Benha Journal of Applied Sciences (BJAS) **print: ISSN 2356–9751**
Vol. (7) Issue (6) (2022), (109-117) **online: ISSN 2356–976x**
http://bjas.journals.ekb.eg

Serum Fibroblast Growth Factor 23 as an Early Biomarker for Detection of Renal Osteodystrophy and Progression of Chronic Kidney Disease in Children

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Abstract

Background: Chronic kidney disease (CKD) is a major public health issue that imposes significant financial burdens on health systems across the world. Calcium and phosphorus levels in the blood are maintained by tubular reabsorption systems in the kidneys. Changes in the mineral metabolism occur as renal disease progresses. Chronic hyperphosphatemia causes FGF23 levels to rise in later stages of CKD. Bone cells are the major source of FGF23's secretion. The regulation of mineral ion homeostasis by FGF23 has been shown. Methods: Sixty youngsters will participate in the trial, which was done at the paediatric nephrology section of Benha University Hospital. Group I consists of 40 individuals with end-stage renal disease. Divided into the following groups based on GFR: Patients in CKD stages I, II, III, and IV were followed up in our paediatric nephrology clinic every three or six months, depending on their health. 2- Patients with CKD stage V were included in subgroup IB (n = 25). (undergoing regular hemodialysis three times per week, with each dialysis session lasting three to four hours). Group II: consists of 20 youngsters who seem to be in good health. It was made up of 10 men and 10 women, all of whom seemed to be of the same age, sex, and social status. Submissions came from all of the subjects: Blood count in its entirety (CBC), Serum creatinine level, blood urea nitrogen (BUN), serum calcium (Ca), serum phosphorus (Po4), serum alkaline phosphatase (ALP), parathyroid hormone (PTH), serum fibroblast growth factor 23 (FGF23) were all measured in this study. We discovered 24 patients with normal radiological results, 14 patients with subperiosteal bone resorption, seven patients with pathological fractures, and one patient with brown tumours (2.5 percent). We found that the concentration of FGF23 in group I (532.5 pg/ml vs. 124.9 pg/ml) was statistically significantly higher than the control group (124.9pg/ml). We discovered a cutoff point of 159.7 pg/ml with a sensitivity of 85%, specificity of 90%, accuracy of 80%, PPV of 94.4 %, NPP of 75%, AUROC of 0.837, and a P value of 0.0001 for FGF23 in predicting CKD. It may be concluded that the early biomarker FGF 23 can be utilised to track the progression of chronic kidney disease in kids.

Key words: FGF23, CKD, renal osteodystrophy, Biomarker Diagnosis.

1.Introduction

GFR less than 60 ml/min per 1.73m2 or kidney damage indicators, or both, for at least three months, regardless of the aetiology, are current worldwide standards for defining chronic kidney disease [1]

On the basis of the cause and GFR category (G1 to G5) and albuminuria, Chronic Kidney Disease (CKD) is classified (A1 to A3). Bone mineral metabolism alters dramatically when kidney function declines, increasing the risk of fractures, cardiovascular disease, and all-cause mortality [2]

In later life, kidney disease is linked to low birth weight (usually defined as 2,500 g) as a result of preterm delivery or intrauterine growth restriction. Consequently, millions of children are born at risk of developing chronic kidney disease later in life and are found to have GFR values below the 90th percentile for their age group [3]

Chronic kidney disease (CKD) affects children, resulting in a variety of undesirable effects, including but not limited to fractures, discomfort, bone abnormalities, and growth failure, which affects their quality of life. The gold standard approach for figuring out the underlying causes and prognosis of bone disease is a bone biopsy [4]

The fibroblast growth factor 23/klotho system has a considerable impact on renal osteodystrophy aetiology, allowing phosphate excretion to increase and calcitriol production to decrease [5]

Osteocytes and osteoblasts in bone create FGF23, an endocrine hormone that regulates phosphate and vitamin D homeostasis [6]

Inflammation and FGF23 production may have a bi-directional relationship. Because both inflammation and an increase in FGF23 are linked to a higher risk of death. The transcription and cleavage of FGF23 may be influenced by both acute and chronic inflammation. FGF23 transcription and cleavage are both enhanced by iron deprivation. Increased FGF23 and C-reactive protein levels are linked to elevated blood phosphate levels in individuals with chronic kidney disease (CKD) and those undergoing dialysis [7]

Hyperphosphatemia has been shown to be an independent risk factor for death in individuals with end-stage renal disease (ESRD). Although blood phosphate levels are within the normal range in most patients with early-stage CKD and healthy persons, greater phosphate levels were linked to a higher mortality risk than lower phosphate levels. phosphate and mortality have been linked to the discovery of FGF23. In addition, elevated FGF23 was linked to an increased risk of death [8]

Fibroblast growth factor 23 (FGF 23) and other markers of calcium and phosphate metabolism in children with chronic renal disease were examined in this study. The serum FGF23 may be used as an early biomarker for the diagnosis of renal osteodystrophy in

all children with CKD, but further research is needed to confirm this.

