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Effect of Early Introduction of Calcium Carbonate on Fibroblast Growth Factor 23 (FGF23) Levels in Children with Normophosphatemic Early Chronic Kidney Disease (CKD)

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ABSTRACT

Background: Fibroblast Growth Factor 23 (FGF23) is considered as a marker of progression of kidney disease. **Objective:** the aim of the study: is to assess the effect of administration of calcium carbonate on serum FGF23 in normophosphatemic children with early stages CKD.

Patients and Methods: Forty children with early CKD were enrolled in this case-control study. The patients were randomly divided equally into two groups A and B. Group A (received daily oral calcium-carbonate as a phosphate binder) over a period of 6 months, and group B (did not receive oral phosphate binder or calcimimetics). Baseline and follow up urea, creatinine, serum phosphate, serum calcium, alkaline phosphatase, 25 hydroxy vitamin D, parathormone (PTH) and serum FGF23 were obtained at the start and at the end of the study period.

Results: Group A showed a significant decrease in serum levels of P, ALP and 25 hydroxy vitamin D (p-values: <0.001, 0.003, 0.0001 respectively). Also, there was non-significant decrease of PTH and serum FGF-23 (p-values: 0.39 and 0.396 respectively). While in group B there was a significant increase in levels of phosphate, PTH and FGF23 (p-values: 0.012, <0.001, <0.001) respectively, in contrast to significant decrease in levels of serum calcium and 25 hydroxy vitamin D (p-values: 0.033 and <0.001 respectively).

Conclusion: Oral calcium-based phosphate binder has a role in decrease production of FGF23 and control secondary hyperparathyroidism in early CKD children.

Keywords: CKD, FGF23, Phosphate binders and PTH.

INTRODUCTION

In children, chronic kidney disease (CKD) became a serious health issue as it became more frequent and related co morbidities[(1)]. Fibroblast Growth Factor 23 (FGF23), along with parathormone (PTH) and 1,25(OH)2D3, is one of three hormones that regulate phosphate homeostasis and is released by osteocytes in the bone [(2)].

Bone mineral disease is one of the consequences of chronic renal disease (CKD-BMD), this results from hyperphosphatemia and an increase in serum FGF 23 level [(3)].

Serum FGF23 level rises in early CKD to control phosphate retention by reducing phosphate reabsorption by renal tubules. With the progression of the renal disease, blood FGF23 levels rise and inhibit 25(OH) 2D3 production, resulting in hypocalcemia and secondary hyperparathyroidism [4].

There is conflicting evidence from earlier studies that suggests using calcium-based oral phosphate binders can either have no effect on FGF23 levels [5] or cause them decrease [(6-8)].

The purpose of this research is to evaluate the effect of administration of calcium carbonate as oral phosphate binder on serum FGF23 in normophosphatemic children with early stages CKD.

PATIENTS AND METHODS

This case control study was conducted on 40 children with normophosphatemic, CKD stages 2 (eGFR: 60-89 mL/min/1.73 m^2), 3a (eGFR:45-59 mL/min/1.73 m^2) and 3b (eGFR: 30-44 mL/min/1.73 m^2) (KDIGO 2012) [9] aged from 2 to 18 years old following at Outpatient Nephrology Clinic, Cairo University Children Hospital.

Patients that fit the following criteria weren't included in the study: patients with hyperphosphatemia [10], marked hypocalcemia (total serum calcium <7 mg/dl) [11], previous or current treatment with phosphorus binders or active vitamin D, malnutrition (serum albumin<3.0 mg/dl) [12], use of phenytoin (may induce vitamin D deficiency) and primary parathyroid disease, or previous parathyroidectomy.

Ethical Consideration:

Research Ethics Committee at Cairo University, Egypt, approved this research. The Ethical Committee approval number is MS-176-2019. Participants' legal

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guardians provided written informed consent to participate in this study. The principles of the Declaration of Helsinki 1967 are fulfilled by each and every procedure employed in this work.

All included patients were subjected to the following:

Full history including (name, age, sex, onset of renal disease and onset of renal impairment) and physical examination including anthropometric measures (weight and height) and vital signs.

