseases.

Methods

Sample collections: The blood samples were collected in the morning under fasting conditions. The age, gender, and medical history of the patients were discussed and recorded. The height and body weight were measured, and 2 ml of elbow venous blood was drawn in patients who met the inclusion criteria. The blood sample was injected into the coagulator tube and placed at room temperature for two

Table 1. Comparison of gender, age and weight in each group

Groups	n	Gender (M/F)	Age (year)	Weight (kg)
PNS	26	22/4	5.90±3.68[a]	24.17±13.51
Renal failure	11	5/6	11.26±2.98[c]	25.76±7.40
Control	20	14/6	6.84±3.62[b]	26.51±16.72
P		0.054	0.002	0.267

Note: a: Comparison of the PNS group and the control group, P > 0.05; b: Comparison of the Renal failure group and the control group, P < 0.05; c: Comparison of the Renal failure group and the PNS group, P < 0.05.

Table 2. Comparison of serum FGF21 levels in different groups

Groups	n	FGF21	z	p
PNS	26	289.65±430.03	2.93	0.003*
Renal failure	11	2605.89±3269.11	3.56	0.000**
Control	20	71.51±68.96	4.42	0.000***

Note: *Comparison of the PNS group and the control group, P < 0.05; **Comparison of the Renal failure group and the PNS group, P < 0.05; ***Comparison of the Renal failure group and the control group, P < 0.05.

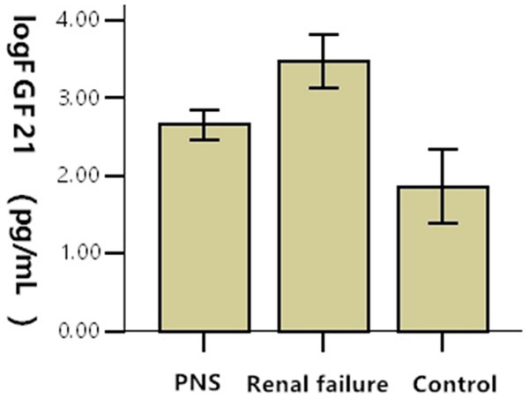

Figure 1. Comparison of serum FGF21 in different groups.

hours or 4°C overnight, and centrifuged for 15 min at 3000 r/min. The supernatant was taken and divided into three parts, each of which was 100 u/L. One part was used for the detection of low-density lipoprotein (LDL-C), triglyceride (TG), total cholesterol (TC), and high-density lipoprotein (HDL-C). The other two parts were stored in a -80°C refrigerator for the unified determination of FGF21.

Assay of the biochemical indexes: The lipid profiles and other indexes, including TC, TG, HDL-C, and LDL-C serum albumin, and 24 h urine protein were detected by the test center of the First Affiliated Hospital of Jinan University.

FGF21 was assayed by the human FGF21 enzyme-linked immunosorbent assay (ELISA) kit 96T×2 (R&D Company, USA). The ELISA method was performed according to Engvall et al. [8]. For quantitative determination of antigens, the radioimmunosorbent technique (RIST) (Wide and Porath, 1966) was used.

Statistic analysis

SPSS 17.0 software was adopted for statistical analysis. The measurement data were expressed as mean ± standard deviation. The Wilcoxon rank-sum test was used to compare two independent samples, and the K-W-H test was used to compare multiple independent samples. The Spearman correlation analysis was used to analyze the correlation between the serum FGF21 level and the blood lipid profiles. $P < 0.05$ was considered statistically significant.

Results

Comparison of the general clinical characteristics

In the present study, there were 26 cases of PNS, 11 cases of chronic renal failure, and 20 cases of normal control.

As shown in **Table 1**, there was no significant difference in the composition ratio of gender and body weight between the groups (P = 0.054 and 0.267, respectively). The differences in age between two groups by pairwise comparison were statistically significant (P = 0.000 and P = 0.003, respectively). There was no significant difference in age between the PNS group and the control group (P = 0.34).

