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Association of serum fibroblast growth factor 23 with calcium metabolism in patients with end-stage renal disease undergoing hemodialysis

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ABSTRACT

Background: The association between the function of fibroblast growth factor 23 (FGF23) and different components of calcium metabolism has remained unclear in patients with renal dysfunction undergoing hemodialysis.

Objectives: The present study aimed to assess the association of the level of FGF23 and calcium metabolism status in hemodialysis patients.

Patients and Methods: This cross-sectional study conducted on 90 consecutive patients suffering end-stage renal disease (ESRD) who underwent hemodialysis. The serum levels of FGF23 and intact parathyroid hormone (iPTH) levels were measured using the ELISA technique.

Results: The serum levels of FGF23 were directly associated with iPTH level (r = 0.251, P = 0.020) and slightly with the duration of dialysis (r = 0.203, P = 0.063). However serum FGF23 was not significantly related to other indices including levels of calcium, phosphorus, magnesium, vitamin D, albumin, and even body mass index (BMI). No difference was found in the level of FGF23 between men and women with ESRD under hemodialysis.

Conclusions: In ESRD patients undergoing hemodialysis, the association of FGF23 with iPTH was detected, while there was not any relationship of FGF23 with other indices including calcium, phosphorus, and vitamin D.

Original Article

Implication for health policy/practice/research/medical education:
In a cross-sectional study conducted on 90 consecutive stable hemodialysis patients, we found that FGF23 influences the bone metabolism in ESRD patients.

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1. Background

Fibroblast growth factor 23 (FGF23) is a hormone encoded by the FGF23 that located on chromosome 12 (1). The family of FGFs is originally produced by osteocytes and osteoblasts in response to increasing the level of calcitriol with the purpose of regulating vitamin D and phosphate metabolism (2). The main effective role of FGF23 is to decrease the reabsorption phosphate as well as to increase its tubal secretion leading phosphaturia that mediated by FGF receptors on renal tubes (3,4). Additionally, FGF23 can also suppress 1-alpha-hydroxylase which mediates calcium and phosphorus reabsorption (5). In this regard, inactivation of FGF23 can result in elevating the level of phosphate. Moreover, this hormone can decrease the level of 1,25-dihydroxyvitamin D and also the plasma level of parathyroid hormone (PTH) (6). Interestingly, the level and activation of FGF23 is directly regulated based on dietary phosphate intake and thus the level of this hormone has a sinusoidal variations (7). In

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fact, high FGF23 levels in response to high phosphate intake induce greater urinary fractional excretion of phosphate, and, by lowering 1,25-dihydroxyvitamin D levels, reduce the efficiency of phosphate absorption in gastrointestinal tract (8). In contrast, by lowering dietary phosphate intake, the level of FGF23 increases, renal phosphate reabsorption increases and the efficiency of phosphate absorption in the gut enhances the resulting increase in 1,25-dihydroxyvitamin D levels. Thus, the level of FGF23 depends on directly phosphate intake. Another pathway for regulation of FGF23 level is activation and secretion of PTH that PTH can stimulate secretion of FGF23 via PTH-mediated increases in 1,25-dihydroxyvitamin D (9). Moreover, increasing level of serum calcium is a powerful stimulator for secretion of FGF23. This hemostasis needs to a stable hemodynamic situation especially on normal renal bed. It seems that in the background of renal impairment or following dialysis, this hormonal balancing may be disturbed (10). Additionally, in some recent studies, the type of dialysis (hemodialysis or peritoneal dialysis) may differently affect serum levels of FGF23 (11).

2. Objectives

The present study aimed to assess the association of the level of FGF23 and calcium metabolism in hemodialysis patients.

