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Original Research Article

A CROSS SECTIONAL STUDY ON FIBROBLAST GROWTH FACTOR 23 AND MARKERS OF PHOSPHATE METABOLISM IN INDIAN CHILDREN WITH CKD

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Abstract

Background: Fibroblast growth factor 23 (FGF23) is a recently discovered phosphaturic peptide hormone that plays an important role in mineral bone disease in CKD children. Although FGF23 is recognized as a marker for CKD progression related to mineral bone disease, data on Indian children with CKD are limited. This study aims to measure plasma FGF23 levels in Indian children with CKD and find its association with disease progression (stages 1 to 5). **Materials and Methods:** A prospective cross-sectional study was conducted over 18 months with children grouped by CKD stages (Group I: CKD stages 1 & 2), Group II (stage 3), Group III (stage 4), and Group IV (stage 5). The association between plasma FGF23 levels, CKD stages, GFR, and phosphate levels was analyzed. Additional markers of phosphate metabolism, including Calcium, Vitamin D, and Parathyroid hormone were also assessed. **Result:** The study enrolled 95 children, with congenital anomalies of the kidney and urinary tract (CAKUT) as the leading cause of CKD (83.2%) followed by Chronic glomerulonephritis (6.3%). FGF23 levels, measured in 82 children, increased as GFR decreased and CKD progressed from stages 1 to 5, with a significant association ($p = 0.019$). Among phosphate metabolism markers, only serum phosphorus significantly correlated with FGF23 ($p<0.001$). **Conclusion:** Children with progressive renal failure are at higher risk of mineral bone disease. FGF23 levels rise with CKD progression and correlate with serum phosphorus in Indian children, suggesting its potential as a biomarker. Further longitudinal multicentre studies are needed to validate its clinical utility.

INTRODUCTION

Chronic kidney disease (CKD) is defined as the presence of kidney damage (ie, albuminuria) or decreased kidney function (ie, glomerular filtration rate [GFR] <60 mL/min per 1.73 m²).[1] Chronic kidney disease (CKD) patients with the progression of renal dysfunction manifest with disturbances in calcium-phosphate metabolism labeled as CKD mineral and bone disorder (MBD).[2] Kidney Disease Improving Global Outcomes (KDIGO) defines CKDMBD as biochemical alterations in the homeostasis of calcium, phosphate, parathyroid hormone (PTH), and vitamin D, but also abnormalities in bone histology, such as renal osteodystrophy (with alterations in bone turnover, mineralization, and volume), longitudinal growth and extraosseous calcifications.[3]

The study on CKD-MBD in the recent decade has shown that Fibroblast Growth Factor23 (FGF23) is an important regulator of phosphate metabolism in addition to other known traditional factors like phosphate, PTH, and calcitriol.[3] FGF23 was first identified as a phosphaturic hormone secreted by bone cells, primarily osteoblasts.[4] GF-23 acts on the kidney to impair Pi reabsorption.[5,6] inhibit the synthesis of 1,25 (OH) 2D (9) and alters production of PTH.[6] Hence, FGF23 has become a focus of research since its discovery and its role as a master regulator of MBD in a short period of its discovery.[7] So, various experimental studies have found that serum FGF23 levels increase with age when GFR declines below 90 ml/min/1.73 m², following renal

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transplantation.[8,9] and also showed it as an early biomarker for CKD as it increases prior to other parameters like creatinine, vitamin D, PTH, and phosphate.[10,11]

So, we need to know if FGF23 levels gradually change from CKD stage 1 to 5 or if the changes in FGF23 levels are influenced by the levels of Phosphate, PTH, etc. If the former is true, then FGF23 can be used in the future, as a prognostic marker of disease progression. If no such consistent pattern of correlation with disease progression is seen, then the levels of FGF23 may have to be interpreted along with other markers of CKD-MBD and the treatment strategy decided accordingly. The objective of the study is to find out what happens to FGF23 levels in a child as the disease progresses from stage 1 to 5. Most available information on this aspect is based on the Caucasian population and data on Indian/South Asian patients, especially in children is very minimal.