Comparison of FGF21 between the groups

It was demonstrated in **Table 2** that there were significant differences in the serum FGF21 between groups by the pairwise comparison among the PNS group, the renal failure group and the control group (Z = 2.93, 3.56 and 4.42, respectively and P = 0.003, 0.000 and 0.000, respectively) (**Figure 1**).

Table 3. Comparison of serum FGF21 between peritoneal dialysis group and hemodialysis group

Groups	n	FGF21
Hemodialysis	7	3543.04±3856.17
Peritoneal dialysis	4	965.88±497.92
P		0.927

The serum FGF21 levels in the PNS group and renal failure group were higher than that in the control group, and serum FGF21 levels in the renal failure group were significantly higher than those in the PNS group and the control group (**Figure 1**, $P = 0.000$).

As shown in **Table 3**, there were four cases in the peritoneal dialysis group and seven cases in the hemodialysis group. The serum FGF21 levels in the two groups were 965.88±497.92 mmol/L and 3543.04±3856.17 mmol/L, respectively. There was no significant difference in the serum FGF21 level between the two groups ($Z = 0.189$, $P = 0.927$).

When assigning the control group into the < 6-year-old subgroup and the > 6-year-old subgroup, we found no significant difference in the serum level of FGF21 (93.69±28.86 vs. 58.47±17.53 mmol/L, $P = 0.292$).

Comparison of the serum lipid profiles between the groups

The levels of serum lipid in patients at different ages: (1) < 6 years old: TC: 10.19±5.67 mmol/L; TG: 2.57±1.99 mmol/L; HDL-C: 2.00±0.93 mmol/L; LDL-C: 5.30±3.68 mmol/L. (2) > 6 years old: TC: 10.55±5.15 mmol/L; TG: 2.42±1.69 mmol/L; HDL-C: 2.00±0.84 mmol/L; LDL-C: 5.30±2.49 mmol/L. There was no significant difference in the blood lipid levels among pediatric patients with nephrotic syndrome of different ages ($P > 0.05$). Thus, for the statistical analysis of the blood lipid levels, the patients were not divided into different age groups.

As shown in **Table 4**, there were statistically significant differences in the levels of TC, HDL-C, and LDL-C between the pediatric patients with PNS and those with chronic renal failure ($Z = -2.96, -3.19, -3.17$, respectively and $P = 0.002$, 0.001, and 0.001, respectively), and there was no significant difference in the levels of TG ($P > 0.05$). There were significant differences in the levels of TG and HDL-C between the pediatric patients with chronic renal failure and the control group ($Z = -4.32$ and -2.07, respectively; $P = 0.000$ and 0.04, respectively). There was no significant difference in the levels of TC and LDL-C ($P > 0.05$). There were significant differences in the levels of TC, TG, HDL-C, and LDL-C between the pediatric patients with PNS and the control group ($P < 0.05$).

When dividing the control group into the < 6-year-old subgroup and the > 6-year-old subgroup, no significant difference in serum lipid profiles was observed (TC: 4.47±0.21 vs. 4.24±0.17 mmol/L; TG: 0.74±0.07 vs. 1.00±0.11 mmol/L; LDL-C: 2.64±0.19 vs. 2.15±0.16 mmol/L; HDL-C: 1.29±0.08 vs. 1.52±0.13 mmol/L, all $P > 0.05$).

Also, when assigning the PNS group into the < 6-year-old subgroup and the > 6-year-old subgroup, we found no significant difference in serum lipid profiles (TC: 10.19±5.67 vs. 10.55±5.15 mmol/L; TG: 2.57±1.99 vs. 2.42±1.69 mmol/L; HDL-C: 2.00±0.93 vs. 2.00±0.84 mmol/L; LDL-C: 5.30±3.68 vs. 5.30±2.49 mmol/L, all $P > 0.05$).

As all children with renal failure were above 6 years old, we did not analyze the serum FGF21 level and lipid profiles in different age groups.

