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Fibroblast growth factor 23 and bone metabolism in children with chronic kidney disease

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Fibroblast growth factor 23 (FGF23) is a circulating protein that regulates the renal reabsorption of phosphate and also inhibits 1-α-hydroxylase production. In adults FGF23 is increased in chronic kidney disease (CKD) and is an important prognostic factor for cardiovascular morbidity. In order to gain insight into the role of FGF23 and other biochemical variables of bone metabolism in children we studied 69 patients at different stages of CKD. FGF23 was found to be significantly elevated in stage 3 compared with stages 1 and 2 of CKD, preceding significant hyperphosphatemia in stage 4 disease. The highest levels of FGF23 were found in stage 5 compared with stages 1 and 2 CKD. The levels of FGF23 positively correlated with parathyroid hormone and phosphate concentrations and negatively with 1,25-dihydroxyvitamin D, the estimated glomerular filtration rate, and tubular phosphate reabsorption. Using multivariate analysis, hyperphosphatemia and low estimated glomerular filtration rate remained the most significant factors. Thus we found that FGF23 likely has an important role in pediatric calcium and phosphate homeostasis, and in vitamin D metabolism, even at an early stage of CKD. Further studies are needed to clarify the role of FGF23 on the pathogenesis of renal osteodystrophy and its impact on cardiovascular morbidity in pediatric patients with CKD.

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Fibroblast growth factors are polypeptide growth factors with diverse biological activities, secreted into circulation with a paracrine and/or autocrine mode of action. They are required in multiple developmental processes including differentiation, cell proliferation, and migration. FGF23 knockout mice showing growth retardation and abnormal phosphate-vitamin D metabolism also gradually die in the postnatal stages.[1]

Fibroblast growth factor 23 (FGF23) is a circulating phosphaturic factor that has an important role in the regulation of inorganic phosphate homeostasis. It is a 227 amino-acid protein with a molecular weight of 25 kDa, which is largely produced by osteocytes.[2] It binds to a family of FGF receptors, likely requiring the transmembrane protein klotho to facilitate cell surface interaction.[3] FGF receptors are ubiquitously expressed, but the most important effects of FGF23 have been described on the kidney and the parathyroid gland.[4]

FGF23 contains a signal peptide and is secreted into the circulation. Interacting with its renal receptors (and klotho), FGF23 inhibits the type IIa and type IIc sodium phosphate co-transporter (NaPi2a/NaPi2c) in the renal proximal tubules and causes phosphaturia.[5–8] In addition, FGF23 suppresses renal 1-α-hydroxylase expression, preventing 1,25-dihydroxyvitamin D production by the kidneys and thereby decreasing the small-bowel absorption of calcium and inorganic phosphate.[9]

Consequently, hypophosphatemia, caused by urinary phosphate wasting, reduced 1,25-dihydroxyvitamin D levels, and osteomalacia are the main characteristics of disorders with increased FGF23 levels, such as tumor-induced osteomalacia[10] and X-linked hypophosphatemic rickets.[11,12] Mutations on the other hand, either in FGF23[13] or in its klotho coreceptor,[14] lead to severe tumoral calcinosis characterized by hyperphosphatemia, increased 1,25-dihydroxyvitamin D levels, and ectopic calcification.

Several other FGF23 effects are less well defined or proven. As clinical studies in adults show, FGF23 may increase the synthesis and release of parathyroid hormone (PTH) and might be a predictor of future secondary hyperparathyroidism in patients on dialysis treatment.[3,15,16] Some evidence suggests that PTH may stimulate FGF23 levels as well. Bone mineralization may also be directly depressed by FGF23 in

adult chronic kidney disease (CKD) patients.[15] Data on children are very scarce; only one study of serum FGF23 in children on peritoneal dialysis has been published, in which no correlation with PTH levels >400 pg/ml could be shown, but FGF23 levels were correlated with decreased osteoid thickness and shorter osteoid maturation time on bone biopsy.[17]

Excessive FGF23 and a deficiency of 1,25-dihydroxyvitamin D are associated with increased mortality in CKD patients.[18] Furthermore, Gutiérrez *et al.*[18] have indicated that FGF23 in adult CKD patients may be a better biomarker for risk assessment than serum phosphate levels. In addition, FGF23 toxicity might contribute to renal death.[19]

Thus, FGF23 has an important role in altered calcium-phosphate homeostasis in adults with CKD and is viewed as a risk factor for both vascular complications and renal dysfunction.[19–21] As no data on serum FGF23 in children across the spectrum of CKD are available, we performed a cross-sectional analysis in pediatric patients treated at our institution.

