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ORIGINAL ARTICLE

Assessment of the Serum Fibroblast Growth Factor 23 Level in Different Types of Rickets

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ABSTRACT

Background: Worldwide, rickets had a significant impact on children and adolescents', growth, and development as well as their general health. The fibroblast growth factor 23 (FGF23) gene, which encodes a secreted protein that is related to the fibroblast growth factors, is present in certain forms of rickets. This study aimed to assess the FGF 23 level among different types of rickets. **Methods:** In this case control study, we included 64 children who were divided into four groups: hypophosphatemic rickets: 16 cases, vitamin D resistance: 16 cases, vitamin D deficiency: 16 cases, and normal: 16 cases. We measured parameters including age, weight, height, ionized serum calcium, total serum calcium, alkaline phosphatase, serum phosphorus, vitamin D, parathormone, serum creatinine, and serum FGF23 levels. **Results:** Ionized and total serum calcium, serum phosphorus, alkaline phosphatase, vitamin D, parathormone, serum creatinine, and serum FGF23 levels showed highly significant differences (P-values < 0.0001). Compared to vitamin D deficiency, hypophosphatemic rickets displayed notably lower levels of serum phosphorus and parathormone. However, the hypophosphatemic rickets group demonstrated significantly higher levels of certain biomarkers in comparison to the vitamin D deficiency group. The prognostic performance of serum FGF23 levels indicated a high area under the curve, with a specificity of 50.0%, and a sensitivity of 93.8% using a cutoff value of 131.5 to identify hypophosphatemic rickets. Univariate and multivariate logistic regression analyses highlighted a significant association between high serum FGF23 levels and the likelihood of hypophosphatemic rickets, even when adjusted for age and weight. **Conclusions:** Our findings highlight the potential of serum FGF23 levels as a diagnostic indicator for hypophosphatemic rickets.
Key words: FGF23; Rickets; Pediatrics.

INTRODUCTION

Rickets is a worldwide problem that has a significant impact on kids' and teens' physical and mental growth and development. The condition, caused by problems in the growth plate cartilage, causes skeletal abnormalities including bowlegs due to improper bone development and mineralization. [1].

To avoid developing nutritional rickets, it's important to get enough vitamin D from food and sunlight. Vitamin D supplementation is effective for vitamin D-deficient rickets, but not for most other forms of rickets [2].

Hypophosphatemic rickets, which necessitates earlier assessment and management using activated vitamin D with or without phosphate supplementations, is a type of vitamin D-resistant rickets triggered by renal phosphate loss in which fibroblast growth factor-23 often plays a great role [3].

Severe rickets, hypocalcemia, increased levels of l,25(OH)2 D, and secondary hyperparathyroidism are all hallmarks of the autosomal recessive condition known as hereditary vitamin D-resistant rickets (HVDRR). Abnormalities in vitamin D receptors have been correlated with HVDRR.

Researchers have identified the VDR gene as a steroid receptor [4].

Patients with these hypophosphatemic disorders have elevated levels of circulating FGF23, in contrast to those who have chronic hypophosphatemia due to other reasons, like vitamin D insufficiency, where FGF23 levels are relatively low. These findings support the usefulness of FGF23 evaluation in the differential diagnosis of hypophosphatemia [5]. The findings demonstrated that FGF23 decreases proximal tubular phosphate reabsorption by downregulating the expression of type 2a and 2c sodium-phosphate transporters in the renal proximal tubule brush border membrane. These sodium-phosphate transporters are responsible for the reabsorption of 80-90% of the phosphate that is filtered out by the glomeruli in the proximal tubules. Additionally, FGF23 decreases the expression of CYP27B1, which codes for an enzyme that converts 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D (1,25(OH)2D) and increases the expression of CYP24A1, which codes for an enzyme that decreases the circulating level of 1,25(OH)2D [6]. So, we aimed this study to assess the FGF 23 level among different types of rickets.

METHODS

This was a case control study that was performed at the Pediatrics Department of Zagazig University Hospitals.

Sample Size: It was done on 64 children divided into 4 groups in duration from December 2022 to July 2023.