Correlation between the serum lipid profiles and albumin, 24 h urine protein in patients with nephrotic syndrome

It can be seen from **Table 5** that TC, TG, and LDL-C were all negatively correlated with serum albumin in pediatric patients with PNS ($R = -0.805$, -0.707 and -0.855, respectively, and $P = 0.000$ in all), as shown in **Figures 2**-**4**. There was no correlation between the serum albumin and HDL-C in pediatric patients with PNS ($R = 0.154$, $P = 0.453$). There was no correlation between TC, TG, HDL-C, LDL-C, and 24 h urinary protein in pediatric patients with PNS ($P > 0.05$).

The correlation between serum FGF21 and serum lipid profiles in each group, and the correlation between serum FGF21 and albumin, 24 h urinary protein in the nephrotic syndrome group

As demonstrated in **Table 6**, there were no correlations between FGF21 and the four items of

Table 4. Statistical *p* value and mean ± standard deviation for comparison of blood lipids (mmol/L) in different groups

Groups	TC	TG	HDL	LDL
PNS	10.34±5.35	2.61±1.84	2.01±0.88	5.23±3.17
Renal failure	5.51±1.73	2.73±1.73	1.23±0.53	2.42±1.07
Control	4.34±0.59	0.88±0.32	1.42±0.36	2.37±0.59
PNS	0.002*	0.857*	0.001*	0.001*
Renal failure	0.072**	0.000**	0.040**	0.730**
Control	0.000***	0.000***	0.002***	0.000***

Note: *Comparison of the renal failure group and the PNS group, P < 0.05; **Comparison of the renal failure group and the control group, P < 0.05; ***Comparison of the PNS group and the control group, P < 0.05.

Table 5. Correlation between serum lipid level and albumin (g/L) and 24 hour urinary protein (mg/kg.d) in patients with PNS group

PNS group	TC	TG	HDL	LDL
Albumin	r = -0.805	r = -0.707	r = 0.154	r = -0.855
	P = 0.000	P = 0.000	P = 0.453	P = 0.000
24 h urinary protein	r = -0.011	r = 0.066	r = 0.187	r = -0.161
	P = 0.956	P = 0.749	P = 0.360	P = 0.432

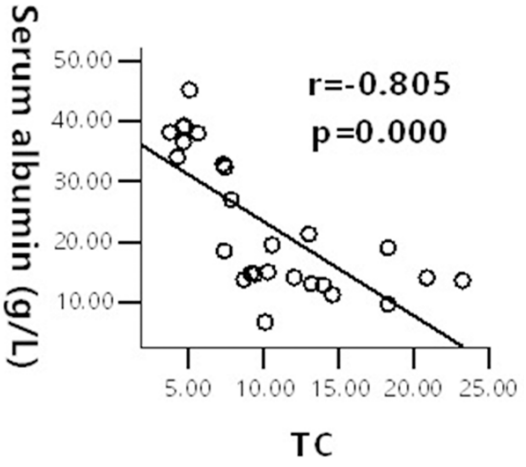

Figure 2. The relationship between TC and serum albumin in children with primary nephropathy.

blood lipid (TC, TG, HDL-C, LDL-C), albumin, and 24 h urinary protein in pediatric patients with PNS. There were also no correlations between the serum FGF21 and TC, TG, HDL-C, and LDL-C in children of the renal failure group and the control group.