To determine eGFR, the Schwartz formula was employed. The Schwartz formula can be used to predict the eGFR from the constant k, plasma creatinine (P Cr) (in mg/dL), and body length (L in cm) [13], as follows: eGFR = (k X L) / P Cr

At different ages, "k" takes on different values: k = 0.4 for preterm infants, 0.45 for full-term infants, and 0.55 for older children (aged 2-12 y) [14].

The patients were randomly divided into two groups. Group A included 20 patients with mean age 7.4 years (12 females and 8 males) who received daily oral calcium-based phosphate binder (calcium carbonate) at lowest dose as mentioned by KDIGO CKD-MBD 2017 [15] over a period of 6 months, and group B included 20 patients with mean age 6.7 years (10 females and 10 males) who did not receive oral phosphate binder or calcimimetics over the same period of time. Over the course of the study, neither group made any dietary changes or restrictions.

Serum samples were drawn from the patients in the two study groups at the beginning and end of this study period during annual outpatient nephrology clinic visits, centrifuged and stored at -20°C to assess urea, creatinine, serum phosphate, ionized calcium, serum calcium, alkaline phosphatase, 25 hydroxy vitamin D, PTH and serum FGF23.

Statistical analysis

The statistical package for the social sciences (SPSS Version 25) software was used to analyze the data collected. Quantitative data were represented as mean, standard deviation, median, and interquartile range, whereas qualitative data were presented as number and percentage. In accordance with parametric and non-parametric data, statistical analysis was performed. The independent T test and the Mann Whitney test were employed to compare numerical variables between two groups, and when comparing the means of the same individuals, the paired sample t-test was used. Non-normally distributed variables were compared using the Wilcoxon signed-rank test.

Pearson's correlation coefficients were used for numerical association. If P-value was 0.05 or less, the level of significance was taken into consideration.

RESULTS

The demographic, clinical and laboratory data of the study group

This case control study included 40 early CKD children divided randomly into two groups. Group A :20 patients (who received phosphate binder) and group B :20 patients (who did not receive phosphate binder). The mean age was 7.4 ±3.2 (3-14) years in group A, while it was 6.7± 2.9 (4-13) years in group B. With female predominance in group A 60% (n = 12). The baseline clinical and laboratory data of both groups were nearly similar as demonstrated in table 1.

Table 1: Baseline Clinical and laboratory data of the study group

	Group A1(n=20)	**Group B1(n=20)**	**P-value**
	Mean±SD /Median(IQR)	Mean±SD /Median(IQR)	
Clinical data			
Weight (Kgs) Median(IQR)	18.5 (10.25)	18.5(8.25)	0.80
Weight SDS Mean±SD	-1.42 ±1.3	-0.62±1.16	0.051
Height (cm) Median(IQR)	110 (37)	100.5 (24)	0.75
Height SDS Mean±SD	-2.3±2.5	-2.27±1.3	0.73
Onset of renal disease (years) Mean±SD	2.3±3.23	1.4±1.9	0.42
Onset of renal impairment(years) Mean±SD	4.2±2.783	2.65±2.007	0.85
Laboratory data			
Hb (gm/dL) Mean±SD	10.885±1.26	10.8±0.92	0.81
TLC ($\times 10^3$/uL) Mean±SD	9.08±2.29	10.1±2.77	0.58
PLT ($\times 10^3$/uL) Mean±SD	332.95±10.4	348.1±80.1	0.58
Na (mmol/L) Mean±SD	140.15±4.25	140.05±3.9	0.94
K (mmol/L) Mean±SD	4.29±0.58	4.3±0.59	0.96
eGFR (mL/min/1.73 m2) Mean±SD	66.6±9.1	68.55±8.9	0.50
Creatinine (mg/dL) Mean±SD	0.98±0.14	0.835±0.11	**<0.001**
Ca (mg/dL) Mean±SD	8.51±0.88	8.65±0.94	0.63
P (mg/dL) Mean±SD	5.615±0.61	5.26±0.54	0.06
ALP (U/L) Mean±SD	272.9±53.15	397.2±62.2	0.54
PTH (pg/mL) Mean±SD	76.3±7.2	65.05±3.21	0.56
25 hydroxy vitamin D (ng/mL) Mean±SD	32.65±8.6	29.65±5.45	**0.01**
FGF-23 (RU/ml) Mean±SD	189.35±9.19	174.87±8.8	0.41

