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Interaction between serum FGF-23 and PTH in renal phosphate excretion, a case-control study in hypoparathyroid patients

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Abstract

Background: phosphate homeostasis is mediated through complex counter regulatory feed-back balance between parathyroid hormone, FGF-23 and 1,25(OH)2D. Both parathyroid hormone and FGF-23 regulate proximal tubular phosphate excretion through signaling on sodium- phosphate cotransporters II_a and II_c. However, the interaction between these hormones on phosphate excretion is not clearly understood. We performed the present study to evaluate whether the existence of sufficient parathyroid hormone is necessary for full phosphaturic function of FGF-23 or not.

Methods: In this case-control study, 19 patients with hypoparathyroidism and their age- and gender-matched normal population were enrolled. Serum calcium, phosphate, alkaline phosphatase,parathyroid hormone, FGF-23, 25(OH)D, 1,25(OH)2D and Fractional excretion of phosphorous were assessed and compared between the two groups, using SPSS software.

Results: The mean serum calcium and parathyroid hormone level was significantly lower in hypoparathyroid patients in comparison with the control group ($P < 0.001$ and $P < 0.001$, respectively). We found high serum level of phosphate and FGF-23 in hypoparathyroid patients compared to the control group ($P < 0.001$ and $P < 0.001$, respectively). However, there was no significant difference in Fractional excretion of phosphorous or 1,25OH2D level between the two groups. There was a positive correlation between serum FGF-23 and Fractional excretion of phosphorous just in the normal individuals ($P < 0.001$, $r = 0.79$).

Conclusions: Although the FGF-23 is a main regulator of urinary phosphate excretion but the existence of sufficient parathyroid hormone is necessary for the full phosphaturic effect of FGF-23.

Keywords: FGF-23, FE PO_4, Hypoparathyroidism, PO_4

Background

Phosphorus (PO_4) has several biologic role in human, and is an essential ion in bone mineral component, cell membrane structure, and energy exchange. Also, it is a second messenger in controlling cellular biochemical activities through phosphorylation or dephosphorylation [1–3]. Kidney plays an important role in PO_4 homeostasis. About 80% of the filtered PO_4 is reabsorbed through specific sodium- phosphate cotransporters (NaPi II_a and II_c) located in the proximal tubule [4–8].

PO_4 serum concentration is kept within the normal range by a complex regulation between intestinal absorption, renal filtration- reabsorption, and bone resorption of PO_4 mediated by regulatory hormones [9–11]. The most important hormones that regulate tubular PO_4 handling, are parathyroid hormone (PTH) secreted by the parathyroid gland, and fibroblast growth factor

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23 (FGF-23), which is an osteocytes derived hormone. FGF-23 decreases serum PO_4 by inhibiting renal PO_4 reabsorption through FGF-23-Klotho (coreceptor) signaling on NaPi II_a and II_c at proximal tubule of the kidney. FGF-23 also suppresses 1,25-dihydroxyvitamin D (1,25(OH)2 D) production by decreasing 1α-hydroxylase expression [12–14]. PTH promotes PO_4 excretion by suppressing NaPi-II in the kidney [15]. PTH also enhances calcium absorption through the direct effect on bones and kidneys, and indirectly increases intestinal calcium and PO_4 absorption via the stimulation of 1α -hydroxylase activity and increase 1, 25(OH)2 D production [16–18]. The same site of action of FGF-23 and PTH in NaPi II_a and II_c at proximal tubule of kidney might raise the question that whether there is an overlapping effect between these hormones or not?

Hypoparathyroidism is a rare endocrine disorder characterized by inappropriately low or absent levels of PTH associated with hypocalcemia and hyperphosphatemia [17, 19]. Hypoparathyroidism might occur as a primary congenital defect or might be due to a secondary cause. The most common cause of secondary hypoparathyroidism is the incidental destruction of parathyroid glands during anterior neck surgeries. Other causes are autoimmune disorders, radiation to the neck and infiltrative disorders of the parathyroid glands [20–22].

In the present study, we aim to evaluate the role of FGF-23 on PO_4 hemostasis in state of low or insufficient PTH in human. Hence, we conducted this case – control study to evaluate whether the renal excretion of PO_4 by serum FGF-23 in patients with hypoparathyroidism was different from normal population or not.

