Significance of changes in FGF23 levels in childhood primary nephrotic syndrome and children who progress to end-stage renal disease

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Abstract. Fibroblast growth factor 23 (FGF23) is an important phosphaturic hormone, yet few studies have focused on FGF23 in children with primary nephrotic syndrome (PNS) and children who progressed to end-stage renal disease (ESRD). This cross-sectional study investigated the significance of changes in FGF23 levels in childhood PNS and children who progressed to ESRD. Of the 41 children included in the study, 17 had PNS with proteinuria and normal renal function (PNS group), 4 had ESRD (ESRD group), and 20 were healthy (control group). Following corticosteroid treatment, patients with PNS and proteinuria entered the remission phase. Serum levels of FGF23, phosphate, parathyroid hormone (PTH), 25-hydroxyvitamin D (25-OH-D), and calcium were measured. It was found that FGF23 levels in the PNS and ESRD groups were higher than those in the control group, while serum 25-OH-D levels were lower. Serum PTH levels increased significantly in the ESRD group. In the control group, FGF23 levels were negatively correlated with serum PTH and positively correlated with serum 25-OH-D. FGF23 levels were positively correlated with serum calcium and corrected calcium levels in children with PNS during the remission phase. Increased FGF23 levels in children with PNS, particularly in children who progressed to ESRD. It was also confirmed that serum FGF23 levels begin to rise in children with PNS prior to Stage 1 chronic kidney disease. These findings indicated that increased FGF23 levels may be associated with the progression and severity of nephrosis in children, and that serum FGF23 levels were useful for early detection of abnormal mineral metabolism in children with PNS.

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Abbreviations: 25-OH-D, 25-hydroxy vitamin D; cCa, albumin-corrected calcium; CKD, chronic kidney disease; ESRD, end-stage renal disease; FGF, fibroblast growth factor; GFR, glomerular filtration rate; PNS, primary nephrotic syndrome; PTH, parathyroid hormone

Key words: PNS, FGF23, mineral metabolism, ESRD, children

Introduction

Primary nephrotic syndrome (PNS) is a chronic kidney disease (CKD) commonly seen in children, with an estimated incidence of 20-70 cases per 1,000,000 individuals and a prevalence of 160 per million individuals (1). Its age of onset is typically around 3-5 years of age, and it occurs more frequently in boys than in girls. Steroid therapy is effective in 85-90% of children with PNS and these children do not progress to renal failure. As its course is prolonged, steroid-resistant nephrotic syndrome (SRNS) is prone to develop to end-stage renal disease (ESRD). ESRD has an incidence of 4.0-17.5 per million individuals and a prevalence of 4.9-38.7 per million individuals in children (2). The ESRD-related mortality rate ranges from 25.0-27.1% (3). Additionally, ESRD is a significant economic burden on society and families. Certain children with PNS gradually progress to ESRD given the insidious nature of the early stages of the disease and a lack of specific predictors. Following long-term therapy, children with PNS may develop mineral metabolism disorder (4).

Fibroblast growth factor (FGF)23 is a phosphaturic hormone that plays a pivotal role in mineral metabolism homeostasis. FGF23 predominantly binds to FGF receptor 1 (FGFR1) (5). The transmembrane protein klotho is a co-factor that enhances cell surface interactions (primarily with FGFR1) *in vivo* by increasing the affinity of FGFR1 for FGF23 (6). FGF23 reduces phosphate reabsorption by the proximal renal tubules and phosphate absorption by the intestinal tract, ultimately leading to a reduction in phosphate levels (7). Further, FGF23 inhibits 1-α-hydroxylase activity in the kidneys, consequently reducing 25-hydroxyvitamin D (25-OH-D) levels (8). According to Meir *et al* (9), parathyroid hormone (PTH) activates nuclear receptor-related protein-1 through PTH receptors and induces FGF23 transcription in bone cells. In another study, mice with overexpression of FGF23 exhibited hyperparathyroidism (10) and clinical studies have revealed that FGF23 increases the synthesis and release of PTH in adults (11). In adult patients with

CKD, FGF23 has been shown to directly inhibit bone mineralization (12). Furthermore, amongst adults with renal insufficiency, increased FGF23 levels have been found to be related to morbidity and mortality (11). The risk of progression of nephrotic disease to ESRD in children may be reduced through earlier detection of and intervention for renal injury. Hypertension, proteinuria, and a low glomerular filtration rate (GFR) may lead to the progression of PNS to ESRD.