2. Patients and methods

The study was conducted in pediatric nephrology unit of Benha University Hospital, and will be carried out on 60 children divided into:

- Group I: include 40 patients with CKD. Divided according to their GFR into:
  1. Subgroup IA: Included 15 patients with CKD stages (I, II, III, and IV) who were following up in our pediatric nephrology clinic every three or six months according to condition.
  2. Subgroup IB: Included 25 patients with CKD stage V (undergoing regular hemodialysis three times per week, with each dialysis session lasting three to four hours).
- Group II: include 20 apparently healthy children. They were 10 males and 10 females, with apparently matched age, sex and socioeconomic average.

Study approval:

An informed consent was obtained from all parents of all patients after full explanation of all benefits and risks of the study.

Inclusion criteria:

- Patients attend and follow up their management in Benha University Hospital during the period of study in the outpatient clinic and inpatient in Pediatric section.
- Patients with CKD of different causes.
- Age range from 2 to 18 years old.

Exclusion criteria:

- Refusing and uncooperative patients or parents.
- Metabolic bone disease caused by other diseases.
- Patients older than 18 years old.

Methods:

All subjects included were submitted:

- Complete history taking.
- Complete clinical examinations.
- Laboratory investigations include: All investigations were done before starting hemodialysis session for patients on HD.
- Complete blood count (CBC).
- Assessment of GFR: by Schwartz formula CrCl = 0.55×Height (cm)/ Serum creatinine (mg/dl)
- Blood Urea
- Serum Creatinine level.
- Serum Ca level.
- Serum Po4 level.
- Serum alkaline phosphatase (ALP).
- parathormone hormone level (PTH).
- Serum fibroblast growth factor 23: FGF23 concentration will be measured by FGF23 ELISA KIT which is based on the principle of double-antibody sandwich technique to detect human FGF23.

Assay Type: Double Antibody Sandwich
Detection Range: 1000 pg/mL-15.6 pg/mL
Intra-assay Precision: ≤ 8%
Inter-assay Precision: ≤ 12%
Storage: -20°C [Short-term should be stored at 4°C (such as ~2 weeks)]
Sensitivity: the minimum detectable Human FGF23 up to 5 pg/mL.

Principle of the Assay: The principle of Double Antibody Sandwich is based on the characteristics of a target analyte with more than two possible epitopes which can be identified by both the pre coated capture antibody and the detection antibody simultaneously.

The pre-coated antibody is an anti-Human FGF23 monoclonal antibody, while the detection antibody is a biotinylated polyclonal antibody. Samples and biotinylated antibodies are added into ELISA plate wells and washed out after their respective additions to the wells. Then Avidin-peroxidase conjugates are added to the wells in after. TMB substrate is used for coloration after the enzyme conjugate has already been thoroughly washed out of the wells. TMB reacts to form a blue product from the peroxidase activity, and finally turns to yellow after addition of the stop solution (Color Reagent C). The color intensity and quantity of target analyte in the sample are positively correlated.

Sample Preparation:

1. Serum: Place collected whole blood in refrigerator at 4℃ overnight. Then centrifuge for 10min at 1000-3000rpm. Take supernatant and either test immediately or place samples at -20℃/-80℃ (1-3 months) for storage.
2. Plasma: Take EDTA, sodium citrate, or heparin as anticoagulant, and add to plasma. Mix well. Centrifuge mixture for 10min at 1000-3000rpm. Take supernatant and test immediately or place samples at -20℃ /-80℃ (1-3 months) for storage.

- Radiological investigations

X-ray on bones: were done on wrist joint, hand, hip joint, femur and foot.