3. Patients and Methods

3.1. Study population

This cross-sectional study conducted on 90 consecutive patients who suffering end-stage renal disease (ESRD) who underwent hemodialysis at dialysis department of Hajar hospital in Shahrekord city in Iran in 2016. All patients aged higher than 20 years and under hemodialysis procedures at least three times a week. Those with history of using corticosteroids or calcitriol were all excluded. After the introduction of nature study, the qualified volunteers participated in the study with informed consent. The study parameters considered into this study were baseline characteristics (gender, age, and body mass index [BMI]), duration of dialysis and also the serum levels of FGF23, calcium, intact parathyroid hormone (iPTH), magnesium, phosphorus, vitamin D, and serum albumin. Weight and height were assessed with a minimum coverage without shoes. The BMI was calculated as the ratio of weight (kg) by the square of height (m) and was recorded in the study forms for each person. The blood samples were then taken from the patients.

3.2. Blood parameters assessment

Serum of blood samples were isolated by centrifugation and were immediately stored at -20°C until analysis. The serum levels of FGF23 and iPTH levels were measured using the ELISA technique. The levels of calcium, magnesium, and phosphorus concentrations were measured by the photometric methods. The serum level of 25-hydroxyvitamin D was also measured using the electrochemiluminescence assay. Serum albumin was measured by the special kits.

3.3. Ethical issues

1) The research followed the tenets of the Declaration of Helsinki, and the research was approved by the ethical committee of Shahrekord University of Medical Sciences.

3.4. Data analysis

For statistical analysis, results were presented as mean ± standard deviation (SD) for quantitative variables and were summarized by frequency (percentage) for categorical variables. Continuous variables were compared using *t* test or Mann-Whitney U test whenever the data did not appear to have normal distribution or when the assumption of equal variances was violated across the study groups. The associations between study parameters were assessed by the Pearson's or Spearman's tests. *P* values of ≤0.05 were considered statistically significant. For the statistical analysis, the statistical software SPSS version 23.0 for windows (IBM, Armonk, New York) was used.

4. Results

Of 90 patients were primarily assessed, the data of five patients were flawed and thus the data of 85 patients were finally analyzed. Of those, 58.9% were male and 41.1% were female. Table 1 describes the mean serum levels of study parameters in men and women. In men as compared to women, the mean serum levels of phosphate (4.91 ± 0.76 mg/dL versus 4.49 ± 3.96 mg/dL, $P=0.034$) and levels of magnesium (2.47 ± 0.31 mg/dL versus 2.27 ± 0.32 mg/dL, $P=0.006$) were significantly higher in men than in women. Furthermore, men had higher serum levels of iPTH as compared to women (657.54 ± 635.20 pg/dL versus 326.14 ± 241.80 pg/ dL, $P=0.008$), while no differences were found in the level of other parameters including serum calcium levels of calcium, albumin, vitamin D, and even FGF23 ($P>0.05$).

As shown in Table 2, the serum levels of FGF23 was directly associated with iPTH level ($r=0.251$, $P=0.020$) and slightly with duration of dialysis ($r=0.203$, $P=0.063$); however FGF23 concentration was not significantly related to other indices including levels of calcium, phosphorus, magnesium, vitamin D, albumin,

Table 1. Comparing serum parameters between men and women

Parameter	Men (n = 49)	Women(n = 36)	P value
BMI, kg/m^2	23.84 ± 5.01	22.48 ± 9.87	0.290
Calcium, mg/dL	8.87 ± 0.58	8.57 ± 0.58	0.376
Phosphorus, mg/ dL	4.91 ± 0.76	4.49 ± 3.96	0.034
Magnesium, mg/ dL	2.47 ± 0.31	2.27 ± 0.32	0.006
Albumin, g/ dL	3.83 ± 0.38	3.68 ± 0.52	0.113
Parathormone, ng/mL	657.54 ± 635.20	326.14 ± 241.80	0.008
Vitamin D, ng/mL	42.33 ± 34.01	43.55 ± 38.64	0.915
FGF23, pg/mL	334.12 ± 367.94	340.37 ± 398.50	0.663

and even BMI. Assessing interactive association between different parameters showed significant associated between serum vitamin D level and calcium ($r=0.232$, $P=0.032$) and also between serum iPTH level and serum magnesium ($r=0.229$, $P=0.035$).