Table 1 | Baseline demographic and clinical characteristics of the pediatric CKD cohort

	N	(%)
Gender		
Male	45	65
Female	24	35
Causes of kidney disease		
Congenital anomalies of kidney and urinary tract	20	28
Congenital nephropathies	12	17
Glomerulonephritis	11	16
Hemolytic uremic syndrome	5	7
Cystic renal disease	13	19
Other	7	13
Medication		
Calcium carbonate	7	10
Sevelamer	13	19
25-Hydroxyvitamin D	26	38
1,25-Dihydroxyvitamin D	37	54

Abbreviation: CKD, chronic kidney disease.

RESULTS

The baseline demographic and clinical characteristics of the CKD cohort are reported in Table 1. Analysis of the biochemical variables in the respective study groups is presented in Table 2.

FGF23, PTH, and phosphate homeostasis

There was a statistically significant increase in the levels of FGF23 and PTH across the various stages of renal dysfunction (Figures 1 and 2).

In normal controls, FGF23 serum levels were 42.9 (±9.4) ng/l. Children with CKD stage 1–2 showed a mean (±s.d.) FGF23 serum level of 47 (±26) ng/l and a serum PTH level of 67 (±47) ng/l. No statistically significant difference was noticed between CKD stage 1–2 patients and the control patients regarding FGF23 levels and the variables of bone metabolism and calcium-phosphate homeostasis. CKD stage 3 patients showed a FGF23 serum level of 144 (±91) ng/l and a PTH serum level of 202 (±148) ng/l. In patients with CKD stage 4, FGF23 serum levels were 313 (±275) ng/l and PTH serum levels were 308 (±220) ng/l. Children on dialysis (CKD stage 5) showed a FGF23 serum level of 734 (±397) ng/l and a serum PTH level of 425 (±371) ng/l. Serum phosphate levels showed a significant increase only in CKD stage 4 and 5 patients relative to CKD 1–2 ($P<0.001$; Figure 3). FGF23 serum levels in CKD stage 5 did not differ significantly between hemodialysis and peritoneal dialysis; also residual renal function had no effect.

Serum concentrations of FGF23 correlated negatively with estimated glomerular-filteration rate (eGFR; $r=-0.57$, $P<0.001$; Figure 4). A positive correlation was found between FGF23 serum levels and serum phosphate levels ($r=0.56$, $P<0.001$; Figure 5).

In addition, there was a positive correlation between FGF23 and PTH serum levels in the combined group of CKD ($r=0.26$, $P=0.04$) and serum FGF23 levels correlated negatively with serum 1,25-dihydroxyvitamin D levels ($r=-0.61$, $P<0.001$; Figure 6). Lastly, there was a negative correlation between tubular phosphate reabsorption and FGF23 ($r=-0.48$, $P<0.001$; Figure 7).

Table 2 | Biochemical and urinary variables according to levels of renal function

Parameter (mean ± s.d.)	CKD 1–2 eGFR >60 (*n*=26)	CKD 3 eGFR 30–59 (*n*=7)	CKD 4 eGFR 15–29 (*n*=11)	CKD 5 eGFR<15 (*n*=25)
Creatinine (mg/dl)	0.83 ± 0.43	1.61 ± 0.66**	3.18 ± 1.18***	7.63 ± 2.68***
eGFR (ml/min per 1.73 m^2)	113 ± 51	41 ± 8***	27 ± 7***	10 ± 2***
Calcium (mmol/l)	2.34 ± 0.12	2.41 ± 0.14§	2.38 ± 0.11§	2.31 ± 0.37§
Phosphate (mmol/l)	1.27 ± 0.25	1.43 ± 0.19§	1.62 ± 0.22***	2.01 ± 0.44***
TPR (%)	83.5 ± 10.8	73.7 ± 7.6*	56.7 ± 18.0***	38.9 ± 28.9***
25(OH)D3 (μg/l)	21.0 ± 11.8	31.2 ± 17.9§	27.1 ± 13.1§	24.3 ± 9.4§
$1,25(OH)_2D3$ (μg/l)	49.4 ± 18.1	50 ± 41.0§	36.8 ± 45.7**	30.9 ± 39.8***
PTH (ng/l)	67 ± 47	202 ± 148*	308 ± 220***	425 ± 371***
FGF23 (ng/l)	47 ± 26	144 ± 91**	313 ± 275***	734 ± 397***

