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Journal of Parathyroid Disease

Journal of Parathyroid Disease 2020,8, e03

Original

Levels of parathyroid hormone and fibroblast growth factor 23 in various stages of pediatric patients with chronic kidney disease

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Abstract

Introduction: Several studies showed the association of high levels of fibroblast growth factor 23 and parathormone with increased risk of bone disease in chronic kidney disease (CKD).

Objectives: We conducted this study to determine the level of fibroblast growth factor 23 (FGF23) and parathormone in stages I and V of CKD.

Patients and Methods: In this cross-sectional study, three groups of children, consisted of 24 children with early stage of CKD, 40 with late stage of CKD (stage V; end-stage renal disease [EDRD] patients) and 21 healthy children enrolled to the study. Patient selection was based on random sampling method. Serum calcium, phosphate, intact parathyroid hormone (iPTH), FGF23 and serum creatinine levels and also glomerular filtration rate (GFR) were measured using standard assays.

Results: This study showed a significantly higher parathyroid hormone (PTH) level in the EDRD hemodialysis group in comparison with the early stage of CKD and control groups ($P<0.001$). Likewise, a significant difference of phosphorus between the EDRD hemodialysis group with the normal group and the early stage of CKD was detected. ($P<0.001$). A significant positive correlation of serum phosphorus with serum levels of FGF 23 in the EDRD patients ($P<0.05$) was seen, while this association in the early stage of CKD was absent ($P>0.05$). According to the results of the receiver operating characteristic (ROC) curve, serum FGF23 was not an appropriate prognostic index for GFR in pediatric patients with CKD ($P=0.07$) (sensitivity 40.8, specificity 83.3, cutoff point 134. 72). Meanwhile, the top of ROC curve shows, iPTH had acceptable sensitivity and specificity for determining different stages of CKD ($P<0.0001$, sensitivity= 100, specificity=97.2, cutoff point = 100.7).

Conclusion: FGF23 is not an appropriate prognostic tool in pediatric patients with early stage of CKD, however, iPTH had an acceptable sensitivity and specificity to determine various stages of CKD.

Keywords: Chronic kidney disease, Fibroblast growth factor 23, End-stage renal disease, Renal osteodystrophy
Glomerular filtration rate

Please cite this paper as: Akhavan Sepahi M, Razavi MR, Heidari M, Haeri MR, Mohammadbeigi A. Levels of parathyroid hormone and fibroblast growth factor 23 in various stages of pediatric patients with chronic kidney disease. J Parathyr Dis. 2020;8:e03.

Introduction

Fibroblast growth factor 23 (FGF23) is a bone-derived hormone that regulates phosphate (P) and vitamin D metabolism. FGF23 principally acts on the tubules of the kidney to induce urinary phosphorus excretion and suppresses 1,25-dihydroxyvitamin D synthesis (1,2).

One of the major concerns in children with chronic kidney disease (CKD) is bone changes, ranging from bone deformities to fractures, which may contribute to permanent disability (2,3), and subsequent alterations in skeletal biology (4,5). These two entities are now known as mineral and bone disorders of CKD (6). Clinical disturbances of renal osteodystrophy include fatigue, muscle weakness, metabolic bone disorders, and increased fracture rate, and changes in the shape of the bones (7,8).

In CKD, laboratory studies indicate an elevated level of phosphorus, alkaline phosphatase, parathyroid hormone (PTH) and decreased levels of calcium (3,9,10). FGF23 is a new phosphatidic hormone, interacted in the mineral homeostasis in CKD (11-13). Recent studies suggest that increased FGF23 is associated with endothelial dysfunction, left ventricular hypertrophy, atherosclerosis,

Received: 15 April 2019, Accepted: 30 July 2019, ePublished: 18 August 2019

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Implication for health policy/practice/research/ medical education

In a study on 24 children with early stage of CKD, 40 with late stage of CKD (stage V; EDRD), we found, plasma fibroblast growth factor 23 was not an appropriate prognostic index for determining different stages of chronic kidney disease in pediatric patients, since, parathyroid hormone (PTH) had an acceptable sensitivity and specificity for this discrimination.

metabolic bone disorders and progression towards end-stage renal disease (ESRD) in patients with CKD (12-19).