Written informed consent was obtained from all participants, the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University. The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Patients:

The study included 64 patients divided into 4 groups Group A: included 16 patients of vit. D resistance rickets, Group B: included 16 patients of vit. D deficiency rickets, Group C: included 16 patients of hypophosphatemic rickets, and Group D; included 16 normal children as a control.

Ages included in the study were between 2 and 18 years. We included clinical cases with vit. D deficiency, resistance rickets, and hypophosphatemic rickets from both sexes. We excluded children with any of the following conditions; any other type of rickets [congenital rickets, renal rickets, neoplastic rickets, etc.], immunocompromised, malignancy patients and patients who had conditions that could affect FGF-23 like acute kidney disease, chronic kidney disease, heart failure, sepsis and tumor induced osteomalacia.

Methods:

All the included children were subjected to complete history taking including personal, complaint, present, past, perinatal, developmental, dietetic history, history of factors contributing to the development of rickets, drug history as well as family history of obesity. The general and local examination was done on all participants with special emphasis on signs of rickets (knock knees, bowed legs, frontal bossing, delayed closure of anterior fontanelle, rachitic rosary, craniotabes, enlargement of the wrists and knees, pigeon chest, growth retardation, Harrison groove, Marfan sign, greenstick fracture, or kyphosis).

Laboratory investigations included serum levels of phosphate, alkaline phosphatase, calcium, parathormone (PTH), 1,25(OH) 2 D, 25(OH)D if needed, and urine calcium/creatinine ratio (U-Ca/Cr). Also, detection of FGF 23 level was performed using Intact sandwich Enzyme-linked immunosorbent assay (ELISA) technique.

Assay Procedure:

The intact FGF-23 assay is an enzyme-linked immunosorbent assay (ELISA) that uses a 96-well plate coated with goat anti-human FGF-23 to which sample is added, and a solution of goat anti-human FGF-23 conjugated to horseradish peroxidase (HRP) for detection. Measurements were given in picograms per milliliter. Five to fifty-two was our FGF23 cutoff. According to the manufacturer, 1 RU/mL is roughly equivalent to 2 pg/mL, which is the unit of measurement used to express the values. ELISA was carried out manually following the kit's instructions. All results have been recorded analyzed and compared.

Administrative design: Approval was obtained from Zagazig University Institutional Review Board (IRB).

Statistical analysis

Information gathered from a patient's medical history, physical examination, laboratory tests, and were coded, processed, and analyzed in Microsoft Excel. To conduct statistical analysis, the gathered data were loaded into SPSS 20.0 (Statistical Package for the Social Sciences). Information was gathered and analyzed statistically. Post hoc analysis and one-way ANOVA tests were employed.

RESULTS

-The mean age of the included children was 4.38 ± 3.84 years, with a range from 0.75 to 16.0 years. The mean weight (±SD) was 18.89 ± 7.04 kg,

ranging from 9.0 to 40.0 kg. The weight Z score was -0.004 ± 1.002. The mean height (±SD) was 92.88 ± 12.71 cm, with a range from 70.0 to 121.5 cm. The mean height Z score was 0.006 ± 0.98 (Table 1).

- One-way ANOVA results revealed significant differences among the groups for all parameters, except for age, weight, and height (P-values > 0.05). The differences in total serum calcium, ionized serum calcium, serum phosphorus, alkaline phosphatase, vitamin D, parathormone, serum creatinine, and serum FGF23 levels were all highly significant (P-values < 0.0001). The serum creatinine levels also showed a significant difference among the groups (P-value = 0.04) (Table 2).
- The post hoc analysis reveals several statistically significant differences between the hypophosphatemia rickets group and the other populations, particularly in terms of calcium levels, phosphorus levels, vitamin D levels, parathormone levels, alkaline phosphatase levels, serum creatinine levels, and serum FGF23 levels (Table 3).
- Compared to the vitamin D resistance group, the results showed that hypophosphatemia rickets demonstrated lower levels of serum phosphorus (p-value = 0.009), vitamin D (p-value < 0.0001), and parathormone (p-value < 0.0001). However, hypophosphatemia rickets showed significantly higher levels of serum Ca (p-value= 02) and serum FGF23 (p-value < 0.0001) compared to vitamin D resistance.
- The results showed that hypophosphatemic rickets had significantly lower levels of serum phosphorus (p-value < 0.0001) and parathormone (p-value < 0.0001) compared to vitamin D deficiency. However, hypophosphatemic rickets showed significantly higher levels of serum creatinine (p-value = 0.020), alkaline phosphatase (p-value < 0.0001), vitamin D (p-value < 0.0001), and serum FGF23 (p-value < 0.0001) compared to the vit D deficiency group(Table 4).
- The results showed that hypophosphatemic rickets had significantly lower levels of total serum calcium (p-value < 0.0001) and ionized serum calcium (p-value < 0.0001). Moreover, hypophosphatemic rickets exhibited significantly lower levels of serum phosphorus (p-value < 0.0001) and vitamin D (p-value < 0.0001) compared to the normal control. However, hypophosphatemic rickets had significantly higher levels of serum creatinine (p-value = 0.007), alkaline phosphatase (p-value < 0.0001), and serum FGF23 (p-value < 0.0001) compared to the normal control (Table 5).