Methods

Patients and method

A total of 38 participants including 19 patients with hypoparathyroidism and their healthy controls were enrolled in this study. The study was performed at Shiraz University of Medical Sciences affiliated endocrine clinics in Fars province, southern Iran, from October 2017 till March 2018. Both groups were matched for age and gender. Hypoparathyroidism was diagnosed on the basis of hypocalcemia (serum calcium less than 8.5 mg/dl) accompanied with documented PTH levels below the lower limit of the normal range.

All hypoparathyroid patients were follow up by an expert endocrinologist. Patients received proper doses of calcium carbonate (500 mg tablet, manufactured Toliddaru pharmaceutical, Tehran, Iran), and calcitriol (0.25 μg capsule, manufactured Zahravi pharmaceutical, Tehran, Iran) to maintain albumin-corrected serum calcium in the low-normal range (8–9 mg/dl) [23]. The exclusion criteria in both groups were renal failure (Glomerular filtration rate less than 60 ml/min), liver failure, other metabolic bone disease (e.g., rickets), hyperthyroidism, and diabetes mellitus. None of the patients received phosphate binder resins during the study.

Laboratory tests

All the samples were taken after 8 h overnight fasting. Blood samples were centrifuged for 15 min at *3000 rpm* and the plasma was collected and stored at − 70 °C till further analysis. All the biochemical studies were performed at the endocrinology and metabolism research center laboratory of Shiraz University of Medical Sciences. Colorimetric assays were used to measure calcium (mg/dL), phosphorus (mg/dL), albumin (g/dL) and alkaline phosphatase (ALP) (IU/L) levels, by using Biosystem SA auto-analyzer, made in Spain. Serum PTH (pg/ml) and 25(OH)D (ng/ml) levels were assessed by Electrochemiluminescence methods produced by Roche company in Germany with Sensitivity, intra- and inter-assay CVs 3.3 and 5.1%, respectively. ELISA method was used to determine the serum intact FGF-23 (pg/ ml) and 1, 25(OH)2D (pmol/l) using Bioassay technology laboratory kit. Intra- and inter-assay CVs for 1,25(OH)2D and FGF-23 were < 8 and < 10%, respectively. Normal references for serum calcium, phosphorus, ALP, PTH, 25(OH)D and 1,25(OH)2D were 8.5–10.5 mg/ dL, 3.5–5.5 mg/ dL, 44–147 IU/L, 10–65(pg/ml), 20–100 ng/ml, and 20 to 45 pg/ml, respectively. Initial morning urine collection was done to determine renal PO_4 clearance. Urinary PO_4 and creatinine concentrations were determined by digital flame spectrophotometer. Fractional excretion of phosphorous (FE PO_4) was done using the following formula: FE PO_4 = [PO_4 (Urine) × Creatinine (Serum)] / [PO_4 (Serum) × Creatinine (Urine)] × 100.

Ethical statement

An informed written consent form was obtained from the participants after explaining the aim, method and goal of the study. Shiraz University of Medical Sciences local Ethics Committee and Vice-Chancellor of research at SUMS approved this study with number 1396-01-01-15,805.

Statistics

SPSS statistical software (version 22, IBM) were used to perform Statistical analysis. Data are mentioned as mean ± SD. Shapiro-Wilk was used to evaluate the normality of data distribution. Normally distributed data were compared using Student's *t*-test, and the Mann–Whitney test was used to compare non-normally distributed ones. Pearson's test and Spearman's ranking test were used to evaluate the correlations between normally distributed parameters and non-normal distributed ones,

respectively. P value less than 0.05 was considered to be statically significant.

Results

A total of 38 participants were enrolled in this study, 19 with hypoparathyroidism as case group and 19 volunteers with normal parathyroid function as the control group. Mean age in the case and control groups was 43.6 ± 17 years and 46.7 ± 15.9 years, which was not statistically significant ($P = 0.57$). Both case and control groups included 5 male and 14 female. Also, there were no significant differences in weight and BMI between case and control groups.

In the case group, 9 patients had hypoparathyroidism due to previous neck thyroidectomy and 10 patients were case of primary hypoparathyroidism. General characteristic of patients and controls are summarized in Table 1.