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate (expressed as ml/min per 1.73 m^2); FGF23, fibroblast growth factor 23; PTH, parathyroid hormone; TPR, renal tubular phosphate reabsorption; 25(OH)D3, 25-dihydroxyvitamin D; $1,25(OH)_2D3$, 1,25-dihydroxyvitamin D.
Statistical difference of CKD stage 1–2 compared with CKD stages 3, 4, and 5, indicated as *P*-value (§not significant, *$P<0.05$; **$P\leqslant0.01$; ***$P\leqslant0.001$).

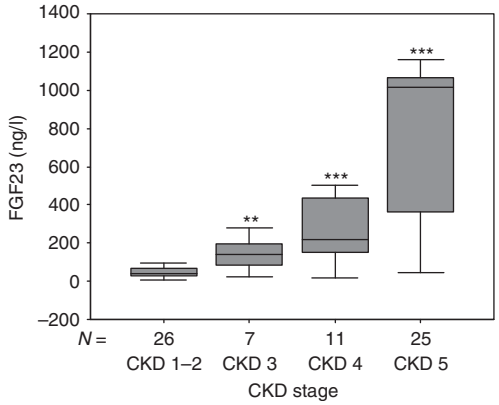

Figure 1 | Increase in serum fibroblast growth factor 23 (FGF23) levels with advanced chronic kidney disease (CKD) stage. $^{**}P<0.01$ CKD 1–2 vs. CKD 3, $^{***}P<0.001$ CKD 1–2 vs. CKD 4, $^{***}P<0.001$ CKD 1–2 vs. CKD 5. Boxes and bars represent the interquartile range and the median value, respectively; whiskers represent the distance to the smallest and largest unbooked sample value.

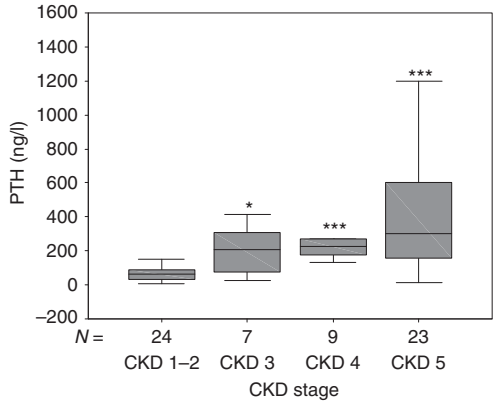

Figure 2 | Increase in serum parathyroid hormone (PTH) levels with advanced chronic kidney disease (CKD) stages. $^{*}P<0.05$ CKD 1–2 vs. CKD 3, $^{***}P<0.001$ CKD 1–2 vs. CKD 4, $^{***}P<0.001$ CKD 1–2 vs. CKD 5. Boxes and bars represent the interquartile range and the median value, respectively; whiskers represent the distance to the smallest and largest unbooked sample value.

In the multivariate analysis, serum phosphate levels, eGFR, and serum 1,25-dihydroxyvitamin D levels were associated with FGF23 levels; serum PTH levels tended to show a significant association (Table 3).

Vitamin D metabolism

Of 61 children, with data on 25-hydroxyvitamin D levels, 26 (42.6%) had vitamin D deficiency (<20 ng/ml) and 21 children (34.4%) showed relative vitamin D insufficiency (20–30 ng/ml). None of them had severe deficiency with 25-hydroxyvitamin D levels below 5 ng/ml.[22] There was no correlation between 25-hydroxyvitamin D levels and eGFR or the biochemical variables of bone metabolism.