MATERIALS AND METHODS

In this prospective cross-sectional study, we focused on FGF23 (Fibroblast growth factor 23), and its role in phosphate metabolism especially as a prognostic marker of disease progression in Indian CKD children. Basic demographic data (such as gender, age, cause of CKD, stage of CKD, medication, and diet) and essential clinical details of children participating in the study were obtained and individuals were graded for CKD stage following the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines,[12] where in eGFR was calculated using original Schwartz Formula.[13] The study participants were grouped according to their stage of CKD (Group I = CKD stages 1 & 2 and groups II, III, and IV as CKD Stages 3, 4, and 5 respectively). The primary objective of the study is to estimate the levels of FGF23 in Indian children with various stages of chronic kidney disease and correlate levels in this marker with disease progression. The secondary objective of the study is to correlate FGF23 levels with other biomarkers involved in phosphate metabolism, to determine the role of FGF23 in phosphate metabolism in children with CKD, and if there were stage-related differences in the role.

Study Subjects: The present prospective cross-sectional study was conducted with the children under the care of the pediatric nephrology unit (outpatients and in-patients) in our tertiary hospital in South India which caters to the population of South and Eastern India. In this study, we recruited 95 children who met the study requirements (inclusion & exclusion criteria). The accompanying parent/guardian was given information regarding the study and the role of a study participant in the investigation. Participants included were between 1-18 years of age with CKD (any stage) not on dialysis defined by estimated glomerular filtration rate (eGFR) < 90 ml/min per 1.73m2 for > 3 months or evidence of kidney damage for >/= 3 months despite a normal eGFR.[12] The participants are enrolled after the parent/guardian has given written consent for participation in this study. Children excluded were those with acute kidney injury (AKI) or with hyperphosphatemic conditions other than CKD that cause an increase in the FGF 23 (e.g. iron deficiency anemia) or with hereditary hypophosphatemia conditions like XLH with increased FGF23. The study was approved by the Institute research and Ethics Committee Ref: IRB Min. No.7986 dated 08-09-2012 and funded by the Institute fluid research grant no CTR-CL-16-SM. It was conducted over an eighteen-month period from December 2012 to May 2014. A total of ninety-five children were enrolled/recruited with purposive sampling.

Biochemical analysis: Overnight 5 ml of fasting blood was collected, and processed, and the plasma was separated and stored at - 80 at the Nephrology lab until FGF23 levels were estimated by ELISA. Plasma C- terminal FGF23 analysis was done in duplicate using a commercial second-generation ELISA kit (Immutopics Int., San Clemente, CA USA). Results of other routine blood tests (serum phosphate, calcium, 25 (OH) 2 vitamin D3, PTH, serum creatinine etc,) were done by the standard methods in our hospital clinical biochemistry laboratory after collecting blood from the children along with FGF 23 sample. PTH levels were measured by Elecys PTH (ECLIA) technology in Pg/ml. 25-hydroxy vitamin D3 was analyzed by radioimmunoassay in ng/ml. Serum creatinine was estimated by kinetic calorimetric compensated by Jaffe's method.

Hyperphosphatemia was defined as serum phosphorus levels more than normal for the age while hypocalcemia was corrected by serum calcium less than 8.5 mg/dl. Corrected calcium was calculated from [0.8+ measured calcium (4- serum albumin)]and Vitamin deficiency as levels less than 30 ng/ml.[14] We defined Hyperparathyroidism as iPTH levels above upper normal for the CKD stages according to Kidney Disease Improving Global Outcomes guidelines.[14]

Statistical methods: Analysis of the results obtained was done using standard statistical methods using SPSS v20 Software (SPSS, Chicago, II, USA). Descriptive statistics (Mean, Median, and Standard deviation (SD) were presented for the various stages with a 95% confidence interval. The levels of FGF23 from CKD stages from I to V were compared and correlated with disease progression. Univariate analysis by Spearman Correlation coefficient was utilized to compare the relation between various markers (calcium, phosphate, PTH, 25-hydroxyvitamin D levels) with FGF23 values in CKD in this study. For analyses, a P value < 0.05 was considered statistically significant.

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RESULTS

A total of 95 children were enrolled in the study after obtaining consent to study the role of FGF23 as a marker in mineral bone disease in CKD children and also its relation with calcium, phosphorus, 25-hydroxyvitamin D, and PTH. Demographic and clinical data were presented in Table 1. 81/95 (85.2%) of the children with CKD were males. Male: Female ratio was 5.7:1. Mean age of the study children was 9.8 years (SD +/- 4.12). Most of the children were older (11-18 years) comprising 48/95 (50.5%).