It is well established that FGF23 is significantly elevated in adult ESRD and is associated with the disturbance of mineral metabolism (13-15). However, it is unclear whether FGF23 is elevated in early renal disease in children and whether FGF23 levels reflect abnormal mineral metabolism and can be used for early detection. It was hypothesized that FGF23 is involved in mineral metabolism disorders and the progression of childhood kidney disease.

Materials and methods

Study participants and inclusion criteria. Three groups of children (<18 years of age) were included in the present study: Children with PNS, ESRD, and a control group. For the PNS group, children with PNS, defined by a GFR >15 ml/min/1.73 m^2 were included unless they had congenital and secondary nephrotic syndrome. The diagnostic criteria for PNS were: i) Proteinuria with urinary protein levels ≥50 mg/kg for 24 h or a urine protein/urinary creatinine ratio (mg/mg) >2.0, and ii) hypoalbuminemia with serum albumin levels ≤25 g/l. The PNS proteinuric phase was characterized by proteinuria, with a urinary protein to creatinine ratio >2.0 or positive results for protein on a urine test for 3 consecutive days. The PNS remission phase was characterized by the absence of edema and protein-free urine for at least 3 consecutive days. Hypoalbuminemia affects calcium concentration and is common in PNS during the proteinuric phase. Albumin-corrected calcium (cCa) levels were calculated using the following equation: cCa in mmol/l=total Ca + [0.02 x (40-albumin [in g/l])] (16). For the ESRD group, children were included if they had GFR <15 ml/min/1.73 m^2. The exclusion criteria for the ESRD group were Henoch-Schönlein purpura nephritis, hepatitis B virus-related nephritis, drug-induced nephritis, Alport syndrome, systemic lupus erythematosus nephritis, congenital urinary tract malformation, or other diagnoses which led to the children developing ESRD. All control participants had normal renal function, no renal disease or family history of renal disease, and no metabolic diseases. The patients were screened according to the inclusion criteria by two senior attending physicians.

A total of 36 children with kidney disease were identified, including 24 patients with PNS and 12 patients with ESRD. Of the 24 children with PNS, 7 were not in the remission stage. Therefore, 17 children with PNS in both the proteinuria phase and remission phase were included. Among the 12 patients with ESRD, 8 were excluded as the primary disease was not nephrotic syndrome. Finally, 21 children with kidney disease (17 with PNS with proteinuria and normal renal function and 4 with ESRD) and 20 healthy children were selected for a cross-sectional observational study. The median ages of the PNS, ESRD, and control groups were 3.80, 10.53, and 2.75 years, respectively. There were 14 males and 3 females, 3 females and 1 male, and 12 males and 8 females in the PNS, ESRD, and control groups, respectively. Patients with PNS and ESRD were admitted to the Department of Pediatric Nephrology, the First Affiliated Hospital of Jinan University, Guangzhou, China, and the 20 healthy children were recruited from the outpatient department of the same hospital. The study was conducted in accordance with the Declaration of Helsinki and approved by the Medical Ethics Committee of the First Affiliated Hospital of Ji Nan University (approval no. 2017-017). Written informed consent was obtained from the parents and guardians of all patients.

Sample collection. A 2 ml sample of venous blood was collected from each child who met the inclusion criteria. The blood samples were centrifuged at 2,415 x g at 4˚C for 15 min. Serum samples were divided into four parts and stored at -80˚C: Two parts were used for the analysis of PTH, calcium, phosphate, and 25-OH-D levels at the Department of Clinical Laboratory of the First Affiliated Hospital of Jinan University. PTH levels were detected using an immunoassay analyzer (UniCel DxI800; Beckman Coulter, Inc.). Serum 25-OH-D levels were detected by the LIAISON® 25-hydroxyvitamin D Assay (cat. no. 310600; DiaSorin, Inc.), which uses chemiluminescent immunoassay technology. The other two parts of the serum samples were used for the detection of FGF23 levels. FGF23 levels were determined using human FGF23 ELISA (cat. no. EZHFGF23-32K; MilliporeSigma) according to the manufacturer's protocol. The absorbance was measured using a microplate reader at wavelengths of 450 and 590 nm (Shenzhen Highcreation Technology Co., Ltd.). Clinical data entry, statistics, and experimental procedures were performed and confirmed by two physicians.