*Hb: hemoglobin, TLC: total leukocytic count, PLT: platelet, eGFR: estimated glomerular filtration rate, ALP=alkaline phosphatase, PTH: parathyroid hormone, FGF-23: fibroblast growth factor 23, IQR: interquartile range, SDS: standard deviation score.
**Normal reference range: ALP: (80-644) U/L, PTH (10-65) pg/Ml, 25 hydroxy vitamin D (deficiency <20, insufficient :20-29, sufficient:30-100) ng/mL.
*** Group A1 (group A at the start of the study period),Group B1 (group B at the start of the study period)

The most common primary renal disease among the study group was congenital anomalies of the kidney and urinary tract (CAKUT) in 50 % (n=20) of cases as shown in table 2.

Table 2: the primary renal disease of both study groups

Etiology		**Group A (n=20)**	**Group B (n=20)**	**Total (**Percent**)**
CAKUT	VUR	7	4	11(27.5%)
	Obstructive uropathy	3	4	7(17.5%)
	PUJ obstruction	0	2	2(5%)
Unknown		3	4	7(17.5%)
MCDK		3	1	4(10%)
FSGS		2	2	4(10%)
HUS		1	0	1(2.5%)
PKD		0	2	2(5%)
TIN		1	1	2(5%)
Total		20	20	40

CAKUT: congenital anomalies of the kidney and urinary tract, VUR: Vesicoureteral reflux, PUJ: pelviureteric Junction, FSGS: focal segmental glomerulosclerosis, HUS: hemolytic uremic syndrome, MCDK: multicystic dysplastic kidney, PKD: polycystic kidney disease, TIN: tubule interstitial nephritis.

In this study it was observed that in the group, which received phosphate binder, there was significant increase of serum levels of creatinine and calcium, in contrast to significant decrease in serum levels of P, ALP and 25 hydroxy vitamin D (Table 3).

Table 3 Comparison of the clinical and laboratory characteristics in Group A at the start and at the end of the study period before (A1) and after receiving P binder (A2)

	A1 group(n=20) Mean±SD /Median(IQR)	**A2 group(n=20)** Mean±SD /Median(IQR)	**P-value**
Weight(kgs) Median(IQR)	18.5(10.25)	19.5(10.25)	**0.004**
Weight SDS Mean±SD	-1.42 ±1.3	-1.01±1.1	**<0.001**
Height(cm) Median(IQR)	110 (37)	111.5(36.2)	**<0.001**
Height SDS Mean±SD	-2.3±2.5	-1.8±2.5	**<0.001**
Hb(gm/dL) Mean±SD	10.8±1.2	11.2±0.8	0.298
TLC(×10^3/uL) Mean±SD	9.08±2.2	8.5±1.3	0.295
PLT(×10^3/uL) Mean±SD	332.9±9.9	313.4±8.4	0.258
eGFR(mL/min/1.73 m^2) Mean±SD	66.6±8.89	64.7±9.3	0.190
Creatinine(mg/dL) Mean±SD	0.89±0.13	0.94±0.11	**0.030**
Ca(mg/dL) Mean±SD	8.5±0.86	10.1±0.89	**<0.001**
P(mg/dL) Mean±SD	5.6±0.61	4.9±0.4	**<0.001**
ALP(U/L) Mean±SD	272.9±53.1	251.5±60.4	**0.003**
Na(mmol/L) Mean±SD	140.1±4.2	139.6±4.1	0.610
K(mmol/L) Mean±SD	4.2±0.58	4.4±0.48	0.323
PTH(pg/mL) Mean±SD	76.3±7.2	74±2.7	0.398
25 hydroxy vitamin D(ng/mL) Mean±SD	32.6±8.6	27.4±5.3	**<0.001**
FGF-23(RU/ml) Mean±SD	189.3±9.2	183.2±8.4	0.396

*Hb: hemoglobin, TLC: total leukocytic count, PLT: platelet, eGFR: estimated glomerular filtration rate, ALP: alkaline phosphatase, PTH: parathyroid hormone, FGF-23: fibroblast growth factor 23, IQR: interquartile range, SDS: standard deviation score.