3. Results

Regarding the demographic data, age and sex: they were divided into: Group I (Patients): 40 patients with CKD. The mean age was 12.48 ± 5.66 years, males were 52.5 % and females were 47.5%. Group I divided into 2 subgroups: subgroup IA (stage I, II, III and IV): Included 15 patients. The mean age was 7.8000 ± 6.07336 years, males were 66.67% and females were 33.33%. Subgroup IB (stage V): Included 25 patients. The mean age was 15.3 ± 2.95 years, males were 44% and females were 56 %. Group II (controls): 20 children. The mean age was 7.07 ± 4.49 Years, males were 50% and females were 50%. 55% lives in urban areas and 45% in ruler areas And 2 patients (10%) shows positive family history of CRF. **(Table 1, 2).**

Height was the most affected parameter, as 65 % of the patients were short (height SD less than -2 SD), 35 % height SD between 2+ to -2. In addition 20 % of patients were underweight as their BMI SD was less than -2 SD, 80% BMI SD between +2 to -2. Weight (mean ±SD) was 29.9±11.64. Height (mean ±SD) was

126.2±20.3. BMI (mean ±SD) was 18.41±3.3. **(Table 2, 3).**

Regarding to GFR, CKD divided into 5 stages: 10% of patients were stage II, 7.5% were stage IIIA, 12.5 % were stage IIIB, 7.5 % were stage IV, and 62.5 % were stage V. **(Table 4, Figure 1).**

We found 24 patients (60 %) with normal radiological findings, subperiosteal bone resorption was found in 14 patients (35%), pathological fractures was found in 7 patients (17.5%) and brown tumors was found in 1 patient (2.5%). Concerning radiological finding in group II (control), found 95% (19 patients) with normal radiological finding and 5% (1 patient) only show healed rickets. Incidence of Sub periosteal bone resorption and Pathological fractures was significantly higher in patients with CKD than control group (P<0.05). **(Table 5).**

Bone pain was found in 32.5% (13 patients), bone deformity in 40% (16 patients) and history of pathological fracture in 17.5% (7 patients). After consideration of radiological finding, manifestations of ROD and laboratory parameters, ROD was positive in 37.5% of patients. Concerning manifestations of ROD in group II (control), found 1 patient (5%) with bone deformity and other manifestations was 0%. ROD was negative in 100% of control patients. The ROD was significantly higher in patients with CKD than control group (P<0.05). **(Figure 2).**

Concerning manifestations of ROD of our patients of group IA (stage II, III, IV) and group IB (stage V), bone pain was positive in 36% in group IB and 26.7% in group IA, bone deformity was found in 48% in group IB and 26.7% in group IA, while history of pathological fractures found in 24% in group IB and 6.7% in group IA. ROD was positive in 48% of group IB and 20% of group IA. There was no statistically significant difference between stage 5 CKD and stage 2, 3, 4 CKD as regard the manifestations of ROD (P>0.05). **(Table 8).**

As regards laboratory parameters of our patients of group I (stage II, III, IV, V) and control group, FGF23 serum level in group I (mean ± SD was 532.5 ± 421.7pg/ml) showed statistically significant increase from group II (control) (124.9 ± 108.9 pg/ml) (P value<0.05). Urea, creatinine, phosphorus, ALP, PTH were significantly higher in patients with CKD than control group (P<0.05). In addition; Ca and GFR were significantly lower in patients with CKD than control group (P<0.05). **(Table 6, figure 3).**

Concerning laboratory parameters of our patients of group IA (stage II, III, IV) and group IB (stage V), FGF23 serum level in group IB (mean ± SD was 756 ± 379.8 pg/ml) were significantly higher than group IA (mean ± SD was 160.12 ± 102 pg/ml) (P<0.05). **(Table 7).**

In respect to other laboratory parameters of different stages of CKD (subgroup IA and subgroup IB), there were highly statistically significant difference between (stage II, III, IV and stage V) where Urea, creatinine, phosphorus and ALP were significantly higher in patients with stage 5 CKD than lower stages (P<0.05). While, Calcium and GFR were significantly lower in patients with stage 5 CKD (P<0.05). **(Table 7).**

As regards sensitivity and specificity of FGF23 in predicting CKD we found cut off point 159.7 pg/ml with sensitivity 85%, specificity 90%, accuracy 80%, PPV 94.4%, NPP 75 %, AUROC 0.837 and P Value <0.0001. **(Table 9, Figure 4).**

Table (1) comparison of the age and sex distribution between patients with CKD and controls.

		Group		χ^2	P- Value
		CKD N=40	**Control N=20**		
Sex	**Male**	21 (52.5%)	10 (50.0%)	0.033	0.855
	Female	19 (47.5%)	10 (50.0%)		
Age / years	**Mean ± SD**	12.48 ± 5.66	7.07 ± 4.49	Z= 4.021	<0.0001

χ^2 (Chi square test)
P- Value (probability of significance)

Table (2) the residence and anthropometric measurements in patients with CKD.