The commonest cause of CKD was found to be CAKUT (Congenital anomalies of the kidney and urinary tract) accounting for 83.2% (79/95) of children followed by Chronic glomerulonephritis in 6.3% (6/95). Posterior urethral Valve was the major cause of CAKUT seen in 63.2% (50/79) followed by Renal Hypo dysplasia seen in 22.7% (18/79) children. Bilateral hydronephrosis was in 7.6% (6) children, Unilateral renal agenesis accounted for 5.06% (4), while Prune belly syndrome was seen in one child.

The mean duration of follow-up of all CKD children was 5.1 (SD +/- 3.18) years. The mean serum creatinine value was 2.78 (SD +/- 2.32) mg/dl. The mean eGFR calculated by the original Schwartz formula was 41.4 (SD +/- 31) ml/min/1.73m2. All the CKD children were grouped into four groups as shown in Table 1. Anemia of chronic disease was observed in 53.6% (51/95) children and almost evenly distributed in CKD 3,4 and 5, less in the early stages of CKD. Inj. Erythropoietin was given to 31[76%] children out of 51 with Anemia but anemia was persisting may be due to poor compliance or low dose. Mean hemoglobin levels in our study were 10.53 (SD +/-1.83) gm/dl. [Table 1]

Biochemical data is shown in Table 2. Out of 95 children enrolled, data from 82 children was shown as we were able to measure FGF23 levels in these children only. The overall mean eGFR value was 41.45 ml/min/1.73m2, which was gradually decreasing from CKD stage 1,2 (86.67 ml/min/1.73m2) to CKD stage 5 (11.41 ml/min/1.73m2). Overall mean serum calcium value was 8.9 mg/dl, which was highest in CKD stage 1,2 (9.34 mg/dl) and lowest in CKD stage 5 (8.18 mg/dl). Overall mean serum phosphorous was 4.61 mg/dl, which was almost equal in all CKD stages. The overall mean value of serum iPTH was 221.2pg/ml, which was lowest in CKD stage 1,2 (52.3 pg/ml) and highest in CKD stage 4 (236.5 pg/ml). The overall mean of serum 25OH D was 25.6 ng/ml, which was almost the same in CKD stages 1,2 and 3 and highest in CKD stage 5 (30.86 ng/ml). Overall mean FGF23 was 248.5 RU/ml, which was found to be increasing with the progression of CKD with the highest value in CKD stage 5 (433 RU/ml).

FGF23 levels with decreasing kidney function

Our study showed that mean FGF23 levels increased gradually with the decline in eGFR i.e, progression of CKD with values showing 47 RU/ml in early stages followed by 210, 302, and 433 RU/ml in CKD stages 3,4 and 5 respectively (Table 2). The negative correlation between FGF 23 and GFR was found to be statistically significant. (Spearmen correlation coefficient r = -0.258, p = 0.019) as depicted in [Figure 1 and Table 3]. FGF23 levels in relation to serum calcium, phosphate, 25hydroxyvitamin D, and PTH are presented in Table 3. The correlation coefficients of eGFR calculated were not significant at a 5% level of significance in any stage of CKD with FGF23 and are presented in [Table 4].