**Normal reference range: ALP:(80-644) U/L, PTH (10-65) pg/Ml, 25 hydroxy vitamin D (deficiency <20, insufficient :20-29, sufficient:30-100) ng/mL.

We noticed that in the group that didn't receive phosphate binder there was significant increase in levels of P, PTH and FGF23, in contrast to significant decrease in levels of serum calcium and 25 hydroxy vitamin D (Table 4).

Table 4: Comparison of the clinical and laboratory characteristics in Group B at the start (B1) and at the end (B2) of the study period

	B1 group(n=20) Mean±SD /Median (IQR)	**B2 group(n=20)** Mean±SD /Median (IQR)	**P-value**
Weight Median (IQR)	18.5(8.25)	18.5(8.5)	**0.005**
Weight SDS Mean±SD	-0.62±1.16	-2.6±1.01	**0.015**
Height Median (IQR)	100.5(24)	104(24)	**<0.001**
Height SDS Mean±SD	-2.27±1.3	-1.75±1.25	**<0.001**
Hb(gm/dL) Mean±SD	10.8±0.92	11±1.17	0.413
TLC(×10^3/uL) Mean±SD	10.1±3.7	9.7±2.7	0.699
PLT(×10^3/uL) Mean±SD	348.1±80.1	346±63.4	0.900
eGFR(mL/min/1.73 m^2) Mean±SD	68.5±8.9	66.8±8.2	0.287
Creatinine(mg/dL) Mean±SD	0.83±0.11	0.87±0.14	0.077
Ca (mg/dL) Mean±SD	8.6±0.94	8.2±0.73	**0.033**
P(mg/dL) Mean±SD	5.2±0.54	5.5±0.72	**0.012**
ALP(U/L) Mean±SD	397.2±62.2	394±47	0.776
Na(mmol/L) Mean±SD	140±3.9	145.2±22.5	0.313
K(mmol/L) Mean±SD	4.3±0.59	4.2±0.43	0.344
PTH(pg/mL) Mean±SD	65.05±3	73.9±8.2	**<0.001**
25hydroxy vitamin D(ng/mL) Mean±SD	29.6±5.4	25.6±5.7	**<0.001**
FGF-23(RU/ml) Mean±SD	174.8±8.8	196.1±8.3	**<0.001**

*Hb: hemoglobin, TLC: total leukocytic count, PLT: platelet, eGFR=estimated glomerular filtration rate, ALP=alkaline phosphatase, PTH: parathyroid hormone, FGF-23=fibroblast growth factor 23, IQR: interquartile range, SDS: standard deviation score.
**Normal reference range: ALP:(80-644) U/L, PTH (10-65) pg/Ml, 25 hydroxy vitamin D (deficiency <20, insufficient :20-29, sufficient:30-100) ng/mL.

In patients who did not receive oral calcium carbonate phosphorous binder it was noticed that there were significant positive correlations between the FGF23 and serum creatinine (r-value:0.55, p-value: 0.05), serum phosphorous (r-value:0.56, p-value: 0.01) and PTH (r-value:0.63, p-value: 0.003) as shown in figures 1, 2, 3.