In contrast, serum 1,25-dihydroxyvitamin D levels showed a significant negative correlation with FGF23 ($r=-0.61$, $P<0.001$) and PTH levels ($r=-0.48$, $P<0.001$). Simultaneous to the relevant increase of serum FGF23 levels in CKD stage 4 and 5, we could document a significant decrease of

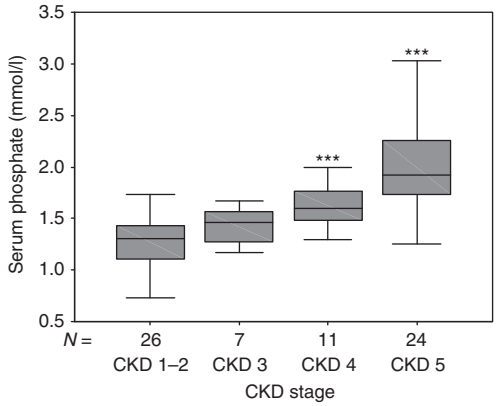

Figure 3 | Increase in serum phosphate levels with advanced chronic kidney disease (CKD) stages. $^{***}P=0.001$ CKD 1–2 vs. CKD 4, $^{***}P<0.001$ CKD 1–2 vs. CKD 5. Boxes and bars represent the interquartile range and the median value, respectively; whiskers represent the distance to the smallest and largest unbooked sample value.

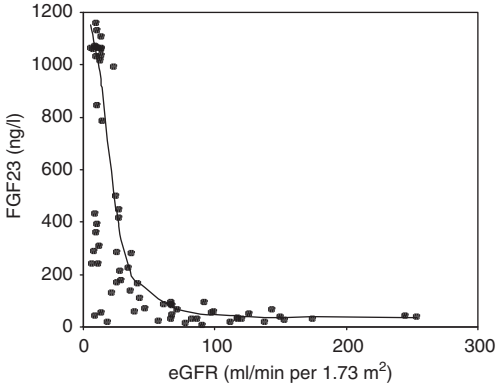

Figure 4 | Correlation of serum fibroblast growth factor 23 (FGF23) levels with estimated growth factor rate ($r=-0.57$, $P<0.001$).

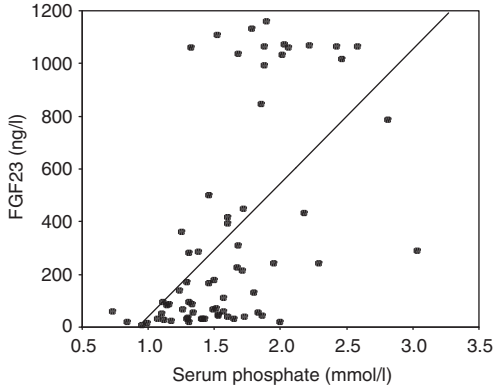

Figure 5 | Correlation of serum fibroblast growth factor 23 (FGF23) levels with serum phosphate levels ($r=0.56$, $P<0.001$).

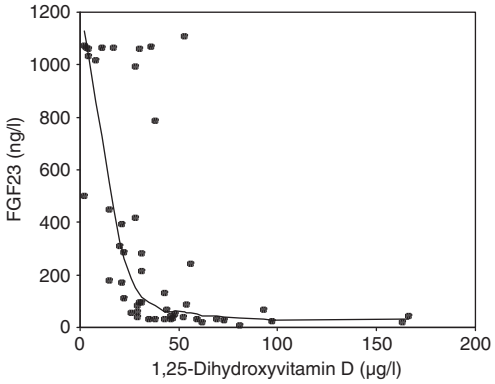

Figure 6 | Inverse correlation of serum fibroblast growth factor 23 (FGF23) levels with serum 1,25-dihydroxyvitamin D levels ($r = -0.61$, $P < 0.001$).