The area under the curve (AUC) of the serum FGF23 level was 0.926, 95% CI [0.85, 1.00], p<0.0001).

A serum FGF23 level of 131.5 was the optimal cutoff value with a specificity of 50.0% and a sensitivity of 93.8% in identifying hypophosphatemia rickets. Univariate and multivariate logistic regression analyses showed associations between the likelihood of hypophosphatemia rickets and high serum FGF23: odds ratio, 3.73, 95% CI, 3.39 – 4.13, p-value <0.0001; odds ratio adjusted for age and weight, 4.92 (CI, 3.59-5.65) (Table 6 and Figure 1).

Table 1: The distribution of the included population.

Variable	Frequency (n=64)	Percentage
Included population		
Hypophosphatemia rickets	16	25%
Vitamin D resistance	16	25%
Vitamin D deficiency	16	25%
Normal	16	25%
Age in years		
Mean ± SD	4.38 ± 3.84	
Min. – Max.	0.75 – 16.0	
Median (IQR)	3.0 (4.5)	
Weight in kg		
Mean ± SD	18.89 ± 7.04	
Min. – Max.	9.0 – 40.0	
Median (IQR)	16 (9)	
Weight Z score		
Mean ± SD	-0.004 ± 1.002	
Min. – Max.	-2.00 – 2.01	

Median (IQR)	0.098 (1)	
Height in cm		
Mean ± SD	92.88 ± 12.71	
Variable	**Frequency (n=64)**	**Percentage**
Min. – Max.	70.0 – 121.5	
Median (IQR)	89.0 (19.12)	
Height Z score		
Mean ± SD	0.006 ± 0.98	
Min. – Max.	-2.66 – 2.26	
Median (IQR)	0.12 (0.50)	
Complaint		
Short stature	6	9%
Delayed in motor growth	22	34%
Joint deformity	2	3%
Abnormal gait	6	9%
Convulsions	8	13%
Joint dislocation	1	2%
Recurrent fracture	4	6%
Diet history		
Breast feeding, yes	28	44%
Artificial feeding, yes	34	53%
Mixed, yes	2	3%
Sun exposure, yes	37	58%
Vit D taking, yes	39	61%
Past history		
Medical history, yes	5	8%
Surgical history, yes	2	3%
Family history, yes	20	31%
Signs of rickets		
Delayed closure of anterior fontanel	45	70%
Variable	**Frequency (n=64)**	**Percentage**
Enlargement of wrist and knee	33	52%
Rachitic rosary, pigeon chest	20	31%
Marfan sign, Harrison grove	23	36%
Bowed legs or abnormal gait	35	55%
Knock knee	20	31%
Radiological signs		
Cupping	23	36%
Splaying	23	36%
Fraying in metaphysis of long bone	22	34%

Table 2: The means (±SD) of each parameter among the included population, and the differences between them using one-way ANOVA test.