The mean serum calcium and PTH level was significantly lower in the case group in comparison with the control group ($P < 0.001$ and $P < 0.001$, respectively). In patients with hypoparathyroidism serum PO_4 was significantly higher than the control group ($P < 0.001$). Serum FGF-23 was higher in patients with hypoparathyroidism in comparison with the control group ($P = 0.001$). However, there was no significant difference between the case and control groups with respect to the mean serum level of 1,25(OH)2D, 25(OH)D, ALP, and FE PO_4 ($P = 0.25$, $P = 0.11$, $P = 0.23$ and $P = 0.08$, respectively).

As shown in Table 2 there was a strong positive correlation between FGF-23 and FE PO_4 in the control; however, this correlation was not observed amongst hypoparathyroid patients. There was no correlation between FE PO_4, serum PO_4, PTH and 1, 25(OH)2 D in both case and control groups. Figure 1 shows the correlation between values of FE PO_4 and serum FGF-23 in both control and case groups (Spearman rho =0.79, $P < 0.001$). In addition, we have done an analysis in our hypoparathyroid patients evaluating the association of FGF23 and serum calcium in 2 separate group of low calcium and normal calcium level. It showed that there was no correlation between calcium and FGF23 in low calcium and normal calcium level groups ($P = 0.598$ and $P = 0.054$, respectively).

Table 1 General characteristics and biochemical studies in both case and control groups and the related comparisons

Variable	control	case	*P* value
Age (y)	46.72 ± 15.89	43.68 ± 17.01	0.57
Weight (Kg)	70.89 ± 14.33	75.06 ± 22.11	0.51
Height (cm)	159.83 ± 10.4	163.47 ± 9.92	0.29
BMI (Kg/m^2)	27.82 ± 3.53	27.75 ± 7.83	0.97
PTH (pg/ml)	57.97 ± 18.06	8.92 ± 4.38	< 0.001
Ca (mg/dl)	9.20 ± 0.46	7.98 ± 0.86	< 0.001
PO_4 (mg/dl)	3.82 ± 0.46	5.26 ± 0.93	< 0.001
ALP(IU/L)	148.22 ± 37.9	132.58 ± 40.69	0.23
1,25(OH)2D (pg/ml)	23.73 ± 17.90	30.57 ± 17.77	0.25
25 (OH)D (ng/ml)	33.56 ± 32.35	53.11 ± 40.71	0.11
FGF23 (pg/ml)	24.66 ± 17.73	47.88 ± 22.14	< 0.001
FE PO_4 (%)	15.77 ± 6.64	16.96 ± 11.40	0.70

BMI Body mass index, *FGF-23* Fibroblast Growth Factor 23, *ALP* Alkaline phosphatase, *PO_4* phosphorus, *Ca* Calcium, *PTH* Parathyroid Hormone, *FE PO_4* Fraction excretion of phosphorus

Table 2 Correlation between fractional excretion of PO_4 and serum biochemical parameters in the case and control groups, separately

		FGF-23	PO_4	PTH
FE PO_4	**Control group**	$P < 0.001$	$P = 0.94$	$P = 0.97$
		cc = 0.79	cc = 0.016	cc = 0.01
	Case group	$P = 0.38$	$P = 0.82$	$P = 0.98$
		cc = − 0.21	cc = − 0.053	cc = 0.005

Discussion

Maintaining serum PO_4 homeostasis necessitates a complex counter regulatory feed-back balance between PTH, FGF-23 and 1,25(OH)2 D [24–26]. FGF-23 and PTH are probably the most important phosphaturic hormones in human [1]. FGF-23 is mainly produced by osteoblasts and osteocytes. Local expression of FGF-23 coreceptor (Klotho) is necessary for its function at the renal proximal tubules [27]. It inhibits renal Phos reabsorption through inhibitory effects on NaPi II_a and II_c at proximal renal tubules [28]. However, there are still controversies about the action site of FGF-23 in the kidney [29]. previous studies had showed that klotho is essentially expressed in distal renal tubules, and alteration in the extracellular signal-regulated kinase (ERK) phosphorylation in distal tubules occurs soon after FGF-23 injection [30, 31]. Therefore, it still remain unclear as how FGF-23 could affect proximal tubules to suppress phosphate reabsorption. Data suggest that FGF-23 might require other factors such as PTH for signal transduction pathway at the proximal tubules [32].