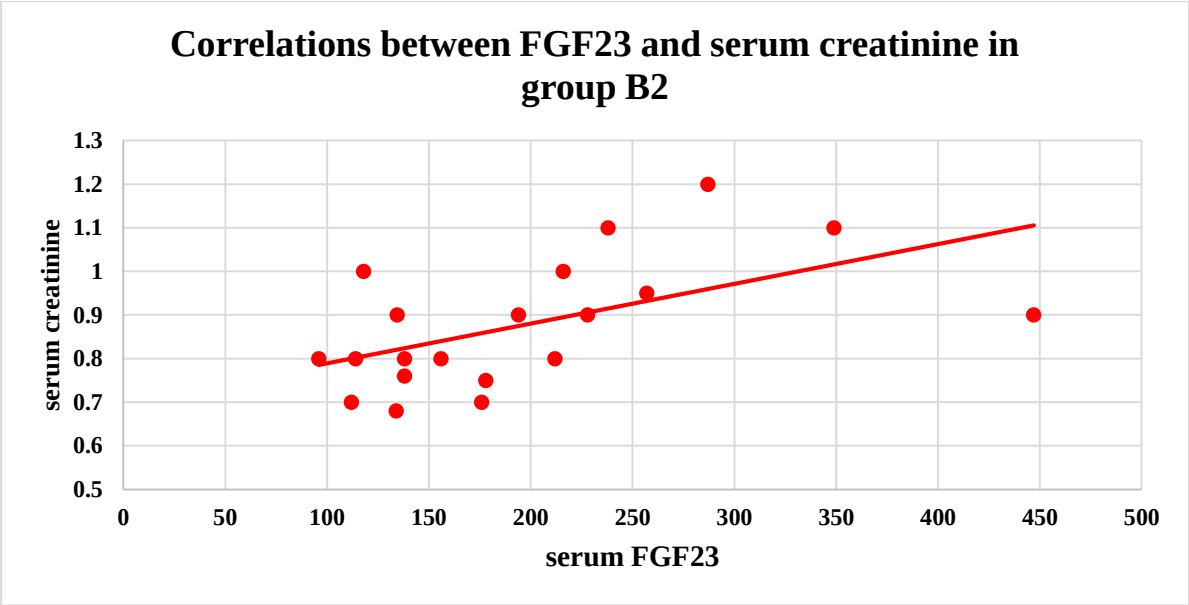

Figure 1: Correlations between FGF23 and serum creatinine in group B2 (i.e., group B at the end of the study period)

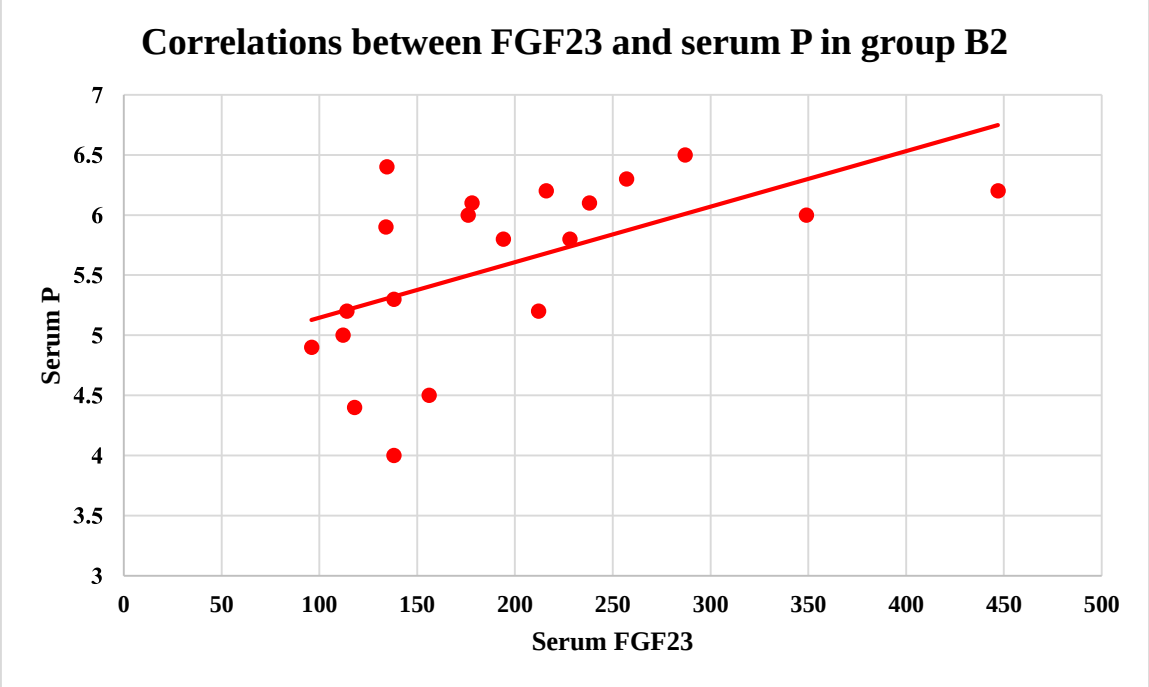

Figure 2: Correlations between FGF23 and serum P in group B2 (i.e., group B at the end of the study period)