Variable	Total population	Hypophosphatemia rickets	Vitamin D resistance	Vitamin D deficiency	Normal control	P- value
Age, years	4.38 ± 3.84	6.18 ± 3.82	4.73 ± 4.43	3.23 ± 3.10	3.39 ± 3.49	0.14
Weight, kg	18.89 ± 7.04	19.11 ± 7.84	17.46 ± 8.85	14.47 ± 6.21	14.79 ± 6.98	0.31
Height, kg	92.88 ± 12.71	106.80 ± 23.63	100.8863 ± 31.71035	88.75 ± 23.28	98.05 ± 22.67	0.30
Total serum Ca,	7.13 ±	8.22 ± 0.98	5.01 ± 0.96	7.89 ± 0.55	10.02 ± 0.63	**<0.0001***

mg/dL	1.89					
Ionized serum Ca, mg/dL	0.99 ± 0.23	0.84 ± 0.11	0.96 ± 0.23	0.89 ± 0.07	1.29 ± 0.11	**<0.0001***
Variable	**Total population**	**Hypophosphatemia rickets**	**Vitamin D resistance**	**Vitamin D deficiency**	**Normal control**	**P- value**
Serum phosphorus, mmol/L	4.10 ± 2.06	1.96 ± 1.02	2.83 ± 1.22	6.75 ± 0.44	4.87 ± 0.52	**<0.0001***
Alkaline phosphatase, IU/L	865.80 ± 588.11	1448.36 ± 252.13	1232.19 ± 550.50	554.33 ± 70.95	198.21 ± 43.57	**<0.0001***
Vit D, mmol/L	38.83 ± 14.98	30.59 ± 4.99	50.09 ± 7.23	20.83 ± 8.41	53.5 ± 2.14	**<0.0001***
Parathormone level, pg/ml	46.95 ± 18.59	30.46 ± 8.45	201.51 ± 53.85	60.53 ± 6.15	31.43 ± 2.41	**<0.0001***
Serum urea, mmol/L	40.70 ± 13.17	39.80 ± 18.40	45.81 ± 10.58	39.6 ± 11.98	36.93 ± 10.09	0.30
Serum creatinine, mg/Dl	0.46 ± 0.20	0.59 ± 0.30	0.45 ± 0.17	0.42 ± 0.11	0.39 ± 0.11	**0.04***
Serum FGF23 Level, pg/ml	129.23 ± 48.36	177 ± 20.49	153.62 ± 7.24	129.6 ± 19.64	53.21 ± 11.12	**<0.0001***

One-way ANOVA was used. P-value less than 0.05 was considered statistically significant.

Table 3: The comparison between Hypophosphatemia rickets and Vitamin D resistance

Hypophosphatemia rickets vs. vit D resistance				
Parameter	**Mean Difference**	**95% Confidence Interval**		**P-value**
		Lower Bound	Upper Bound	
Total serum Ca, mg/Dl	3.21	1.98	5.62	**0.02**
Ionized serum Ca, mg/dL	-0.11*	-0.22	-0.006	**0.039**
Serum phosphorus, mmol/L	-0.87*	-1.51	-0.23	**0.009**
Alkaline phosphatase, IU/L	216.17	-15.06	447.40	0.066
Vit D, mmol/L	-19.51*	-24.10	-14.92	**<0.0001**
Parathromone level, pg/ml	-31.76*	-39.66	-23.87	**<0.0001**
Serum urea, mmol/L	-6.02	-15.61	3.57	0.214
Serum creatinine, mg/Dl	0.136	-0.001	0.27	0.052
Serum FGF23 Level, pg/ml	23.38*	11.99	34.76	**<0.0001**

Table 4: The comparison between Hypophosphatemic rickets and Vitamin D deficiency

Hypophosphatemic rickets vs. vit D deficiency				
Parameter	**Mean Difference**	**95% Confidence Interval**		**P-value**
		Lower Bound	Upper Bound	
Total serum Ca, mg/Dl	0.33	-0.31	0.97	0.307
Ionized serum Ca, mg/dL	-0.04	-0.15	0.07	0.424
Serum phosphorus, mmol/L	-4.79*	-5.44	-4.14	**<0.0001**
Alkaline phosphatase, IU/L	894.02*	659.22	1128.82	**<0.0001**
Vit D, mmol/L	9.76*	5.09	14.42	**<0.0001**
Parathromone level, pg/ml	-30.08*	-38.09	-22.06	**<0.0001**
Serum urea, mmol/L	0.19	-9.55	9.93	0.968
Serum creatinine, mg/dL	0.17*	0.03	0.31	**0.020**
Serum FGF23 Level, pg/ml	47.40*	35.84	58.95	**<0.0001**

Table 5: The comparison between Hypophosphatemia rickets and the normal control.