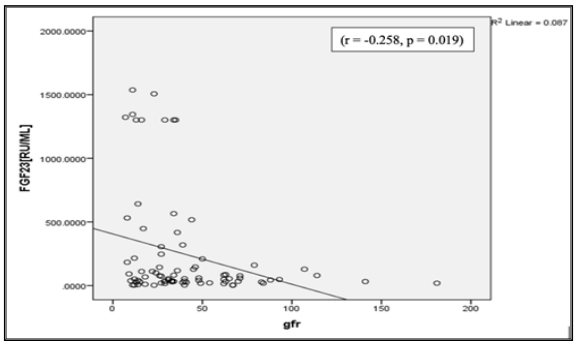

Figure 1: Correlation of FGF23 with eGFR in ml/min/1.73m^2

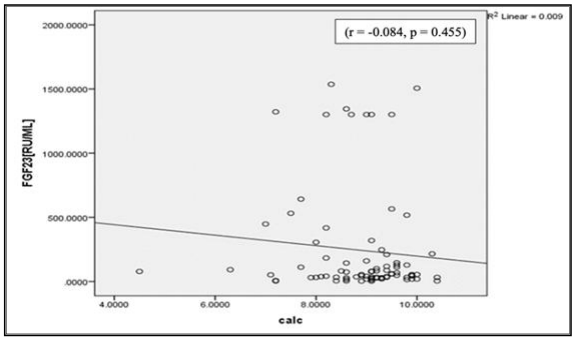

Figure 2: Correlation of FGF23 with Serum calcium (mg/dl)

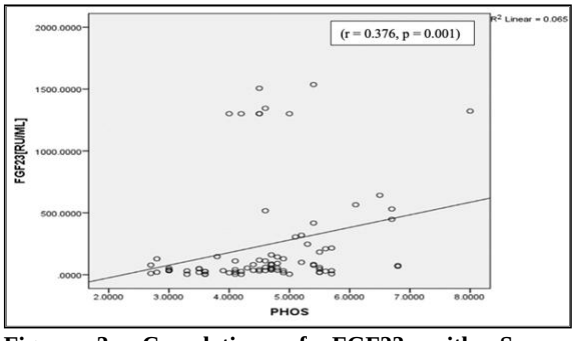

Figure 3: Correlation of FGF23 with Serum phosphorus (mg/dl)

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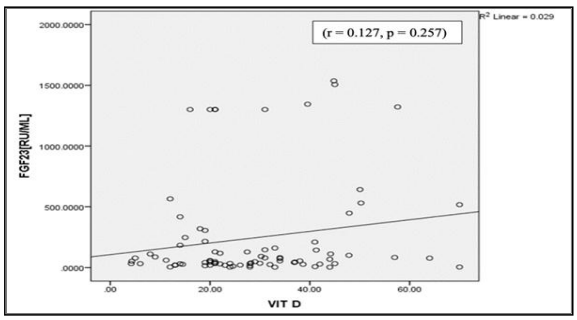

Figure 4: Correlation of FGF23 with 25-hydroxyvitamin D (ng/ml)

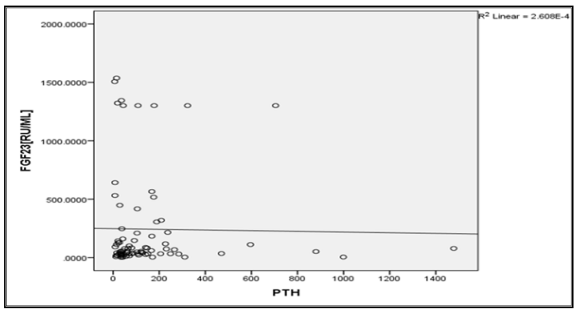

Figure 5: Correlation of FGF23 with Parathyroid hormone (pg/ml).

Mean FGF23 levels measured in 4 groups of CKD based on their eGFR were compared with mean serum calcium levels. Mean Serum calcium levels were in the normal range in all stages of CKD but were lower as the stage of CKD increased. FGF23 levels were found to increase with a decrease in serum calcium. However, the correlation was not statistically significant. (Spearmen correlation coefficient (r = -0.084, p=0.455) as presented in [Figure 2].

Mean FGF23 when compared with serum phosphorus levels in this study had shown, that as FGF23 values increased with the progression of CKD, serum Phosphorus levels also increased with the progression of CKD. The correlation between FGF23 and serum Phosphorus was statistically significant. (Spearman correlation coefficient r = 0.376, p < 0.001) as shown in [Figure 3].

25-hydroxyvitamin D levels correlated with FGF23 levels in various CKD stages and was observed that 25-hydroxyvitamin D levels increased with a decline in renal function. A positive Correlation was observed between FGF23 and 25hydroxyvitamin D but was not statistically significant as depicted in Figure 4. (Spearman correlation coefficient r = 0.127, p<0.257).

FGF23 levels were compared with PTH in our study children and we found that mean PTH levels were showing variable values although FGF23 increased with a decline in renal function. The correlation between FGF23 and PTH levels was not significant statistically as presented in Figure 5. (Spearmen correlation coefficient r = 0.013, p = 0.908).