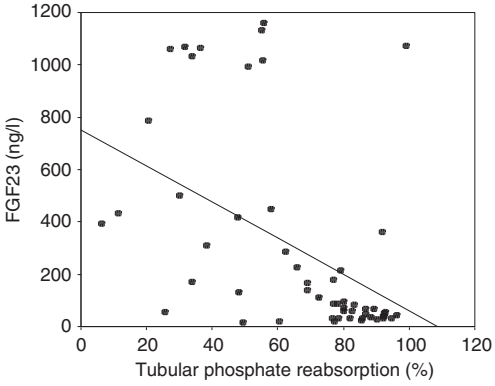

Figure 7 | Inverse correlation of serum fibroblast growth factor 23 (FGF23) levels with tubular phosphate reabsorption ($r = -0.48$, $P < 0.001$).

Table 3 | Factors associated with fibroblast growth factor 23: multivariate regression analysis using FGF23 levels as dependent variable

Independent variables	β-coefficient	s.e.	*t*	*P*	R^2
Phosphate (mmol/l)	479.1	101.2	4.74	<0.001	0.64
eGFR (ml/min per 1.73 m^2)	−2.6	0.77	−3.39	0.002	
$1,25(OH)_2D3$ (µg/l)	−3.2	1.40	−2.30	0.03	
PTH (ng/l)	−0.3	0.15	−1.91	0.06	

Abbreviations: eGFR, estimated glomerular filtration rate (expressed as ml/min per 1.73 m^2); FGF23, fibroblast growth factor 23; PTH, parathyroid hormone; $1,25(OH)_2D3$, 1,25-dihydroxyvitamin D.

1,25-dihydroxyvitamin D levels in these stages of renal failure compared with CKD stage 1–2.

FGF23 levels were independent of age in all CKD stages and in the control patients.

DISCUSSION

This is the first study assessing FGF23 serum levels in all stages of CKD in children. In accordance with earlier studies of adult patients, we were able to show that FGF23 levels increase gradually with CKD and are already significantly elevated in CKD stage 3. This increase is highly correlated with hyperphosphatemia, with the degree of renal dysfunction, and with deficiency of 1,25-dihydroxyvitamin D.

Our data extend the findings of the study by Wesseling-Perry *et al.*,[17] who analyzed children on peritoneal dialysis with hyperparathyroidism >400 pg/ml with a different FGF23 assay. Because of this kind of patient selection, they could not show a correlation between PTH and FGF23 as in our study. However, they very well showed a decreased osteoid thickness in patients with high FGF23 levels. Thus, future studies may delineate more specific mechanisms of altered FGF23/PTH-induced bone pathology in CKD, possibly even at early stages.

Several recent studies in adults have elaborated different threshold levels at which glomerular filtration rate FGF23 levels show a significant increase. Our data indicate that a significant elevation occurs already below an eGFR of 60 ml/min per 1.73 m^2. Shigematsu *et al.*[23] found a rise in FGF23 levels at an eGFR below 30–80 ml/min per 1.73 m^2, Gutiérrez *et al.*[16] suggested a cut-off-level of 60 ml/min per 1.73 m^2, whereas Westerberg *et al.*[24] showed that FGF23 levels do not change until CKD stage 4 (eGFR <30 ml/min per 1.73 m^2). Owing to these different findings, the various methods used to measure the eGFR make it difficult to estimate its influence correctly. This may also relate to a few patients with overt hyperfiltration as calculated by creatinine clearance.

Nevertheless, despite such differences in the exact timeline, we can also show an elevation of FGF23 in the early stages of CKD, which reaches significance starting from CKD stage 3. Whether age-related factors have an additional role has to be evaluated in further studies.

The role of FGF23 in phosphate metabolism of individuals with normal renal function has recently been investigated. Antoniucci *et al.*[25] showed an immediate phosphaturic response after phosphate load without changes in FGF23. In contrast, Isakova *et al.*[26] illustrated that longer periods of high phosphate intake lead to an increase in FGF23 production. Another study described that FGF23 increases with the rate of phosphate intake.[27] No data on children reflecting phosphate homeostasis with special regard to FGF23 in CKD are available.

Regarding the effect of FGF23 on phosphate homeostasis in CKD, our pediatric study could show a positive correlation of FGF23 with serum phosphate levels and could confirm serum phosphate levels as the strongest predictor of FGF23 elevation. As in adult CKD patients, a first significant increase in phosphate levels occurred in CKD stage 4. On the other hand, upregulation of FGF23 was already shown in CKD stage 3. This supports the concept that FGF23 mitigates hyperphosphatemia in chronic renal failure because FGF23 elevation precedes hyperphosphatemia.[16] This is supported by the negative correlation between FGF23 and tubular phosphate reabsorption.