Hypophosphatemia rickets vs. normal control				
Parameter	**Mean Difference**	**95% Confidence Interval**		**P-value**
		Lower Bound	Upper Bound	
Total serum Ca, mg/dL	-1.80*	-2.45	-1.15	**<0.0001**
Ionized serum Ca, mg/Dl	-0.45*	-0.56	-0.34	**<0.0001**
Serum phosphorus, mmol/L	-2.91*	-3.57	-2.25	**<0.0001**
95% Confidence Interval	**95% Confidence Interval**	**95% Confidence Interval**		**95% Confidence Interval**
		Lower Bound	Upper Bound	
Alkaline phosphatase, IU/L	1250.14*	1011.33	1488.96	**<0.0001**
Vit D, mmol/L	-22.91*	-27.65	-18.17	**<0.0001**
Parathromone level, pg/ml	-0.97	-9.13	7.18	0.812
Serum urea, mmol/L	2.86	-7.05	12.77	0.565
Serum creatinine, mg/Dl	0.20*	0.06	0.34	**0.007**
Serum FGF23 Level, pg/ml	123.79*	112.03	135.54	**<0.0001**

Table 6: Area under the curve (AUC) for Serum FGF23 Level in hypophosphatemia rickets.

	Area under the curve (AUC)	**Confidence interval of AUC**		**P value**	**Optimal cutoff value**	**Sensitivity**	**Specificity**
Hypophosphatemia rickets	0.926	0.850	1.00	***<0.0001**	>131.5	93.8%	50.0%

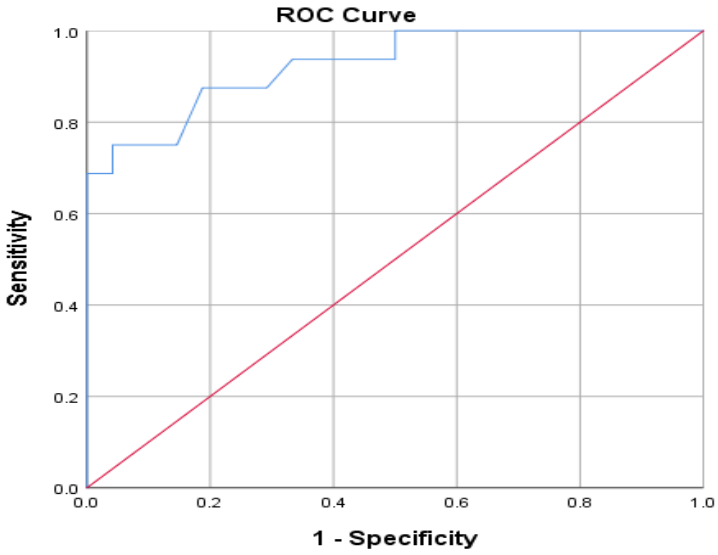

Figure 1: Receiver operating characteristic curve for FGF23 at optimal cutoff level for predicting hypophosphatemia rickets.

DISCUSSION

Bone-derived FGF23 is a phosphaturic hormone that controls blood phosphate levels by inhibiting phosphate reabsorption in the renal proximal tubules and in the intestine [5].

The purpose of this research was to compare the levels of fibroblast growth factor 23 (FGF 23) across hypophosphatemic, vitamin D deficient, and vitamin D resistant rickets. We also compared vitamin D deficient, hypophosphatemic, and vitamin D resistant rickets patients with healthy controls on some additional criteria.

Our study showed no significant difference among the compared groups regarding age, weight, and

height. The mean age (±SD) of the included children was 4.38 ± 3.84 years, with a range from 0.75 to 16.0 years. The mean weight (±SD) was 16.45 ± 7.61 kg, ranging from 9.0 to 40.0 kg. The mean height (±SD) was 98.53 ± 25.96 cm, with a range from 70.0 to 180.0 cm.

Similarly, a study by Kubota *et al*. [7] involving 24 children with vitamin D deficiency and 8 children with hypophosphatemia rickets, showed consistent results. The study showed no significant difference in terms of age, weight, and height.