Hyperphosphatemia is also considered as a risk factor for cardiovascular disease, as well as bone disease (15, 16). Higher levels of FGF23 are related to more suppression of PTH release (9). However, in many patients with early or late stages of CKD, the level of serum phosphorus remains normal because of an increase in FGF23 and PTH levels. Regarding the limitations of serum phosphorus level used as the primary indicator of bone disease, FGF23 level in early stages of CKD seems to be useful as a screening tool (20). A recent study showed, FGF23 is an independent factor that is associated with the progression of ESRD, since the increase in FGF23 begins at an early stage CKD (21). Several studies have shown that inhibition of FGF23 production, is an effective way to correct early bone changes (9).

Objectives

We conducted this study to determine correlation between FGF23 with stages I and V (end-stage renal disease [EDRD]) of CKD.

Patients and Methods

Study protocol

This cross-sectional study was conducted in the center of Hazrat-e-Masoumeh hospital (May2015 to December 2017).

Data collection

Population study was selected by random sampling method and demographic data was collected using a questionnaire, which was conducted by an expert research team. All subjects were interviewed by an expert pediatric nephrologist. In summary, after signing the informed consent by parents, the study applicants were evaluated by a multidisciplinary team using a structured clinical and laboratory evaluation. At the end of the first visit, each patient was selected based on GFR (glomerular filtration rate) according to Schwartz equation (22). Thus, 24 children with early stage of CKD, 40 children with late stage CKD (ESRD) as well as 21 healthy children were enrolled the study. The serum level of FGF23 was compared in these three groups.

The early stage CKD with GFR ≥ 90 mL/min/1.73 m^2 and late stage CKD (ESRD) with GFR< 15 mL/min/1.73 m^2 were the inclusion criteria. Control group was selected from normal GFR level, without any kidney structural abnormalities.

Blood samples drawn through vein puncture, sera were separated from the samples and stored at -20℃ till assay. Serum calcium, phosphorus, intact PTH (iPTH), FGF23 and creatinine levels were measured using standard assays. Serum level of iPTH was measured by Abnova (Human) ELISA Kit (Taiwan), and serum FGF23 was measured by Abcam (Human) ELISA Kit (Taiwan).

Ethical issues

The research followed the tents of the Declaration of Helsinki. The Ethics Committee of Pediatric Research Center in Qom University of Medical Sciences approved the study (# MUQ.REC.1394.118). Accordingly, written informed consent was taken from parents of children before the study.

Statistical analysis

Descriptive were presented in mean, median and percentages. For analytics, Mann-Whitney U and Kruskal–Wallis tests were utilized. Receiver operating characteristic (ROC) curve analysis was used to estimate the sensitivity and specificity of FGF23 as a quantitative factor and also for determining the cut of point. For correlations, Pearson's correlation test was applied. Moreover, area under curve (AUC) was estimated for the predicted cut of point. Statistical test was conducted in SPSS version18 and MedCal software. A significance level of <0.05 was adopted for interpretation of all study results.

Results

In this study 42 children (49.4%) were female and 43 (50.6%) were male. Table 1 presents the comparing of FGF23, iPTH, P and GFR as a prognostic index in patients with different stages of CKD.

In general, a significant difference between mean of age, iPTH, P and GFR among three groups was detected ($P<0.001$; Kruskal–Wallis test). However, post hoc tests revealed a significantly higher PTH level in the ESRD hemodialysis group in comparison with the early stage of CKD and the control group ($P<0.001$, for both early stage of CKD and the control group). Likewise, a significant difference of phosphorus between the ESRD hemodialysis group with the normal group and the early stage of CKD was existed ($P<0.001$ and $P<0.001$; Table 2). Mann-Whitney U test showed a significant difference of iPTH between males and females in the ESRD hemodialysis groups (median [max, min]= 196.3 [20.85, 663.6] versus median [max, min] = 409.6 [29.16, 2933] pg/mL; $P=0.024$; with more values in females). The comparison of FGF level between females and males showed a significant difference among them in the early stage of CKD group (median [max,min]=117.8 [100.5, 998] pg/

mL versus median [max, min] = 197.8 [116.4, 1246.4] pg/mL; $P=0.026$; with more values in females). There was no significant difference in the studied variables between males and females in normal subjects (Table 3).