5. Discussion

The functional association between FGF23 and parathyroid glands has been clearly described. FGF23 can affect parathyroid gland and its secretory action by connecting FGF23-especific receptors in the gland (Klotho-FGFR1c) leading decrease of PTH production and secretion through activation of the mitogen-activated protein kinases (MAPK) pathway. This pathway is accurately regulated in healthy condition leading a hemodynamic stability condition. However, in ESRD patients, both FGF23 and PTH levels increase, explaining the resistance of the parathyroid glands to FGF23 (12). More remarkably, by progressing renal failure, FGF23 may lose its ability to inhibit PTH expression. Even with treating parathyroid dysfunction by a stabilized form of recombinant FGF23, the level of both markers significantly increased (13). Thus, similar to healthy conditions, in ESRD patients, a direct functional link between FGF23 and parathyroid secretory function was existed. However, despite association between FGF23 and PTH levels, FGF23 was not associated with other metabolites related to PTH levels including calcium, phosphorus, and vitamin D indicating an abnormal metabolic status related to calcium metabolism in ESRD patients. It has been demonstrated that parathyroid tissue cultured can upregulate PTH secretion and cell proliferation in response to FGF23. In other words, FGF23 is now accepted as an inducer of parathyroid cell proliferation and PTH secretion. This association may lead to hyperactivation and hypersecretion of FGF23 leading secondary hyperparathyroidism in kidney disease patients (14).

Table 2. The association of FGF23 with other biomarkers

Parameter	r coefficient	P value
BMI, kg/m^2	-0.87	0.4٢4
Calcium, mg/ dL	-0.97	0.376
Phosphate, mg/ dL	0.01	0.999
Magnesium, mg/ dL	0.008	0.943
Albumin, g/dL	0.050	0.950
Parathormone, pg/mL	0.251	0.020
Vitamin D, ng/mL	-0.091	0.414
Duration of dialysis (mon)	0.230	0.063
BMI, kg/m^2	-0.870	0.429

The role of FGF23 in calcium metabolism in renal disease condition has been also assessed in some studies. In an animal study (15), compared to healthy experimental models, all vitamin D metabolites were negatively correlated with PTH, FGF-23, and phosphorus concentrations, whereas in our study, FGF23 was only associated with PTH level. In those with nephrotic syndrome, simultaneous decreasing the levels of vitamin D and FGF23 was also shown (16). However, in our study, the change in vitamin D level was independent to the levels of serum FGF23. It seems that the changes in FGF23 concentration is caused by hemodialysis, not directly by renal dysfunction. In other words, the pathological change in FGF23 is induced by hemodialysis pathways independent to abnormal changes following renal dysfunction. It has been shown that in patients with chronic kidney disease not yet on dialysis, the correlation between FGF23, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, ApoA, ApoB, iPTH, calcium, phosphorous, alkaline phosphatase, 25-hydroxyvitamin D, BMI, waist girth, serum triglyceride and cholesterol was not significant (17), which all might be significant after starting hemodialysis. The detectable association between duration of dialysis and levels of FGF23 in our study can be another reason for this claim.

6. Conclusions

Considering the results of current study, there is not any relation between FGF23 level and phosphor, magnesium and vitamin D in hemodialysis patients. The level of FGF23 has a positive and significant correlation with the duration of hemodialysis. The FGF23 level has a negative and non-significant correlation with

serum calcium.

Limitations of the study

Main limitation of our study was small proportion of patients. We suggest multi-centric studies on this aspect of hemodialysis patients.

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Authors' contribution

All authors contributed to the study. NA and PJ conducted the research. NA, ST and PJ prepared the data and prepared the primary draft. All authors read and approved the final manuscript.

Conflicts of interest

The authors declared no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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