Statistical analysis. Statistical analysis was performed using SPSS 22 (IBM Corp.). Normally distributed data are presented as the mean ± standard deviation. Skewed data are presented as the median and interquartile range. Differences between multiple groups were compared using a Kruskal-Wallis test followed by a Dunn-Bonferroni post hoc test.

Categorical data were analyzed using a Fisher's exact test. Spearman's correlation analysis was used to analyze the correlation between the FGF23 levels and mineral metabolism parameters. FGF23, PTH, and 25-OH-D levels were log-transformed for further analysis. $P<0.05$ was considered to indicate a statistically significant difference.

Results

The median ages of the PNS, ESRD, and control groups were 3.80 (2.70-8.40), 10.53 (7.35-12.54), and 2.75 (1.63-5.48) years, respectively. There was a significant difference in age between the control and ESRD groups ($P=0.036$). There were 14 males and 3 females, 3 females, and 1 male, and 12 males and 8 females in the PNS, ESRD, and control groups, respectively; the distribution of sex amongst the groups did not differ significantly ($P>0.05$). Table I shows the characteristics of each group. In the control group, taking the median age as the time node, the serum FGF23 levels of those >2.75 years was 2.12 (1.60,4.61), and that of those

Table I. Characteristics of the study participants.

Characteristic	PNS, n=17	ESRD, n=4	Control, n=20
Age, median years (P25-P75)	3.80 (2.70-8.40)	10.53 (7.35-12.54)	2.75 (1.63-5.48)
Sex, n (%)			
Female	3 (18)	1 (25)	8 (40)
Male	14 (82)	3 (75)	12 (60)
Medication, n (%)			
Vitamin D	7 (41)	1 (25)	-
Calcitriol	1 (6)	2 (50)	-
Calcium administration	7 (41)	3 (75)	
Glucocorticoid	8 (47)	2 (50)	-
Immunosuppressant	5 (29)	0 (0)	-
Hemodialysis	0 (0)	1 (25)	-
Peritoneal dialysis	0 (0)	3 (75)	-

PNS, primary nephrotic syndrome; ESRD, end-stage renal disease.

Table II. FGF23 and mineral metabolism parameters of the participants.

Group	FGF23, pg/ml (P25-P75)	Calcium, mmol/l	Phosphorus, mmol/l	25-OH-D, ng/ml (P25-P75)	PTH, pg/ml (P25-P75)
PNS, n=17	6.98 (2.24-11.12)[a]	2.08±0.21[a]	1.67±0.24	9.22 (6.14-20.79)[a]	13.72 (10.10-25.62)[b]
Remission phase, n=17	2.99 (2.23-4.37)[c]	2.42±0.09[d]	1.51±0.25	15.20 (8.98-19.55)[e]	-
ESRD, n=4	1,866.0 (341.51-3,225.25)[f]	2.02±0.37[f]	1.24±0.08	27.55 (6.86-51.19)	234.53 (195.89-266.38)[f]
Control, n=20	2.12 (1.48-3.30)	2.46±0.13	1.74±0.27	42.10 (26.7-57.66)	13.56 (8.5-20.03)

[a]PNS vs. control group, P<0.05; [b]PNS vs. ESRD, P<0.05; [c]Remission phase vs. ESRD, P<0.05; [d]PNS vs. Remission phase, P<0.01; [e]Remission phase vs. control group, P<0.01; [f]ESRD vs. control group, P<0.05. 25-OH-D, 25-hydroxy vitamin D; PNS, primary nephrotic syndrome; PTH, parathyroid hormone; ESRD, end-stage renal disease; FGF23, fibroblast growth factor.

<2.75 years was 2.14 (1.48,4.00; <2.75 years vs. >2.75 years: Z=−0.11, P=0.91). There was no association between FGF23 levels and age in the healthy control group (r=-0.14, P=0.55) (data not shown).