Discussion

The results of the present study demonstrated that the serum levels of TC, TG, HDL-C, and LDL-C in pediatric patients with active PNS were higher than those in the control group. At the same time, it was confirmed that TC, TG, and LDL-C were negatively correlated with serum albumin in pediatric patients with active PNS. The higher the level of blood lipid in the body, the more serious the hypoalbuminemia. These findings were consistent with the report on 378 pediatric patients with PNS and 200 healthy children by Peng et al. [9]. Hypoalbuminemia can cause a decrease in plasma colloid osmotic pressure and stimulate the increased synthesis of hepatic LDL-C. Meanwhile, it can also lead to the decrease of LDL-C scavenging enzymes and an increase in the level of TG and LDL-C [10], which are closely correlated with hyperinsulinemia under fasting conditions and can increase the risk of hyperlipidemia (HLP) [11]. Excessive lipid deposition in the glomerular or tubular extracellular matrix can stimulate the formation of foam cells, cause glomerulosclerosis and tubulointerstitial injury, and eventually develop into chronic renal failure. Meanwhile, renal impairment also affects lipid metabolism. Peng et al. [9] found that TC, HDL-C, and LDL-C were positively correlated with urinary protein. However, there was no correlation between blood lipids and urinary protein in the present study, which might be due to a deviation caused by the small sample size. Jiao et al. [12] confirmed that there was a significant negative correlation between the degree of hypoalbuminemia and the level of urine protein via experiments in rats. In the present study concerning the albumin and 24 h urine protein in 26 pediatric patients with active PNS, we failed to find any correlation between the above two factors.

In the present study, pediatric patients with chronic renal failure were treated with dialysis, including four cases with peritoneal dialysis and seven cases with hemodialysis. Compared with those in the control group, the difference in TG and HDL-C in pediatric patients with renal failure was statistically significant, especially the increase of TG, which indicated that there was lipid metabolism disorder in pediatric patients with renal failure, and the finding was

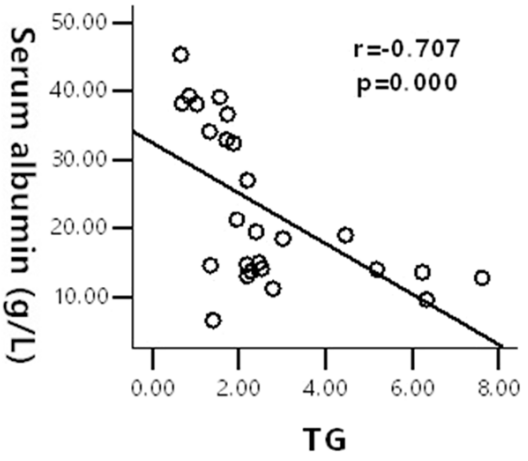

Figure 3. Correlation between serum albumin and TG in children with primary nephrotic syndrome.

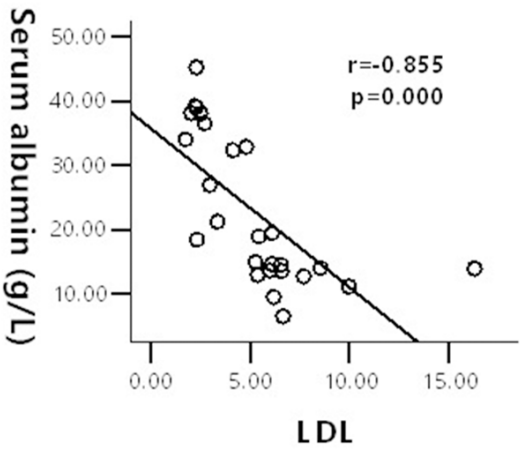

Figure 4. Correlation between serum albumin and LDL in children with primary nephrotic syndrome.