Accordingly, Table 4 shows a significant positive correlation of serum phosphorus with serum levels of FGF 23 in hemodialysis patients ($P<0.05$), while this association in the early stage of CKD was absent ($P>0.05$). Similarly, Table 5 shows no significant correlation of iPTH with the study variables in the late and early stages of CKD ($P>0.05$). According to the results of the ROC curve, the FGF23 was not an appropriate prognostic index for GFR in pediatric patients with CKD ($P=0.07$) (sensitivity 40.8, specificity 83.3, cutoff point 134. 72; Figure 1). Meanwhile, the top of ROC curve shows, iPTH index had acceptable sensitivity and specificity for determining different stages of CKD ($P<0.0001$, sensitivity= 100, specificity=97.2, cutoff point = 100.7; Figure 2).

Table 1. Comparison of FGF23, PTH, P and GFR differences between genders in each CKD stages

	Mean± SD Median [min, max]				
	FGF(pg/mL)	**PTH(pg/mL)**	**Phosphorus(mg/dl)**	**GFR(cc/min/ 1.73 m²)**	**Age(months)**
End stage CKD (I)	435.32±417.95	447.76±505.23	6.135±1.67	1.80±1.62	6.38±2.22
(n=40)	210.45 [86.3, 1457.0]	320 [20.85, 2933.0]	5.55 [3.5, 9.2]	1 [1,5]	5.75 [3.5, 16]
Early stage of CKD (II)	313.40±331.74	40.56±23.60	3.69±0.52	100.75±14.76	4.83±3.6
(n=24)	150.75 [100.5, 1246.4]	34.43 [8.55, 100.7]	3.70 [3.0, 5.3]	100.2 [80, 120]	3.4 [0.2, 13]
Healthy children (III)	454.84±441.83	31.94±12.21	3.48±0.33	72.6±12.81	1.40±2.17
(n=21)	243.5 [83, 1270.0]	31.54 [10.26, 59.28]	3.5 [3, 4.2]	70 [60, 95]	1 [0.12, 8.0]

Table 2. Comparison of variables between groups

	Between groups comparison	**Mean Difference (I-J) ± SD**	***P* value**
PTH	I v.s II	407.20 ±91.81	0.001**
	I v.s III	415.83±94.54	0.001**
	II v.s III	8.62±105.89	0.999
Phosphorus	I v.s II	2.45 ±0.31	0.001**
	I v.s III	2.66±0.32	0.001**
	II v.s III	0.21±0.36	0.976
GFR	I v.s II	-98.95 ±2.61	0.001**
	I v.s III	-70.82±2.73	0.001**
	II v.s III	28.13±3.02	0.029*

P* value < 0.05, *P* value<0.001 and pairwise analysis using by Dunn's test.

Table 3. Comparison of FGF23, PTH, P and GFR differences between genders in each CKD stage