Table 1: Baseline demographic and clinical data of study CKD children.

Characteristics	**All children (N = 95)**	
	Number	**Percentage**
Demographics		
Age in years (mean)	9.8	
Gender		
Male	81	85.26%
Female	14	14.73%
Cause of CKD		
Congenital anomalies of urinary tract	79	83.20%
Hereditary nephropathies	4	4.20%
Glomerulonephritis	6	6.30%
Cystic renal diseases	2	2.10%
Other renal diseases	4	4.20%
Stage of CKD		
Stage 1 and 2	21	22.10%
Stage 3	31	32.70%
Stage 4	27	28.40%
Stage 5	16	16.80%
Anaemia	51	53.60%
Medication		
Calcium based phosphate binder	69	72.60%
25-hydroxyvitamin D	27	28.40%
1,25-hydroxyvitamin D	23	24.20%
Erythropoetin	31	32.60%
Diet		
Vegetarian diet	73	76.80%
Mixed diet	22	23.20%

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Table 2: Biochemical parameters of phosphate metabolism in study children by CKD stage groups

Parameter (reference value)	Overall (N=82) Mean ± SD	CKD stage 1,2 eGFR > 60 (n=18) Mean ± SD	CKD stage 3 eGFR 30- 59 (n=27) Mean ± SD	CKD stage 4 eGFR 15-29 (n=20) Mean ± SD	CKD stage 5 eGFR< 15 (n=17) Mean ± SD
eGFR (ml/min/1.73m2)	41.45±31	86.67±31.97	41.3 ± 9.46	24.9 ±6.58	11.41± 2.37
Serum calcium (mg/dl)	8.9±0.98	9.34±0.63	9.16±0.59	8.69±1.22	8.18 ±1.06
Serum phosphorus (mg/dl)	4.61±1.01	4.69±0.75	4.52±0.73	4.52±1.31	4.9±1.39
Serum iPTH (pg/ml)	221.2±263.6	52.3±27.8	122.9±67.8	236.5±356.4	192.8±301.6
Serum 25OH D (ng/ml)	25.6±14.52	27.72±13.74	27.33±16.52	29.46±13.5	30.86±15.56
Plasma FGF-23 (RU/ml)	248.5±358.53	47.57±41.77	210.83±349.27	302.03±474.41	433.6±570.3

CKD: chronic kidney disease, eGFR: estimated glomerular filtration rate in ml/min/1.73m2, 25OH D: 25-hydroxyvitamin D, FGF23: Fibroblast growth factor23, iPTH: intact Parathyroidhormone.

Table 3: Correlation between Serum FGF23 with other markers of phosphate metabolism

Parameter	C-terminal FGF23	p-value
1.eGFR	- 0.258	0.019
2. Calcium	- 0.084	0.455, ns
3. Phosphate	0.376	0.001
4.25-hydroxyvitamin D	0.127	0.257, ns
5. PTH	0.013	0.908, ns

Table 4: Correlation of serum FGF23 with other variables in various stages of CKD

Variables	CKD I & II	III	IV	V
eGFR	0.315	0.036	-0.150	-0.349
Calcium	-0.111	-0.007	-0.007	0.120
Phosphorus	0.343	-0.049	-0.026	0.460
25-hydroxyvitamin D	0.325	-0.049	-0.026	0.460
Parathyroid hormone	-0.044	0.175	-0.155	-0.318

DISCUSSION

Though most of the studies done on the role of FGF23 in CKD were in adults with very few available in caucasian children, none were done in Indian/south Asian CKD children. As far as our knowledge goes our study is the first study among Indian children, to look at the role of FGF23 in phosphate metabolism in chronic kidney disease (CKD). Ninety-five children with CKD by NKF-K/DOQI guidelines were recruited in our cross-sectional study and we were able to analyze FGF23 samples of 82 children because of sampling and FGF23 kit availability.[12]