PTH also increases renal PO_4 excretion at proximal tubule of the kidney by reducing apical membrane NaPi II_a and II_c [14, 33, 34]. Moreover, PTH increases FGF-23 gene expression [35]. In addition to kidneys, parathyroid gland also express considerable amount of klotho and FGF-23 receptor [36]. On the other hand, FGF-Klotho complex could activate the MAPK pathway leading to decreased PTH mRNA and PTH secretion [37–39]. Olena et al. showed that the phosphaturic actions of PTH, are blunted by FGF-23 or Klotho deficiency.

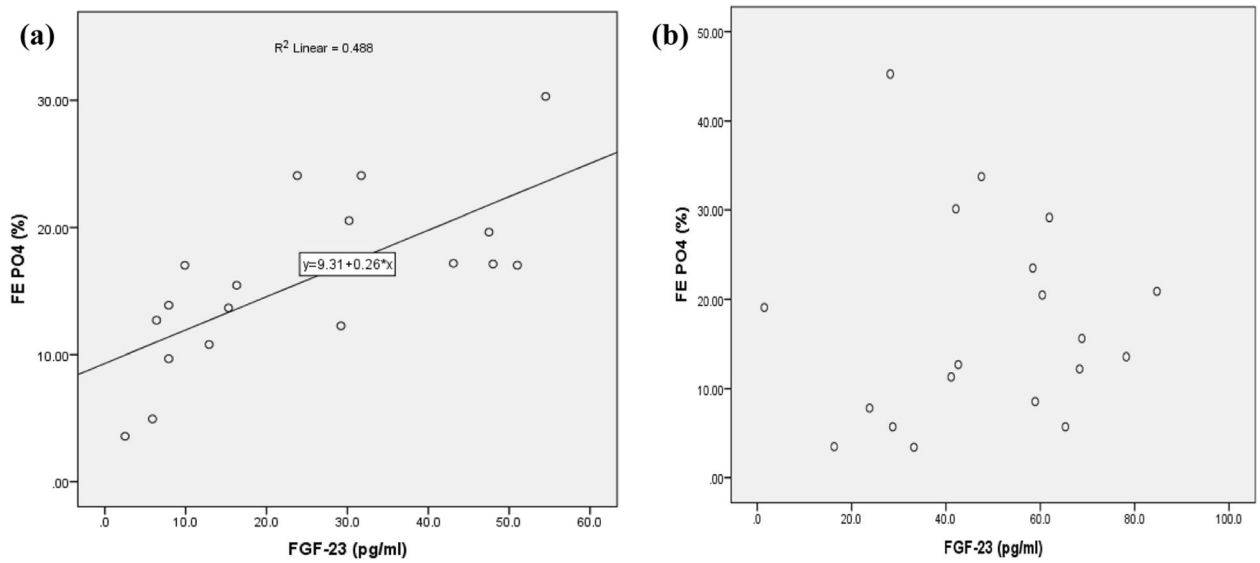

Fig. 1 The correlation between values of serum FE PO_4 and FGF-23 in control group (**a**) and hypoparathyroid cases (**b**)

Hence, FGF-23 might be an important modulator of PTH signaling in the kidney [40].

Although the regulatory counterbalance between FGF-23 and PTH secretion was investigated, there is still insufficient information about the role of PTH on phosphaturic function of FGF-23 in human. Study of phosphaturic effect of FGF-23 in normal human physiology might be confounded by the fact that PTH and FGF-23 have some overlapping effects on PO_4 excretion. Hence, the present study on hypoparathyroid patients and normal population provides an opportunity to observe whether the phosphaturic effect of FGF-23 is independent of PTH or not.

In the present study, we detected high serum level of PO_4 and FGF-23 in hypoparathyroid patients compared to the control group; however, we found no significant difference in FE PO_4 or 1,25(OH)2 D level between the two groups. Also, we found a strong positive correlation between serum FGF-23 and FE PO_4 in the control population, but this correlation was absent in hypoparathyroid patients. These findings could suggest that although the FGF-23 is one of the main regulator of urinary PO_4 excretion, the existence of intact PTH is necessary for the full phosphaturic effect of FGF-23. However, further relevant human studies are warranted.