Group	**Gender**	**FGF (pg/mL)**	**PTH (pg/mL)**	**Phosphorus (mg/dL)**	**GFR**
End stage CKD (I)	Male (n=43)	481.77±463.77	246.2±179.4	6.15±1.73	2.07±1.83
		299.5 [101.2,1457]	196.3 [20.85, 663.6]	5.4 [4,8.9]	1 [1,5]
(n=40)	Female (n=42)	407.44±395.27	568.71±596.13	6.13±1.67	1.64±1.50
		167.4 [86.3,1409.1]	409.6 [29.16,2933]	6 [3.5,9.2]	1 [1,5]
	P value	0.498	0.024*	0.890	0.581
Early stage of CKD (II)	Male (n=43)	365.8±365.9	36.64±179.21.66	3.75±0.62	97.07±14.60
		197.8 [116.4,1246.4]	31.1 [8.55, 96.55]	3.8 [3,5.3]	100 [80,120]
(n=24)	Female (n=42)	240.0±278.43	46.66±26.48	3.6±0.34	105.90±14.10
		117.8 [100.5,998]	39.4 [14.67,100.7]	3.5 [3.1,4]	110 [80,120]
	P value	0.026*	0.369	0.138	0.625
(III)Normal subjects	Male (n=43)	490.9±460.47	31.99±10.76	3.54±0.31	72.50±12.67
		298 [85.6,1270.7]	31.27 [10.26, 48.81]	3.5 [3.1,4.2]	70 [60,95]
(n=21)	Female (n=42)	382.771±426.85	31.82±15.69	3.36±0.38	72.86±14.1
		121.2 [83,1003.8]	35.03 [13.17,59.28]	3.5 [3,4]	70 [60,95]
	P value	0.255	0.913	0.322	0.999

Table 4. Correlation FGF23 with GFR, iPTH and phosphorus with age in various stages of CKD

		PTH	GFR	AGE	Phosphorus (mg/dL)
End Stage of CKD (n=40)	FGF	0.014	-0.113	-0.278	0. 374*
Early Stage of CKD (n=24)	FGF	-0.116	-0.397	-0.392	-0. 040

* *P* value < 0.05,** *P* value < 0.001.

Table 5. Correlation PTH with FGF23, GFR, P and age in various stages of CKD

		FGF	GFR	AGE	Phosphorus (mg/dL)
End Stage of CKD (n=40)	PTH	0.014	-0.223	-0.277	-0. 052
Early Stage of CKD (n=24)	PTH	-0.116	-0.027	0.283	-0.211

* *P* value < 0.05,** *P* value < 0.001.

Discussion

CKD is associated with a series of changes in the metabolism of minerals as well as multiple bones and cardiovascular diseases (2). The bone changes are major concern in a patient with CKD whom adequate replacement therapy was not done (1).

FGF23 is an independent factor, which is associated with progression of CKD to ESRD, and increase in FGF23 begins in the early stage CKD (20,21).

High levels of FGF23 can cause other extrarenal abnormalities like increasing the risk of bone changes in patients with CKD (11,12).

In addition, elevated levels of FGF23 represented as an independent risk factor for cardiovascular disorders and vascular dysfunction (decrease in vascular dilatation) in these patients (13, 14). Left ventricular hypertrophy and subsequent arrhythmias are the other heart problems related to increment of FGF23 (18).

Our study showed that in early stages of CKD, an inverse relationship between GFR with phosphorus and PTH were existed, however, changes in FGF 23 was not statistically significant. It means that once GFR index decreased, phosphorus and PTH levels were increased.

In one study, Gutiérrez et al, concluded that in early stages of CKD, an increment in serum FGF23 levels was existed, even before serum phosphate and calcium concentrations became abnormal. They concluded that increased FGF23 level is presumably a central factor in the early pathogenesis of secondary hyperparathyroidism (13). In another study Chudek et al showed increased serum FGF23 level did not precede the rise in serum PTH level and did not occur before stage-3 CKD in elderly persons (19). In addition, a cross sectional study conducted by Pavik et al (2013), in patients with early stages of CKD, a clear correlation between GFR and FGF-23 was detected. When they have a decrease in GFR, there was an increase in serum levels of FGF-23 (21).