The median FGF23 serum levels in the control, PNS, and ESRD groups were 2.12 (1.48-3.30), 6.98 (2.24-11.12), and 1,866.00 (341.51-3,225.25) pg/ml, respectively (Table II). The serum FGF23 levels of the PNS group were significantly higher than that of the control group (P=0.038). FGF23 levels were significantly higher in the ESRD group than in the remission stage of PNS (P=0.014) and control group (P=0.001). PTH levels were significantly higher in the ESRD group than in the PNS group (P=0.025) and control group (P=0.006). The PNS group had significantly lower serum calcium and 25-OH-D levels than the control group (P=0.0001). The serum 25-OH-D levels in the control group were significantly higher than that in the remission stage of PNS (P=0.008). The serum Ca levels in the ESRD group were significantly lower than that in the control group (P=0.017). In the PNS subgroup analysis, the median serum FGF23 levels were not significantly higher in patients in the proteinuric phase than in those in the remission phase (6.98 and 2.99 pg/l, respectively; P=0.867). Serum calcium levels were significantly higher in the remission phase compared with that in the proteinuric phase (P=0.001). These results are shown in Table II and Fig. 1A-E.

FGF23 levels were significantly positively correlated with serum calcium and cCa levels (r=0.518, P=0.033, and r=0.648, P=0.005, respectively) in the PNS remission phase. For the control group, FGF23 and 25-OH-D levels were significantly positively correlated (r=0.505, P=0.046), but FGF23 and iPTH levels were significantly negatively correlated (r=-0.651, P=0.006). FGF23 was not found to exert any effects on mineral metabolism factors in the PNS proteinuric phase; these results are shown in Table III.

Discussion

Adult patients with ESRD exhibit elevated levels of FGF23; however, data on FGF23 in childhood PNS and patients who have progressed to ESRD is scarce. The results of the present study showed that FGF23 levels begin to rise in early-stage PNS with normal GFR, serum phosphate, and calcium levels. In contrast, Van Husen *et al* (17) and Bacchetta *et al* (18) reported elevated levels of FGF23 in children with Stage 3 and Stage 2 CKD, respectively. De Seigneux *et al* (19) found