		CKD patients N=40	
		No	**%**
Residence	**Urban**	19	47.5 %
	Ruler	21	52.5 %
Built	**average built**	22	55.0 %
	Under built	18	45.0 %
Weight in kg	**Mean ± SD**	29.9 ± 11.64	
	(Min-Max)	(9.4 - 55.60)	
Height in cm	**Mean ± SD**	126.2 ± 20.3	
	(Min-Max)	(79 - 163)	
BMI	**Mean ± SD**	18.41 ± 3.3	
	(Min-Max)	(13.65 - 25.54)	

Table(3) Z score for height, BMI of studied cases (N=40).

	No.	%
Z score for height		
SD between 2+ to -2	14	35
SD below -2	26	65
SD above +2	0	0.00
Z score for BMI		
SD between +2 to -2	32	80
SD below -2	8	20
SD above +2	0	0.00

Table (4) the stages of CKD in the patients.

CKD stage	CKD patients N=40	
	No	**%**
CKD stage 2	4	10 %
CKD stage 3A	3	7.5 %
CKD stage 3B	5	12.5 %
CKD stage 4	3	7.5 %
CKD stage 5	25	62.5 %

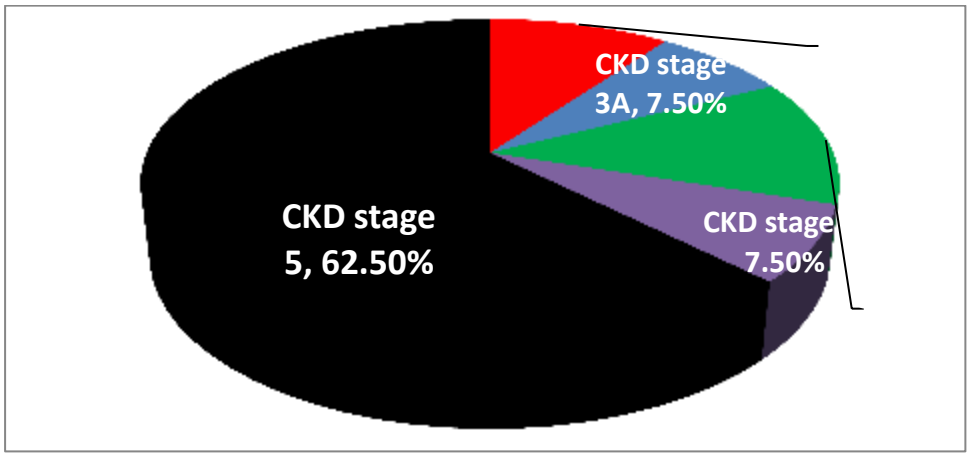

Fig. (1) Pie chart showing the stages of CKD in the patients.

Table (5) comparison of the bone x-ray findings between patients with CKD and controls

		Group CKD N=40	Control N=20	χ^2	P- Value
bone.x.ray	**Normal**	24 (60.0%)	19 (95.0%)	10.1	0.006
	Sub periosteal Bone resorption	14 (35%)	0 (0.0%)	12.1	0.002
	Pathological fractures	7 (17.5%)	0 (0.0%)	6.6	0.035
	Brown tumor	1 (2.5%)	0 (0.0%)	1.42	0.491
	healed rickets	0 (0.0%)	1 (5.0%)	2.03	0.362