consistent with the research results of Cheng et al. [13]. Chen et al. [5] investigated 200 patients with CKD and 36 mice, and found that with the progress of CKD, the level of serum FGF21 in patients gradually increased. At the same time, they also found that with the increase of the intervention dose of FGF21, the degree of kidney injury in mice models with CKD increased. The kidneys are the main organs used to eliminate FGF21, but FGF21 cannot be effectively eliminated by blood purification. Stein et al. [6] also suggested that the serum FGF21 might be correlated with renal excretion by investigating patients with long-term hemodialysis. In the present study, the level of serum FGF21 in the PNS group and the renal failure group was significantly higher than that in the control group, with the highest level being found in the renal failure group. There were statistically significant differences in the level of serum FGF21 when performing the pairwise comparison among the PNS group, the renal failure group, and the control group. The reason for the increase of serum FGF21 in the renal failure group could be because that the molecular weight of FGF21 is relatively large at approximately 20 kDa [14], and conventional low flux hemodialysis cannot clear the medium and large molecules in the blood [15]. In pediatric patients with chronic renal failure, excess FGF21 cannot be excreted via the urine, which eventually leads to the accumulation of serum FGF21 in the body. Cheng et al. [13] found that the level of FGF21 in patients with end-stage renal disease and residual renal function was significantly lower than that in patients without residual renal function, so the kidney can be considered to be the main organ to excrete FGF21. The present study also revealed that the level of serum FGF21 in the peritoneal dialysis group was lower than that in the hemodialysis group, although there was no significant difference between the two groups. It should be noted that the sample numbers were small, so the difference might become statistically significant if the sample size was increased. The significant increase of serum FGF21 in the PNS group and the renal failure group might also be due to the increase of compensatory production of FGF21 in order to meet the needs of metabolic disorders caused by these diseases. It might also be due to the resistance of the body to the action of FGF21 caused by PNS, resulting in the increase of compensatory production of FGF21. It was found through the above analysis that with the aggravation of the injury to renal function, the ability to clear serum FGF21 level in vivo would become weaker.

Animal studies have found that serum FGF21 can significantly regulate the levels of blood glucose and lipid [16], increase insulin sensitivity [17], protect the function of islet β cells [18], and reduce the risk of cardiovascular disease [19]. In the present study, it was found that the serum levels of FGF21 and lipids in pediatric patients with active PNS and those with chronic renal failure were increased, with the highest serum FGF21 recorded in pediatric patients with renal failure. There was no corre-

Table 6. The correlation between logarithm of FGF21 and serum lipid (mmol/L) in each group

Item	TC	TG	HDL	LDL	Albumin	24 h urinary protein
PNS	r = 0.202	r = 0.064	r = 0.204	r = 0.069	r = -0.122	r = -0.168
	P = 0.321	P = 0.757	P = 0.317	P = 0.737	P = 0.551	P = 0.411
Renal failure	r = 0.196	r = 0.337	r = 0.460	r = 0.041	-	-
	P = 0.564	P = 0.311	P = 0.154	P = 0.905		
Control	r = -0.314	r = -0.172	r = -0.094	r = -0.208	-	-
	P = 0.178	P = 0.468	P = 0.692	P = 0.380		

lation between the serum levels of FGF21 and the levels of TC, TG, HDL-C, and LDL-C in pediatric patients with active PNS and those with chronic renal failure. In pediatric patients with PNS, glomerulus and podocytes are injured in the active phase with more serious renal injury in pediatrics with chronic renal failure. It could be inferred that serum FGF21 could be correlated with the degree of renal injury. However, whether the increased serum FGF21 level in these two groups of patients is due to the impairment of renal function, or whether the increased serum FGF21 level aggravates renal injury remains unclear.

Limitations in the present study

There were some limitations in this study. (1) The sample size was small, and there might exist some experimental deviations. (2) As a cross-sectional and observational study, we could only investigate the association between various parameters, rather than evaluate the pathogenesis. (3) The serum samples from pediatric patients with PNS after recovery were not studied in the present study, and the changes of FGF21 in children could not be observed dynamically. The above problems are expected to be improved in future research. (4) The mean age of patient with renal failure was significantly older than that in the other two groups. Whether age would affect the serum level of FGF21 and lipid profiles needs to be explored in future studies.

Conclusion

The level of serum FGF21 in pediatric patients with active PNS possessing normal renal function was significantly higher than that in the control group, and the level of serum FGF21 in pediatric patients with chronic renal failure was significantly higher than that in the nephrotic group and the control group. The more serious the renal injury is, the higher the level of serum FGF21 would be. The level of serum FGF21 in pediatric patients with PNS may be correlated with the degree of renal injury.

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This study was conducted with approval from the Ethics Committee of the First Affiliated Hospital of Jinan University (No: 2017-017). This study was conducted in accordance with the declaration of Helsinki. All the guardians gave consent to conduct the study and signed informed consent.

Disclosure of conflict of interest

None.

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