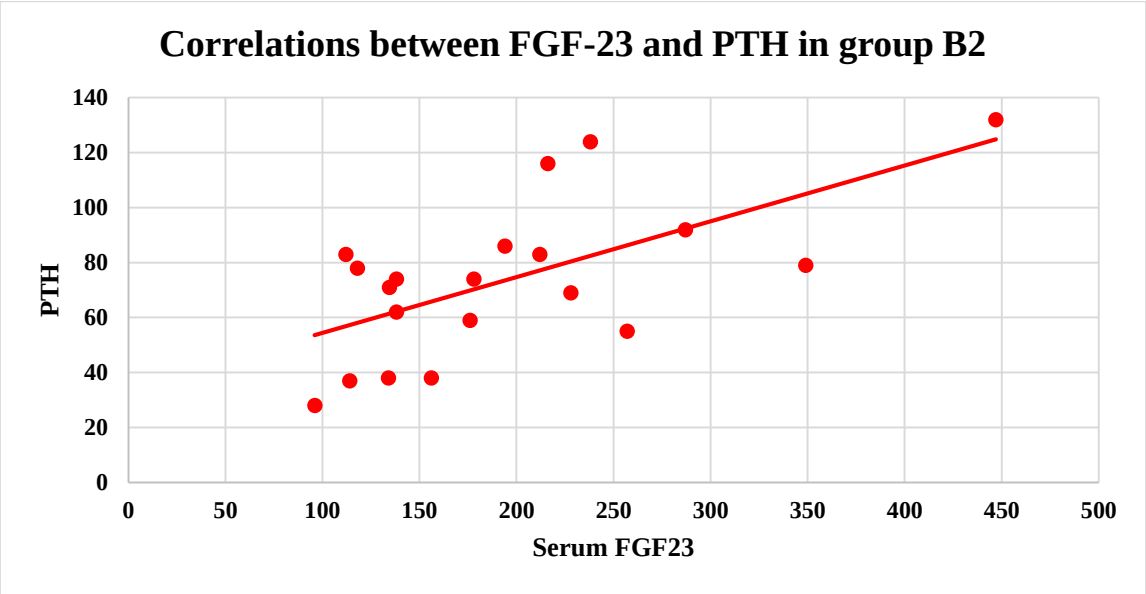

Figure 3: Correlations between FGF23 and PTH in group B2 (i.e., group B at the end of the study period).

DISCUSSION

This case control study showed that early introduction of calcium carbonate in early normophosphatemic CKD children controls FGF23 production. FGF23 is considered as a marker of progression of kidney disease [4]. FGF23 level rises in early stages of CKD in response to increase serum phosphate as a result of decreased the number of functioning nephrons leading to decrease phosphate reabsorption by renal tubules maintaining normal serum phosphate in early stages of CKD [2].

The participants in this study were normophosphatemic, thus we used the lowest amount of calcium carbonate as mentioned by KDIGO CKD-MBD 2017[(15)] to prevent the development of hypophosphatemia.

In this study, it was noticed that the use of calcium carbonate as a phosphate binder decreased the serum FGF23 but not statistically significant and when compared to CKD children who did not receive calcium carbonate, it was found that they had significant increase FGF23, that means indirectly administration of oral phosphate binder as calcium carbonate decreased level of FGF23 in early CKD children.

This agrees with several studies, but in adults that showed that the oral phosphate binders decrease level FGF23 weather in normal individuals [16], normphosphatemic[5] or hyperphosphatemic CKD patients[17, 18]. Some studies showed no effect on serum FGF23 but they used lanthanum for a duration of two weeks only and compared to placebo [8].