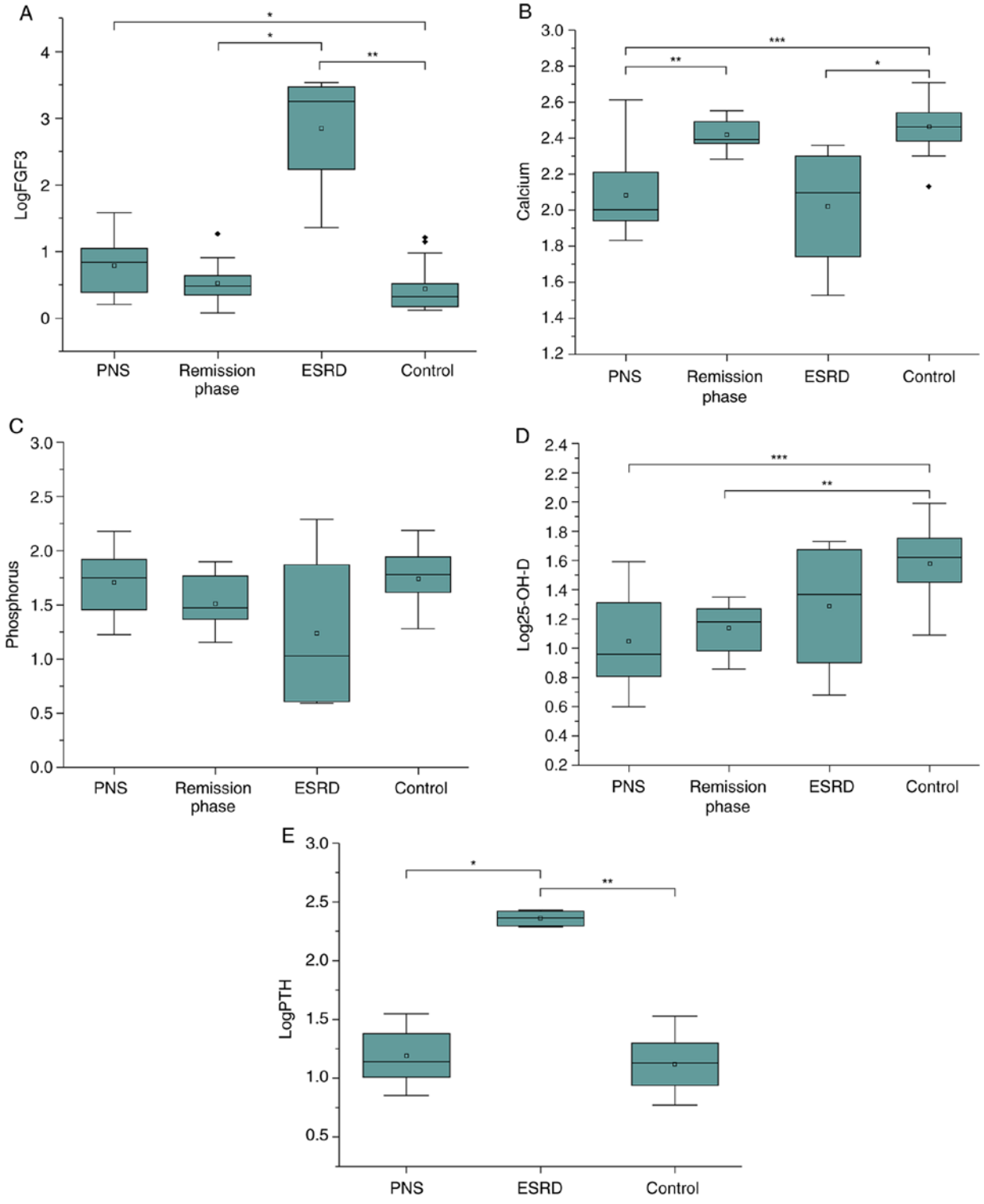

Figure 1. (A) The serum FGF23 levels of the PNS group were significantly higher than that of the control group (P=0.038). FGF23 levels were significantly higher in the ESRD group than in the remission stage of PNS (P=0.014) and control group (P=0.001). (B) Serum calcium levels were significantly increased in the remission phase and control groups compared with those in the PNS group (P=0.001 and P=0.001, respectively). The serum calcium levels in the ESRD group were significantly lower than that in control group (P=0.017). (C) There were no significant differences in the serum phosphate levels of each group. (D) The PNS group and the remission stage had significantly lower 25-OH-D levels than the control group (P=0.0001 and P=0.008, respectively). (E) PTH levels were significantly higher in the ESRD group compared with the PNS and control groups (P=0.025 and P=0.006, respectively). 25-OH-D, Serum 25-hydroxy vitamin D; ESRD, end-stage renal disease; FGF23, fibroblast growth factor 23; PTH, parathyroid hormone; PNS, primary nephrotic syndrome. *P≤0.05, **P≤0.01, ***P≤0.001.

that the concentration of FGF23 at the time of relapse in eight children with PNS was higher than that in remission; patients in this study were treated with corticosteroids, which may have influenced the results. Yadav *et al* (20) reported reduced levels of vitamin D and found that urinary losses may lead to lower levels of FGF23 in adults with untreated PNS.

Table III. Correlation between logFGF23 and mineral metabolism parameters in patients with PNS and the control group.

	Proteinuric phase[a]	Remission phase[a]	Control[a]
Ca, mmol/l	-0.178 (0.494)	0.518 (0.033)	0.262 (0.282)
cCa, mmol/l	0.115 (0.660)	0.648 (0.005)	-
P, mmol/l	0.241 (0.351)	0.003 (0.992)	0.467 (0.051)
25-OH-D, ng/ml	-0.007 (0.978)	0.230 (0.473)	0.505 (0.046)
Log PTH, pg/ml	-0.022 (0.935)	-	-0.651 (0.006)
cCa*P, mg^2/dl^2	0.231 (0.372)	0.156 (0.551)	-

[a]Values are presented as r (P-value). 25-OH-D, 25-hydroxy vitamin D; PTH, parathyroid hormone; cCa, albumin-corrected calcium; FGF23, fibroblast growth factor.

Bacchetta *et al* (18) showed that corticosteroid therapy was associated with increased FGF23 levels in children with CKD. In the present study, FGF23 levels in the PNS subgroup in remission were lower than those in the subgroup with proteinuria. Therefore, the reason for the increase in FGF23 levels in the proteinuria stage of PNS may be related to proteinuria or PNS disease itself.

FGF23 levels were significantly increased in patients who progressed to ESRD. Decreased kidney function may lead to increased FGF23 levels in ESRD and higher levels correlate with more severe kidney disease. In adult CKD, high levels of FGF23 are considered a risk factor for progression to ESRD (21). Although FGF23 levels began to increase in patients with PNS with normal GFR, they increased significantly in patients who progressed to ESRD in this study, indicating that high FGF23 levels may also be a risk factor for disease progression in children.