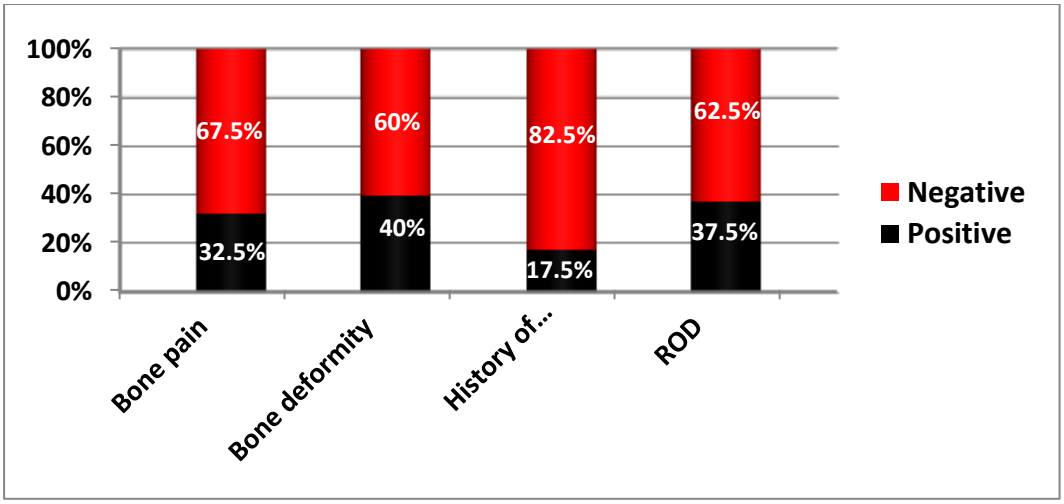

Fig (2) Bar chart showing the manifestations of ROD in patients with CKD.

Table (6) comparison of the laboratory parameters between patients with CKD and controls.

	Group		Mannwhitny U test	P-value
	CKD N=40 Mean ± SD	Control N=20 Mean ± SD		
CBC.HB (gm/dl)	11.2± 2.39	11.7 ± 1.5	t= -0.986	0.329
Urea/prediaysis (mg/dl)	122.9 ± 57.6	18.2 ± 3.6	11.447	<0.0001
Creatinine/prediaylsis (mg/dl)	5.48 ± 3.25	0.5975 ± 0.16	9.488	<0.0001
Calcium (mg/dl)	8.64 ± 1.19	9.6 ± 0.76	t= -3.775	<0.0001
Phosphorus (mg/dl)	4.6 ± 1.02	4.3 ± 0.42	t= 1.572	0.121
Alkaline Phosphatase (IU/L)	323.7 ± 413.4	189.8 ± 54.8	2.013	0.051
Parathyroid hormone PTH (pg/ml)	159.7 ± 197	48.4 ± 22.01	3.530	0.001
FGF 23 (pg/ml)	532.5 ± 421.7	124.9 ± 108.9	5.740	<0.0001
GFR	22.9 ± 20.2	114.4 ± 9.9	-23.457	<0.0001

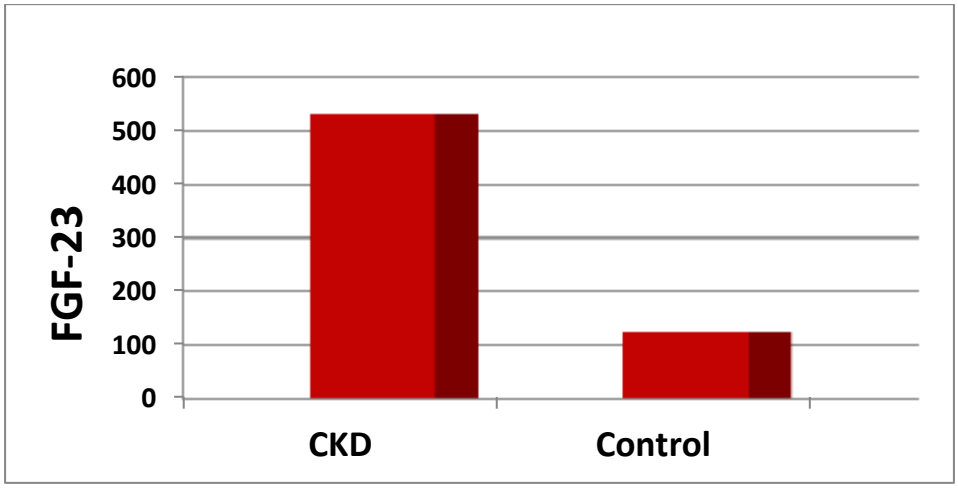

Fig. (3) Bar chart showing comparison of the FGF-23 between patients with CKD and controls.