In vitro and *in vivo* studies have shown that FGF23 reduces serum levels of 1,25-dihydroxyvitamin D by suppressing the expression of the key converting enzyme 1-α-hydroxylase. In

our pediatric cohort this association could be confirmed. Similar to other authors, we could find a significant negative correlation between 1,25-dihydroxyvitamin D and FGF23 levels. In addition, it is shown by Saito *et al.*[28] that FGF23 is regulated by 1,25-dihydroxyvitamin D levels as well, which can perform a negative feedback mechanism to reduce the further production of activated vitamin D. To what extent the increase in FGF23 levels is influenced by the routine treatment with calcitriol in some of our patients remains unclear.

In our study, we could find a relatively high rate of 25-hydroxyvitamin D deficiency, the storage form of vitamin D, and substrate for renal 1-α-hydroxylase, in children with CKD stage 4 and 5. Recent data support this finding.[29] This fact might have influenced the suppression of 1,25-dihydroxyvitamin D as well.

A deficiency of 1,25-dihydroxyvitamin D and excessively elevated FGF23 levels seem to be associated with increased mortality in CKD patients. The most relevant determinant of mortality in these patients, irrespective of other biochemical changes, seems to be hyperphosphatemia.[18] It is important to consider that serum phosphate levels in chronic renal diseases can be influenced by multiple factors such as dietary intake, use of phosphate-binding medication, and abnormal skeletal conditions. If used for risk assessment, serum phosphate levels can be misleading, especially when phosphate levels are within the normal range.

Recent studies have suggested that under normophosphatemic conditions, FGF23 may be a better biomarker for risk assessment.[21] The pathological importance and prognostic significance of increased serum levels of FGF23 need additional studies. Particularly, its influence on long-term outcome in pediatric patients with CKD is still not well understood. In this context, the impact of FGF23 as a prognostic factor for growth failure and renal osteodystrophy, for cardiovascular morbidity, and for the progression of renal failure should be evaluated.

The development of secondary hyperparathyroidism has an important role in the pathophysiology of chronic kidney disease–mineral and bone disease. Its influence on cardiovascular morbidity due to increased vascular calcification is evident.[30] Moreover, elevated FGF23 levels have been suggested to be an important predictor of future secondary hyperparathyroidism in patients on hemodialysis.[31] Hyperphosphatemia and reduced circulating levels of 1,25-dihydroxyvitamin D contribute to elevation of PTH levels.

This study confirms the finding that FGF23 levels are positively correlated with PTH levels. In contrast, in the multivariate analysis this effect is no longer significant, but tends to show a significant association ($P = 0.06$). This likely is a reflection of the influence of phosphate level on PTH.

Nevertheless, our data support the hypothesis that there might be a co-regulation of PTH and FGF23 in children as well.[24] Clearly, this aspect deserves further studies.

Similar to FGF23 levels, serum PTH levels are negatively correlated with tubular phosphate reabsorption and positively correlated with phosphate levels. Recent human and animal studies suggested that FGF23 and PTH act independently regarding their phosphaturic effect. In addition, there might be a different biological effect of these phosphatonins on the IIa and IIc sodium phosphate co-transporter (NaPi2a/NaPi2c) in the renal proximal tubules.[2,7]

In summary, in this study we show for the first time that FGF23 is increased also in children with CKD. As in adult patients, there occurs a gradual increase in FGF23 with the decrease in glomerular filteration rate in chronic renal failure. An increase in FGF23 can be shown in CKD stage 3, whereas phosphate levels first increase in CKD stage 4. Thus, FGF23 elevation seems to precede hyperphosphatemia.

FGF23 seems to suppress the production of activated vitamin D in children with CKD, as suggested by the inverse correlation between FGF23 and 1,25-dihydroxyvitamin D levels. Thus, FGF23 must be regarded as a potential uremic toxin in children, when losing its hyperphosphaturic action secondary to a decreasing number of viable nephrons in renal failure.