Our investigation involved a comparison between two distinct groups: the hypophosphatemia rickets group and the vitamin D resistance group. The findings indicate that, in contrast to the vitamin D resistance group, the hypophosphatemia rickets group exhibited notably lower levels of serum phosphorus and lower levels of vitamin D.

However, the hypophosphatemia rickets group displayed notably higher levels of serum calcium and higher levels of serum FGF23 when compared to the vitamin D resistance group.

When comparing these results with earlier research, certain studies support our findings. For instance, a previous study by Yamazaki and Michigami [8] found that children with hypophosphatemic rickets had significantly lower levels of serum phosphorus than children with to vitamin D resistance group. The children with hypophosphatemia rickets also had significantly lower levels of vitamin D than the children with other forms of rickets.

Additionally, another study found that children with hypophosphatemic rickets had significantly lower levels of serum phosphorus than children with other forms of rickets. The children with hypophosphatemic rickets also had significantly lower levels of vitamin D than the children with other forms of rickets [9].

The observed differences in serum phosphorus and vitamin D levels between the hypophosphatemia rickets group and the vitamin D resistance group can be attributed to the underlying physiological and biochemical processes that characterize these two distinct types of rickets. Hypophosphatemia rickets, as the name suggests, is primarily characterized by abnormally low levels of serum phosphorus. This condition arises due to impaired renal reabsorption of phosphorus in the kidneys, leading to reduced levels of phosphorus in the bloodstream. This, in turn, affects bone mineralization and growth, resulting in the classic features of rickets such as bone deformities and growth retardation [10].

Our findings indicated that hypophosphatemic rickets displayed notably lower levels of serum phosphorus and parathormone compared to cases of vitamin D deficiency. The differences were statistically significant, as reflected by the calculated mean differences, confidence intervals, and p-values.

However, the same hypophosphatemic rickets group demonstrated significantly higher levels of certain biomarkers in comparison to the vitamin D deficiency group. Notably, elevated levels of serum creatinine, alkaline phosphatase, vitamin D, and serum FGF23 were observed. The observed higher levels of these markers in the hypophosphatemic rickets group highlight distinct physiological and biochemical characteristics associated with this type of rickets

When comparing these results with previous research, several studies are in agreement with our findings. The study by Kuboto *et al*. [7] documented similar trends in serum phosphorus and parathormone levels among hypophosphatemic rickets and vitamin D deficiency groups

Regarding FGG23, consistent results were provided by Kubota *et al*. [7] who found that serum FGF23 levels were notably higher in infants with hypophosphatemia rickets compared to infants with vitamin D deficiency. The study indicated that FGF23 could serve as a valuable indicator for distinguishing between hypophosphatemia rickets and vitamin D deficiency

Further, another study found elevated FGF23 levels in patients with hypophosphatemic rickets, whereas vitamin D deficiency tends to exhibit lower FGF23 levels. These findings suggest that the measurement of FGF23 holds significance in effectively distinguishing between different causes of hypophosphatemia [5].

Outstandingly, another study showed that FGF23 levels below the threshold of 19 pg/ml emerge was considered as a valuable discerning criterion, enabling the differentiation between individuals afflicted with rickets stemming from vitamin D deficiency and those whose rickets results from an excess of FGF23, a condition also marked by concurrent vitamin D deficiency [11].

Our results showed that the hypophosphatemic rickets group displayed notably reduced concentrations of total serum calcium and ionized serum calcium in comparison to the normal control group. The differences were statistically significant, indicating a substantial disparity in calcium levels. This observation is consistent with previous research studies that have highlighted the influence of phosphate deficiency on calcium metabolism.

Furthermore, the analysis revealed that the hypophosphatemic rickets group exhibited significantly diminished levels of serum phosphorus and vitamin D when contrasted with the normal control group. This significant variance in phosphorus and vitamin D levels reaffirms the link between phosphate regulation and bone health.

The hypophosphatemic rickets group demonstrated elevated concentration of alkaline phosphatase, and serum FGF23 compared to the normal control group. These disparities were statistically significant, illustrating the profound impact of phosphate deficiency on various biochemical markers.