In the late stage CKD once GFR index decreased, phosphorus and PTH levels were increased which means a statically significant inverse relationship between GFR and PTH and phosphorus as well as direct relationship between FGF23 with phosphorus level. However, in many

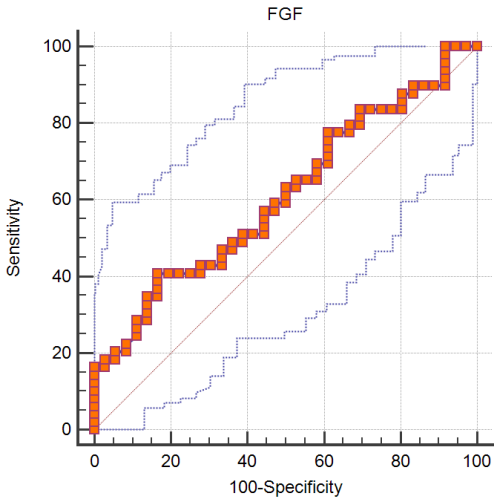

Figure 1. Sensitivity and specificity of the FGF23 index (ROC curve). According to the results of the ROC curve, the FGF23 was not an appropriate prognostic index for GFR in pediatric patients with CKD (*P* = 0.07) (sensitivity = 40.8, specificity = 83.3, cutoff point = 134.72).

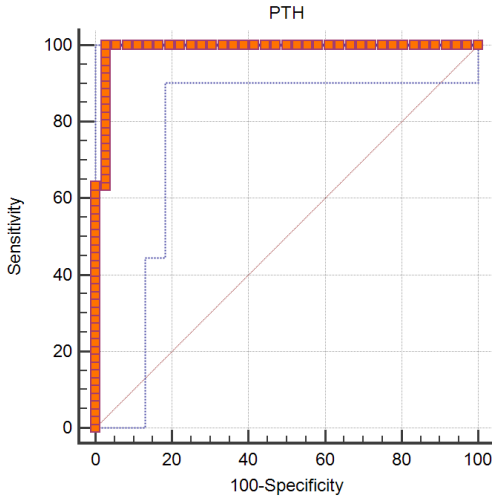

Figure 2. Sensitivity and specificity of the iPTH index (ROC curve). On top of that ROC curve showed, PTH index had acceptable sensitivity and specificity for determining different stages of CKD (*P* <0.0001, sensitivity = 100, specificity = 97.2, cutoff point = 100.7).

patients with CKD, the level of serum phosphorus remains normal because of an increase in FGF23 or iPTH levels. Alternatively, higher FGF23 levels were not associated with higher levels of phosphorus (9).

According to our results, the FGF23 was not an appropriate prognostic index for determining different stages of CKD in pediatric patients, however in PTH had an acceptable sensitivity and specificity for prognosis.

In conclusion, results of our study showed no significant correlation between FGF23 and GFR in early or late stages of CKD. The study by Fliser et al showed the same results. They concluded that plasma FGF-23 is an indicator of the progression of CKD but its role is unclear (23, 24).

Conclusion

In this study, we found, plasma FGF23 was not an appropriate prognostic index for determining different stages of CKD in pediatric patients with chronic renal failure, but PTH index had acceptable sensitivity and specificity for it. More researches need to be conducted to find the exact role of FGF23 in CKD.

Limitations of the study

Our study was conducted to a limited proportion of patients and the study was single-center. We suggest more investigation of this subject.

Authors' contribution

MAS, MRR and MH were the principal investigators of the study. MAS, MRR, MH and MRH participated in preparing the concept and design. AM participated in data collection and statistics. MAS, MRR, MH and MRH revised the manuscript and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

Acknowledgments

The authors of the present study sincerely Pediatric Clinical Research of Development Center of Hazrat Massomeh Hospital in Qom University and Dr Hosini, Dr Arsang, for suggesting this study and all patients who participated in the study. The authors also would like to thank Pegah Noorshargh, from Alzahra Research Institute, Isfahan University of Medical Sciences, Isfahan, for re-analysis the data.

Conflicts of interest

The authors declare that they have no competing interest.

Ethical considerations

Ethical issues (including plagiarism, misconduct, data fabrication, falsification, double publication or submission, redundancy) have been completely observed by the authors.

Funding/Support

Pediatric Clinical Research of Development Center Hazrat Massomeh Hospital in Qom University of Medical Sciences financially supported the present study (ref #P/13771/34).

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