In consequence, the PTH levels increase and can further aggravate chronic kidney disease–mineral and bone disease, and also influence cardiovascular morbidity already in children.[32] This positive correlation of hyperparathyroidism with FGF23 serum levels could be reproduced in our pediatric cohort as well. Further studies into FGF23 physiology are needed to clarify its role in the pathogenesis of renal osteodystrophy, including growth failure in pediatric CKD patients.

In conclusion, FGF23 is a novel and important biomarker in children with chronic renal failure. It might be an early indicator of and contributor to uncontrolled calcium and phosphate homeostasis with its consecutive negative effect on bone disease, growth failure, and cardiovascular morbidity.

MATERIALS AND METHODS

Study population

We recruited 69 children with CKD from the outpatient clinic of the Department of Pediatric Nephrology, University Medical Center, Hamburg-Eppendorf, Germany. Almost all pediatric CKD patients attending our outpatient department during the study period were included. Blood samples were drawn and serum was stored at −30°C until analysis. Written consent was obtained from all patients and their parents, and samples were stored as approved by the local ethics committee. Ten children with normal renal function admitted to a minor surgery served as controls (mean age 12.5 (±4.1) years (range 3.7–16.8 years)), as published normal values refer to a different assay.[33] No data are available regarding the influence of age or pubertal stage on FGF23 levels.

Patient characteristics including relevant medication are shown in Table 1. Of the 69 patients with CKD, 45 (65%) were male and 24 (35%) were female. The mean (s.d.) age was 10.2 (±5.3) years (range 3 months to 17.9 years).

The etiology of CKD was congenital anomalies of kidneys and the urinary tract (hypodysplasia, urethral valves, prune belly syndrome) in 20 patients (28%), congenital

nephropathies (cystinosis, focal segmental glomerulosclerosis, syndromes) in 12 patients (17%), glomerulonephritis in 11 patients (16%), hemolytic uremic syndrome in 5 patients (7%), cystic renal diseases (autosomal-recessive polycystic kidney disease, autosomal-dominant polycystic kidney disease, nephronophthisis) in 13 patients (19%), and other renal diseases in 9 (13%) patients. In all, 11 children were treated with hemodialysis and 14 with peritoneal dialysis; 16 of the dialysis patients showed a residual glomerular filtration rate.

In the treatment of chronic kidney disease–mineral and bone disease, we adhere to the 'KDOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Children With Chronic Kidney Disease'.[34] In our cohort, 26 of 69 (38%) patients received 1000 IU/day 25-hydroxyvitamin D and 37 (54%) patients were treated with calcitriol. Phosphate binders were used in 20 (29%) patients, calcium carbonate in 7 (10%) patients, and sevelamer in 13 (19%) patients.

CKD classification

eGFR was calculated individually using the Schwartz formula.[35] A classification into CKD class 1–5 was performed according to The National Kidney Foundation Kidney Disease Outcome Quality Initiative (NKF K/DOQI) Guidelines.[36]

Biochemical analysis

Routine serum biochemistry for phosphate, calcium, creatinine and urinary electrolytes, and urinary creatinine was assessed by standard methods at the Department of Clinical Chemistry, University Medical Center, Hamburg-Eppendorf. PTH levels were analyzed for biointact PTH (1–84) measured by an automated chemiluminescence immunoassay system (DiaSorin, Saluggia, Italy). 25-hydroxyvitamin D levels were measured by a chemiluminescence immunoassay system (Roche, Basel, Switzerland) and 1,25-dihydroxyvitamin D levels by a radio immunoassay using a kit from Diasorin. Serum intact FGF23 concentrations were measured by a second-generation, two-site, monoclonal antibody ELISA (Kainos Laboratories International, Tokyo, Japan). This assay has earlier been shown to recognize the biologically active, intact FGF23.[37]

Statistical analysis

All statistical analyses were performed using SPSS software, version 13 (SPSS, Chicago, IL, USA).

Parametric or non-parametric tests and multivariate analysis were used as appropriate. For all analyses, a P-value <0.05 was considered to be statistically significant.

DISCLOSURE

All the authors declared no competing interests.

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