Table (7) comparison of laboratory parameters between patients with stage 5 CKD and lower stages.

	group		Mannwhitny U test	P-value
	stage 5 CKD N=25 Mean ± SD	stage 2,3,4 CKD N=15 Mean ± SD		
CBC.HB (gm/dl)	11.1 ± 2.58	11.3620 ± 2.10240	-0.344	0.733
Urea/prediaysis (mg/dl)	153.64± 50.1	71.8000 ± 21.39159	7.146	<0.0001
Creatinine/prediaylsis (mg/dl)	7.6 ± 1.98	1.9200 ± 0.93213	12.294	<0.0001
Calcium (mg/dl)	8.29 ± 1.1	9.2267 ± 0.99890	-2.679	0.011
Phosphorus (mg/dl)	4.84 ± 1.01	4.1933 ± 0.92618	2.072	0.046
Alkaline Phosphatase (IU/L)	428.6 ± 494.2	148.8667 ± 71.33409	2.782	0.010
Parathyroid hormone PTH (pg/ml)	193.6 ± 236.6	103.32 ± 81.8	1.742	0.091
FGF 23 (pg/ml)	756 ± 379.8	160.12 ± 102	7.411	<0.0001
GFR	10.6 ± 2.45	43.3 ± 20.4	-6.184	<0.0001

Table (8)comparison of the manifestations of ROD between patients with stage 5 CKD and lower stages.

		group			
		stage 5 CKD n=25	stage 2,3,4 CKD n=15		
Bone pain	**Positive**	9 (36.0%)	4 (26.7%)	0.372	0.542
	Negative	16 (64.0%)	11 (73.3%)		
Bone deformity	**Positive**	12 (48.0%)	4 (26.7%)	1.778	0.182
	Negative	13 (52.0%)	11 (73.3%)		
History of pathological fracture	**Positive**	6 (24.0%)	1 (6.7%)	1.951	0.162
	Negative	19 (76.0%)	14 (93.3%)		
ROD	**Positive**	12 (48.0%)	3 (20.0%)	3.136	0.101
	Negative	13 (52.0%)	12 (80.0%)		

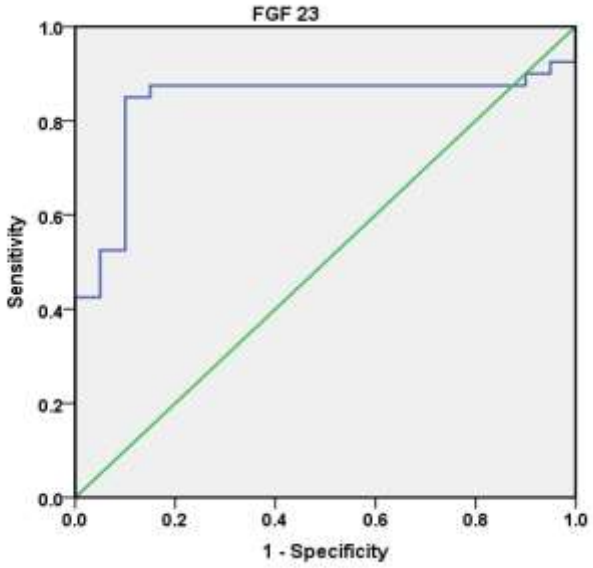

Fig. (4) ROC curve for the diagnostic accuracy of FGF-23 in predicting CKD.

Table(9) Sensitivity and specificity of FGF-23 in predicting CKD

Parameter	Cut off	P-Value	AUROC	Sensitivity	Specificity	PPV	NPP	Accuracy
FGF-23	159.7	<0.0001	0.837	85%	90%	94.4%	75%	80%

4.Discussion

FGF 23 and other calcium-phosphate metabolism characteristics were tested in children with chronic renal disease to see whether they may be used as diagnostic tools. In all children with CKD, test if blood FGF23 may be utilised as an early biomarker for the diagnosis of renal osteodystrophy**.**

The investigation was done at Benha University Hospital's paediatric nephrology unit on 60 youngsters. Group I: comprises 40 individuals with CKD. 15 individuals with CKD stages I-III were included in the subgroup IA (I, II, III, and IV). A total of 25 individuals with CKD stage IB were included in the study. Group II consists of 20 children who appear to be in good health**.**

The height findings were in agreement with previous Egyptian investigations. Using standard deviation charts, Lofty et al., 2015 (9), revealed that 90% of their patients were short. Short stature was reported in 80 percent of the patients in the research by El Shafie et al., 2016-a (10). When it comes to height, however, the evidence from wealthy nations tends to be less severe. It is possible that the increasing influence on height is related to CKD patients being diagnosed and treated more slowly**.**