Despite significantly elevated FGF23 levels, it was found that serum phosphate levels were normal in children with PNS. Several factors, including calcium and vitamin D levels, dietary phosphate intake, and skeletal conditions can affect serum phosphate levels. Trautvetter *et al* (22) demonstrated that high phosphate intake leads to elevated FGF23 levels, but there has been limited research on the mechanism of action of FGF23 on phosphate metabolism in children with PNS. Siomou *et al* (23) observed a positive correlation between serum phosphate and FGF23 levels, whilst another study demonstrated no association (24). The present study found no significant correlation between serum phosphate and FGF23 levels in children with kidney disease. Our results suggested that serum phosphate levels may not be a sensitive measure of early-stage CKD in children.

FGF23 levels in the PNS remission phase positively correlated with serum calcium and cCa levels. Shimada *et al* (25) found that dietary calcium supplementation increased the mRNA expression of FGF23 in mice lacking the vitamin D receptor, suggesting that calcium has an independent effect on FGF23 levels. Furthermore, previous studies have found that patients receiving hemodialysis with dialysis solution containing high levels of calcium, and/or taking oral calcitriol had high serum levels of FGF23 (26). However, the mechanisms underlying the relationship between FGF23, and ionized calcium are yet to be fully elucidated.

Hyperphosphatemia and low 25-OH-D levels in patients with ESRD can result in increased PTH levels, which often leads to secondary hyperparathyroidism (14). In the present study, FGF23 and PTH levels in children who progressed to ESRD were increased. There is a negative feedback loop between FGF23 and PTH, whereby PTH signaling activates protein kinase A, which increases FGF23 expression and secretion, and the secretion of PTH is inhibited by FGF23 (27). In ESRD, expression of the klotho receptor is decreased and FGFRs are downregulated which can result in the resistance of parathyroid cells to FGF23 (28). Here, it was found that patients with PNS had lower serum 25-OH-D levels. In agreement with this, Pavix *et al* (29) found a decrease in 25-OH-D levels during the early stage of kidney disease. Lower levels of 25-OH-D in children with PNS may be due to lower levels of outdoor activity and reduced vitamin D synthesis as compared to healthy children. In children with PNS with proteinuria, vitamin D and calcium-binding proteins are lost through urine (30) and there is a decrease in the activity of 1-α hydroxylase, which is essential for converting $25(OH)D_3$ into $1,25(OH)_2D_3$ (13).

In the present study, both FGF23 and 25-OH-D levels were significantly altered in early renal disease, which may indicate the involvement of FGF23 and 25-OH-D in mineral metabolism disorders during their early stages. Whilst there was no correlation between FGF23 and mineral metabolism-related factors in the PNS group, this may have been affected by abnormal calcium and phosphate metabolism. This result suggests that FGF23 levels may be influenced by the disease itself, in addition to mineral metabolism.

In the control group, FGF23 levels of children >2.75 years old compared to those <2.75 years old were not significantly different. There was no correlation between FGF23 levels and age in the control group. Bacchetta *et al* (18) also found that FGF23 serum levels increased after 15 years of age as phosphate decreased. In this study, all children were <15 years of age; age may have little effect on serum FGF23 levels in young children with CKD.

The present study has some limitations. First, as a single-center study, the sample size was small. Second, as the study was cross-sectional and observational, it was not possible to examine the mechanisms underlying the relationships between variables. Third, the ELISA kit used initially in this study was discontinued, so the number of patients in the

study could not be increased to compensate for any potential differences.

In conclusion, the present study showed that FGF23 levels began to rise in children with PNS before Stage 1 CKD, and FGF23 levels may be associated with the progression and the severity of nephrosis in children. This study suggests that serum FGF23 levels are useful for the early detection of abnormal mineral metabolism in children with PNS.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

FY, SZ and ZG performed the clinical diagnosis and treatment. SP and DL collected the specimens. DL and FY performed the experiments. DL and SP analyzed the data. DL and FY wrote the manuscript. DL and FY confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and was approved by the First Affiliate Ethics Committee of Jinan University Affiliated Hospital (Guangzhou, China; approval no. 2017-017).

Patient consent for publication

The parents and/or legal guardians of all study participants provided written informed consent for publication.

Competing interests

The authors declare that they have no competing interests.

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