Previous investigations have also noted similar trends, aligning with our present findings. A study by Prentice *et al*. [12] included 46 patients who had bone deformities typical of rickets and were from 1.1 to 16.4 years old, consisting of 30 males and 16 females who were active rickets by radiological signs and elevated plasma phosphatase. Patients had higher levels of 1,25-dihydroxyvitamin D and total alkaline phosphatase than local children, lower levels of plasma phosphate, and higher levels of 1,25-hydroxyvitamin D. Fasting morning plasma samples were examined for levels of FGF23, phosphate, and other biochemical biomarkers of interest. The outcomes were compared to those obtained from locally stored youngsters. The levels of FGF23 in rickets patients were noticeably greater than those in local children.

According to our study, serum FGF23 cut-off was from 5 -52 pg\ml. The area under the curve of the serum FGF23 level was 0.926. A serum FGF23 level of 131.5 was the optimal cutoff value with a sensitivity of 93.8% and specificity of 50.0% in identifying hypophosphatemia rickets.

The precise interplay between phosphate and FGF23 is still unclear, despite FGF23's function in regulating serum phosphate levels through inhibiting renal tubular reabsorption. Nevertheless, it is well-established that 1, 25(OH) 2D acts as a crucial systemic regulator of FGF23 expression. An alternative explanation for the augmented FGF23 levels could be attributed to the lifestyle advice promoting adequate sun exposure and dietary adjustments, which might alleviate hypovitaminosis D, even though post-intervention 25-hydroxyvitamin D (25(OH)D) levels were not quantified [13].

The measurement of FGF23 levels proves to be of utmost value when diagnosing untreated patients grappling with phosphopenic rickets. This differentiation is pivotal in distinguishing between FGF23-mediated rickets and other forms. Patients with tumor-induced osteomalacia (TIO), which often improves following tumor excision, and those with congenital hypophosphatemic diseases were also likely to have abnormally high or low levels of FGF23 [14].

Patients with FGF23-mediated diseases can be identified by the presence of hypophosphatemia in both children and adults and intact FGF23 values of more than 30 pg/mL. An intact FGF23 cutoff limit of 27 pg/mL successfully distinguishes FGF23-mediated hypophosphatemia from FGF23-independent instances, as shown in recent studies in adults. Furthermore, in comparison to FGF23-independent hypophosphatemia, a cFGF23 cutoff threshold of 90 RU/mL correctly diagnoses TIO [14].

High serum FGF23 was associated with an increased risk of hypophosphatemia rickets in both univariate and multivariate logistic regression studies, even after adjusting for age and weight.

Similar results were obtained by the study of Kuboto *et al*. [7] The area under the curve for serum FGF23 exhibited a notably more pronounced level of statistical significance in comparison to other measurements, such as PTH and 1,25(OH)2D. These outcomes imply that when distinguishing between patients with vitamin D deficiency and those with hypophosphatemia rickets, serum FGF23 measurements might offer greater utility compared to assessments involving PTH and 1,25(OH)2D

Limitations

There are certain limitations in our study. Firstly, the sample size might be relatively small, with 16 cases in each group. The results may not apply to a wider population because of this. Understanding FGF23 levels concerning the various forms of rickets may require a bigger and more representative sample.

Secondly, since the study was conducted in a single outpatient clinic of a specific hospital, there is a potential for selection bias. The patient population might not fully represent the diversity and characteristics of all individuals with different types of rickets. This could affect the external validity of the study.

Thirdly, the study was an observational study, which means that while it can show correlations between factors, it cannot prove cause and effect. Therefore, while the study aimed to explore the relationship between FGF23 levels and other parameters among different types of rickets, it cannot definitively conclude that elevated FGF23 directly causes rickets or vice versa.

CONCLUSIONS

The prognostic performance of serum FGF23 levels indicated a high area under the curve, with a specificity of 50.0% and sensitivity of 93.8% using a cutoff value of 131.5 to identify hypophosphatemic rickets. Univariate and multivariate logistic regression analyses highlighted a significant association between high serum FGF23 levels and the likelihood of hypophosphatemic rickets, even when adjusted for age and weight. These findings highlight the potential of serum FGF23 levels as a diagnostic indicator for hypophosphatemic rickets.

Conflict of interest: None.

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