Occurring in 17.5 percent of our patients, obstruction of the urinary tract was followed by glomerulonephritis and the nephrotic syndrome (15 percent each). Other reasons found include: 12.5% congenital, 7.5% HUS, 5% PUV, 5% anaemia, 2.5% SLE, 2.5% stone, 2.5% Oxalouria, 2.5% nephrotoxic medication, and 2.5% others. Congenital causes (48 percent) and inherited nephropathies (10 percent) are the most frequent causes of CKD in the United States, according to a study published in 2012. One-fourth of all cases were due to glomerulonephritis. It was shown that glomerulonephritis was the most common cause of kidney failure in children ages 12 and older. In Turkey and other Middle Eastern nations, congenital causes of CKD (47–62 percent) are the primary cause of CKD, followed by inherited nephropathies (17 to 30 percent). Consanguineous marriages are more common in the Middle East than in Europe, which may explain why there are more hereditary illnesses there than in Europe. Congenital malformation of the urinary tract (68.6 percent), followed by focal segmental glomerulosclerosis, hemolytic uremic syndrome, polycystic kidney disease, juvenile nephronophthisis, and nephrolithiasis, were the underlying nephropathies that led to CKD, according to a study published in 2011**.**

One patient was discovered to have a brown tumour on his or her thigh, which was the only abnormality detected in the radiological results of 24 of our patients (60%) who had imaging tests that are the most commonly used and most accessible to the general population (2.5 percent). According to Ziókowska and colleagues, 2001 (13), the radiological results of patients with chronic kidney disease were 45.1 percent normal and 44.9 percent abnormal, which may be attributable to the fact that majority of the patients had advanced stages of CKD. Pseudofractures account for 19% of cases, whereas 23.8 percent had subperoneal resorption, according to Demircin et al., 1998 (14). An increase in bone resorption has been found in patients with CKD. There was also a decrease in the rate of bone formation and a reduction in bone mineralization. Osteoporosis was discovered in just 6.5 percent of patients with DXA-measured BMD, whereas no patients had osteoporosis in the lower back or whole hip, according to a study by El-Husseini A, et al., 2022 (16). A total of 44.8 percent of patients were found to have osteopenia at the whole hip, 35.5% at the femoral neck, and 9.7% at the lumbar spine**.**

٣٧.٥percent of patients tested positive with ROD based on radiological findings, ROD symptoms, and laboratory data. All of the patients in the control group tested negative for ROD. Compared to the control group, individuals with CKD had a substantially greater ROD (P=0.01). Ferreira A. C., et al., 2022 (17) showed that more than half of the patients in a group of kidney transplant candidates have ROD (64.2 percent of patients).

There was a significant difference in the phosphorus levels between patients with and without ROD (P0.05). Patients with ROD, on the other hand, had substantially lower levels of calcium and GFR (P0.05). CKD-MBD measures indicate characteristic changes as CKD advances, including a decrease in blood calcium and an increase in serum P, total alkaline phosphatase, and PTH levels, according to Graciolli F. G.,et al., 2017(15). In addition, bone mineralization was impaired and bone formation was reduced. In Ferreira A. C., et al., 2022(16), high levels of PTH and a younger age were linked to rapid bone turnover. Low levels of PTH and advanced age, on the other hand, were linked to lower bone turnover. However, there was no change in the amount of FGF23. FGF-23 was discovered to be negatively linked with bone formation rate by Graciolli F. G.,et al., 2017(15). CKD patients' bones were also shown to have an increased expression of FGF-23. Bone production and resorption biochemical indicators considerably increased in both CKD groups than in the control group, according to Siomou E; et al., 2011(14**.(**

In Group I, the mean Hb level was 11.2 gm/dl 2.39 gm/dl (patients). In accordance with KDOQI standards, a target Hb level of 11–12 g/ dl is advised. According to the findings of Elshafie et al, 2016-(10), the mean Hb level in their research was 11.9 g/dl**.**

In comparison to group II (the control), the FGF23 serum level in group I increased statistically significantly (P value 0.05). Patients with CKD had substantially higher levels of urea, creatinine, phosphorus, ALP, and PTH than those in the control group (P0.05). Furthermore, individuals with CKD had substantially lower Ca and GFR than the control group (P0.05). Siomou E., et al., 2011(10) found that FGF-23 levels were considerably higher in both CKD groups (CKD stages 3-4 and CKD stage 5) than in the controls (p0.0001), whereas Pi and iPTH levels were only higher in the CKD5 (p0.0001).