We observed in the group of patients who received oral phosphate binder that there was a significant increase in serum creatinine, but without significant decrease in eGFR because those patients showed significant increase in their height. In this study, eGFR was measured using Schwartz's formula [(13)], and the patient's height had an impact on it.

Skin production is the main source of vitamin D, supplying more than 90% of the serum vitamin D levels. 7-dehydrocholesterol (provitamin D3) transforms into vitamin D3 (cholecalciferol) while receiving ultraviolet B from the sun. Vitamin D3 is transformed by the liver into 25-hydroxyvitamin D (25(OH) D), which is assumed to be physiologically inert but is usually recognized as the best biomarker of vitamin D status. The physiologically active form of vitamin D, 1, 25[OH] 2D (calcitriol), is produced in the kidney by the metabolism of 25(OH) D [(19)]. Furthermore, vitamin D deficiency in CKD children is popularly reported as there is decrease levels of both 1, 25 dihydroxy vitamin D and 25 hydroxy vitamin D [20, 21].

We didn't include any patients who were taking any form of vitamin D because it raises the serum level of FGF23 [22], And increased FGF23 levels, in turn, causes 1,25-hydroxyvitamin D levels to decline [23].

We observed that the serum levels of 25-hydroxyvitamin D in both study groups was significantly decreased when compared to their base line values. This agrees with several studies that revealed increased FGF23 level caused decrease vitamin D level [21, 22], but in our work, we did not find a significant correlation between FGF23 and 25 hydroxy vitamin D level. This could explain the cause of decrease vitamin D level in group B, but in group A even with the use of oral phosphate binder there was decrease in vitamin D level. This could be explained that the use of calcium-based phosphate binder led to significant increased serum calcium (p-value :<

0.001) and decreased PTH production and in turn caused decrease vitamin D level [24].

This is consistent with research on adult patients who had moderate to severe grades of CKD, to evaluate the impact of different types of oral phosphate binders on serum vitamin D and vitamin D metabolites levels showed that calcium-based phosphate binders caused decrease level of 1, 25[OH] 2D compared to non-calcium-based phosphate binders. The authors explained that calcium supplementation reduced PTH production, which reduced 1,25-dihydroxyvitamin D production without affecting FGF23[24].

In this study, we observed that the serum PTH decreased when calcium carbonate was used as a phosphate binder. but not statistically significant decrease and when compared to CKD children who did not receive calcium carbonate, it was found that they had significant increase in PTH, also those children who did not received oral calcium carbonate phosphorous binder had significant positive correlations between the FGF23 and PTH (r-value:0.63). We can conclude that administration of calcium carbonate in early CKD children may have a role in control of development of hyperparathyroidism in CKD children [25].

This agrees with a study that showed that calcium supplementation in calcium-based phosphate binder decreases PTH level in CKD through increasing serum calcium [5, 24]. Additionally, the use oral phosphate binders in CKD patients controls hyperphosphatemia and in turn decreases PTH level by lowering serum phosphate [26].

The study limitations include the necessity for a cross-over research to examine the actual impact on FGF23 on the same patients of receiving or not receiving oral calcium-based phosphate binder. Also, the importance of using different forms of oral phosphate binders in addition to compare the effects of calcium- and non-calcium-based phosphate binders on FGF23.

CONCLUSIONS

In children with early CKD, oral calcium-based phosphate binder can reduce FGF23 production and control secondary hyperparathyroidism.

DECLARATIONS

-Authors' contributions:

The submitted manuscript is the work of the authors. All authors have contributed to authorship, have read and approved the manuscript. Conception and design of study was by Samuel Helmy Makar. Acquisition of data: by Bahaa Kamal Elsakhawy, Laboratory analysis work by Balsam Sherif Fahmy, Analysis and/or interpretation of data: Eman Abobakr and Bahaa Kamal Elsakhawy, The manuscript's initial design: Eman Abobakr, Reviewing the manuscript closely for significant intellectual content: Samuel Helmy Makar. Approval of the version of the manuscript to be published: All authors.

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