In the presence of normal parathyroid and kidney function inappropriate high serum FGF-23 could result in urinary PO_4 loss and hypophosphatemia such as X-linked dominant hypophosphatemic rickets (XLH), [41–44], autosomal dominant hypophosphatemic rickets [45, 46], Autosomal recessive hypophosphatemic rickets (ARHR) [47, 48] or Fibrous dysplasia (FD)/McCune–Albright syndrome [49]. As well as some acquired disorders such as Tumor-induced osteomalacia (TIO) [50–52].

Previous studies showed that mean serum PO_4 levels in hypoparathyroid patients remained above the normal range, even in the presence of high serum FGF-23 level [53].Yamashita et al. showed that in transient hypoparathyroidism high serum level of FGF23 and hyperphosphatemia will be normalized only after parathyroid recovery [54]. Animal studies also showed that PTH-null mice experienced high PO_4 in spite of high circulating FGF-23, resembling participants with hypoparathyroidism in the present study [55]. In another study on hypoparathyroid patients, treatment with rhPTH could reduce serum PO_4 level from the upper normal range to the normal values parallel with increased urinary PO_4 excretion [56–58]. These findings also support our hypothesis about the importance of PTH in phosphaturic action of FGF-23. Another explanation by Gracia-Iguacel et al. was that PTH may have effect on phosphaturic function of FGF-23 through the serum calcium level [59]. Also, some studies showed that FGF23 have positive correlation with serum calcium [60, 61]. In our study, we found no correlation between calcium and FGF23 in low calcium and normal calcium level hypoparathyroid patients. However, the number of hypoparathyroid patients in low Ca group was just 7, which could affect the results. Another important issue in this regards was that normal renal function is necessary for this association. In some patients with chronic kidney disease, high serum phosphate was observed in spite of high serum PTH and FGF23 level [62]. Also, it was shown that in chronic kidney disease patients treated with hemodialysis, FGF23 could predict the progression of secondary hyperparathyroidism. Interestingly, in these patients

total parathyroidectomy could decrease high serum FGF-23 level to normal values [63, 64].

In spite of many strengths of this study that evaluated FGF23 function in hypoparathyroid patients, we had some limitations. This study was a case-control cross sectional study, which could be better if we design an interventional clinical trial to evaluate the effect of PTH in hypoparathyroid patients in the future.

Conclusion

The present study could suggest that although the FGF-23 is one of the main regulator of urinary PO_4 excretion, the existence of sufficient parathyroid hormone is necessary for the full phosphaturic effect of FGF-23. We hypothesized that PTH might play a role in PO_4 excretory signal pathway of FGF-23. However, further in vivo and in vitro studies are necessary to determine the mechanism of action of parathyroid hormone on PO_4 excretory function of FGF-23.

Abbreviations

1,25(OH)2 D: 1,25-dihydroxyvitamin D; 25OHD: 25-hydroxy vitamin D; ALP: Alkaline phosphatase; Ca: Calcium; CKD: Chronic kidney diseases; DXA: Dual-energy X-ray absorptiometry; FE PO: Fractional excretion of phosphorous; FGF-23: Fibroblast growth factor 23; PTH: Parathyroid hormone; PO_4: Phosphorus; SUMS: Shiraz University of Medical Sciences; NaPi II_a and II_c: Sodium- phosphate cotransporters

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Authors' contributions

FS: design, data gathering, Analysis, preparing the manuscript. AS: design, data gathering, preparing the manuscript. SRK: design, data gathering, preparing the manuscript. GHRO: design, data gathering, preparing the manuscript and the correspondence. All authors have read and approved the manuscript.

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Shiraz University of Medical Sciences local ethic committee and vice-chancellor of research at SUMS approved this study with number 1396-01-01-15805. All the patients signed a written informed consent form after a session explaining the aim, method and goal of the study for each participant.

Consent for publication

All the patients signed a written informed consent form to publish their data in manuscript after a session explaining the aim, method and goal of the study.

Competing interests

Gholamhossein Ranjbar Omrani, Azita Salehifar, Seyed Reza Kassaee and Forough Saki declare that they have no conflict of interest.

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