Most of the CKD children were males which was comparable to a study on CKD done in another center in North India,[15] which may be attributed to gender-selective health care-seeking behavior of Indian parents with a bias towards the care of male children. Congenital anomalies of kidney and urinary tract (CAKUT) with obstructive uropathy (60%) were found in more children of our study. It is comparable to a study done in Italy by Bonaurdo et al,[16] while a study in India showed only 30% of Children had obstructive uropathy as the main cause.[15] We reported the type of diet taken by our study children as shown in Table 1. and the majority were on a vegetarian diet (76.8%). This is important as a high phosphate diet was found to cause rapid deterioration of CKD according to some studies.[17,18]

Our first major finding was that mean FGF23 values were observed to increase with the progression of renal disease i.e., with a decrease in eGFR. Also, we have observed a positive correlation with PTH and serum phosphorus. We found that FGF23 levels were significantly high from CKD stage 3 to 4,5 relative to stage 2 with the highest values seen in CKD stage 5. This was similar to various adult,[19,20] and pediatric studies,[21,22] although done with different assays and have both predialysis and dialysis children as subjects. Few studies,[17,23] have found that FGF23 levels do not change until CKD stage 4. This discrepancy may be due to various methods for GFR estimation and also some patients with overt hyperfiltration due underlying etiology of CKD. The highest value of 1350 RU/ml was observed in 4 children- two each in CKD stage IV and V suggestive of decreased clearance in CKD and severity of mineral bone disease which was observed in some studies.[24]

As serum phosphorus values increase with the progression of CKD, FGF23 levels increased with the progression of CKD in our study children with a significant positive correlation between FGF23 and serum phosphorus which was comparable to a study by Van Husen et al,[9] and Balmukhanova A.[25] This increase may be due to decreased clearance of FGF23 with progression of renal dysfunction or compensatory response to excrete excess phosphate.[19,21] Some studies also described the role of longer duration and higher intake of phosphate-

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containing diet as a cause of the rise in FGF23.[17,26] However, only a few children in our group were found to have hyperphosphatemia the reason being intake of a predominantly vegetarian diet (76%) when compared to Caucasian children taking more animal-based diets irrespective of socioeconomic status and race.[27]

25-hydroxyvitamin D deficiency was observed in more children (69%) when compared with the other studies on the prevalence (40%) of Vitamin D deficiency in CKD and healthy population,[28] 25-hydroxyvitamin D levels were correlated with FGF23 levels in various CKD stages although results were depicted as statistically insignificant. We observed that 25 (0H) 2 Vitamin D levels increased with a decline in renal function. The increase in 25-hydroxyvitamin D in our study could be attributed to increased intake of Vitamin D supplements to control mineral bone disease from early stage of CKD

We did not measure 1,25 (0H) 2 Vitamin D (Active vitamin D) as it is a difficult assay with a short half-life and unavailability of the assay. If measured it would have given a better measure of the Vitamin D status in renal failure. It is known that 1,25 (0H) 2 Vitamin D decreases with the progression of CKD due to suppression by rising FGF23 levels, as it is technically challenging and expensive compared to measuring other markers, the clinical significance of this is uncertain.

PTH measured in our study children found that mean PTH levels were showing Variable values although showing higher than normal values in stages 3,4 and 5 but slightly lower values in stage 5 suggestive of secondary hyperparathyroidism when compared to 3 and 4 CKD stages.

FGF23 levels were compared with PTH in this study and showed a positive Correlation, as compared to,[29] but was not significant statistically as shown in results by univariate analysis It needs further studies as our data supports the theory of co-regulation by parathyroid and FGF23 on phosphate metabolism.[12,30]

The strength of our study is that it is specifically focused on Indian children. Results gained from our study may contribute to the development of preventive measures, early detection strategies, and targeted interventions aimed at reducing the incidence and impact of CKD in Indian children.

The limitations of our study are that the small sample size in each stage of CKD, cross-sectional, and FGF23 kits are not easily available commercially and are expensive- hence it may be a while before the FGF23 assay becomes the standard of assessment in children with CKD. As the study is cross-sectional we cannot ascertain the temporality of the observed correlation.

CONCLUSION

We conclude that Fibroblast Growth Factor 23 was noted to increase with the progression of CKD and FGF 23 correlated well with serum phosphate levels-thus it may be helpful in monitoring the severity and progression of metabolic bone disease but needs a longitudinal study with a large cohort of children can only prove it as an effective biomarker for mineral bone disease.

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