Significantly greater FGF23 serum levels were seen in group IB (P 0.05) than group A. Siomou et al. (2011) observed similar findings. Van Husen et al, 2010 (18) revealed that FGF23 serum concentrations were adversely linked with the predicted rate of renal clearance. There was no significant difference in FGF23 serum levels between hemodialysis and peritoneal dialysis. This study found no significant differences in FGF23 levels and bone metabolism and calcium-phosphate balance between CKD stage 1–2 patients and the control group in terms of these variables**.**

Patients with stage 5 CKD had considerably greater levels of urea, creatinine, phosphorus, and ALP than those in the earlier stages of the disease, a result that was statistically significant (P0.05). As a result, stage 5 CKD patients had substantially decreased calcium and GFR levels (P0.05). The levels of FGF23 and PTH were observed to rise significantly as renal impairment progressed, according to Van Husen M., et al. (2010). Patients in stages 4 and 5 of CKD had significantly higher serum phosphate levels than those in stages 1–2 of the disease. GFR was considerably lower in patients who had reached the end point of progression (FLISER D et al., 2007 (19)). In addition, their phosphate, PTH, and FGF23 levels were much greater. Patient's on traditional hemodialysis had lower haemoglobin and ionised calcium levels, as well as greater P and PTH, total alkaline phosphatase (TAP) and FGF-23, according to Graciolli F. G.,et al, 2017(15). A drop in blood ionised calcium was seen in patients with CKD stages 2 and 3, as was a rise in serum P, total alkaline phosphatase, and FGF-23. Serum iPTH, phosphorus, and c-terminal FGF-23 associated adversely with eGFR in El-Husseini A, et al., 2022(16**.(**

A link between FGF23 and glomerular filtration rate (GFR) was found to be statistically significant in group I. (patients with CKD). Patients' age, urea, creatinine, phosphorus, and alkaline phosphatase all had positive relationships with the association, which was negative for calcium and GFR (P0.05). A positive association between FGF23 serum levels and serum phosphate levels was shown by Van Husen et al., 2010(16). In the combined CKD group, FGF23 and PTH serum levels had a positive association, but total serum calcium had a negative correlation. A study by Wan M., et al. (2013) demonstrated that FGF23 associated adversely with age in children with CKD1–3, but not in children with CKD1–5 or those on dialysis. FLISER D et al., 2007 found Patients with mild to severe CKD were included in their research. CKD progression causes a rise in serum FGF23 levels in tandem with a decrease in GFR and an increase in serum phosphate and PTH concentrations in the bloodstream. When looking for independent predictors of CKD development, FLISER D et al., 2007(17) discovered that only GFR at the beginning of the study, c-terminal FGF23, and intact FGF23 remained significant**.**

Patients' blood levels of calcium, phosphorus, urea, creatinine, haemoglobin, alkaline phosphate, and PTH were not linked to FGF23 level in subgroup IA (STAGE 2, 3, 4; P>0.05). Age, weight, height, BMI, and GFR were. In individuals with STAGE 5 CKD, there was a statistically significant positive connection between FGF-23 and PTH (P0.05). An link between FGF-23 concentrations and age or body mass index (BMI) was not identified; however, these relationships did not remain after taking into account the effects of iPTH concentrations in patients with CKD (Siomou E. et al. 2011). FGF-23 levels were found to be considerably higher in CKD5 patients, who had greater serum Pi levels, than they were in controls, according to Siomou E. et al. (2011). Van Husen et al., 2010 found significant negative correlation between FGF23 and eGFR in advanced stages of the disease. Dialysis patients had the greatest levels of FGF23, according to a 2013 study by Wan M., et al. FGF23's estimated glomerular filtration rate was adversely associated with FGF23's (eGFR). Serum phosphate (P) and parathyroid hormone (PTH) had no association with FGF23 in this group. According to Ziolkowska et al., 2014 [21] there was no significant link between FGF23 and eGFR in children studied, which may be related to the fact that their investigation was limited to children with CKD stage 3-5**.**

As for the cutoff point for FGF23's ability to accurately predict kidney disease, we found that it had a sensitivity and a specificity of 85 percent, 90 percent, and 80 percent, as well as an accuracy of 80 percent, a PPV of 94.4 percent, an NPP of 75 percent, and an AUROC of 0.837 and a P value of 0.0001**.**

Despite receiving appropriate care, many CKD patients continue to exhibit symptoms and indications that impair their ability to lead a normal life. Early on, calcium and phosphorus levels remained normal, while FGF23 levels spiked, statistically significantly correlated with GFR**.**

5. Conclusion

FGF 23 may be utilised as an early biomarker for the progression of chronic kidney disease in children, since it was shown to be significantly greater in CKD patients than controls in both the early and late phases of the illness (stages II, III, and IV). Even in the early stages and before the development of CKD in these children, we advocate evaluating FGF 23 in frequent follow-up.

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