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Association Between Uremic Pruritus and Serum Level of Fibroblast Growth Factor 23 in Hemodialysis Patients in North of Iran: An Observational Study

Elham Ramezanzade [1], Zeinab Azimi [2,*], Narges Alizadeh [2] and Ali Monfared [1]

[1] Urology Research Center, Razi Hospital, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran
[2] Department of Dermatology, Razi Hospital, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran

[*] *Corresponding author*: Department of Dermatology, Razi Hospital, School of Medicine, Guilan University of Medical Sciences, P. O. Box: 41448-95655, Rasht, Iran. Tel: +98-13155537500, Email: sz.azimi@yahoo.com

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Abstract

Background: Chronic itch (CI) in hemodialysis (HD), also called uremic pruritus (UP), is a common, distressing, and unpleasant symptom. Fibroblast growth factor 23 (FGF23) is a bone-secreted phosphaturic factor. Several bone diseases can accompany kidney diseases. It is unclear whether the common disturbance of calcium/phosphate homeostasis can cause CI in chronic kidney disease.
Objectives: This study investigated the association between FGF23 and UP among HD patients in northern Iran.
Methods: Patients undergoing maintenance HD at four referral medical centers were recruited in this cross-sectional survey. The enzyme-linked immunosorbent assay was used to evaluate serum FGF23 levels. An interview questionnaire was used to analyze the various aspects of pruritus.
Results: Of 237 subjects, 54.01% had UP. There was no difference in serum FGF23 levels between patients with and without UP (413.17 $\pm$ 416.97 vs. 410.81 $\pm$ 444.49, P = 0.85). Those with UP required dialysis for a longer period (P = 0.02). FGF23 was shown to be associated with parathyroid hormone in UP (P = 0.02, r = 0.41).
Conclusions: There was no linear correlation between FGF23 and UP in this study.

Keywords: Fibroblast Growth Factor 23, Uremic Pruritus, Hemodialysis, Atorvastatin, Parathyroid Hormone

1. Background

Uremic pruritus (UP) is a frequently experienced, tormenting, and challenging problem in advanced or end-stage renal disease (1). There has been an ongoing debate regarding if UP in chronic renal disease (CDK) is caused by the common disturbance of calcium/phosphate homeostasis (2, 3). Recently, a vicious circle of metabolic derangements, including malnourishment, inflammation, and arteriosclerosis, has been proposed that may clarify the overwhelming morbidity and mortality in hemodialysis (HD) patients. Among other factors contributing to UP in HD, inflammation sounds the most deleterious (4, 5). Fibroblast growth factor 23 (FGF23) is a key player in regulating calcium/phosphate. It has been revealed that high levels of FGF23 have been linked to increased inflammation, morbidity, and mortality in those with CDK (6).

2. Objectives

In the present study, we investigated the prevalence of UP among HD patients. We assessed serum FGF23 levels and other demographic and biochemical parameters. We tried to find the factors potentially influencing the FGF23 level in HD patients.

3. Methods

3.1. Patients

This analytical observational multicenter study was performed between May and November 2018. The institutional review board of Guilan University of Medical Sciences approved the study protocol. All the participants gave their informed consent. The inclusion criteria included all HD patients aged over 18 years admitted to four dialysis centers in Guilan province. Those HD patients with primary pruritic skin lesions, infectious cutaneous

disorders such as scabies, inflammatory skin disorders like atopic dermatitis, lichen planus, prurigo nodularis, and neoplastic skin diseases such as mycosis fungoides were excluded from the study. Those suspected of senile xerosis were treated with emollients and reevaluated one month later. The patients were asked for chronic itch (duration above six weeks). The characteristic of itch was defined as at least three episodes of itch during two weeks or less, the itch happening several times a day and lasting for more than five minutes, and annoying (7). Then, the patients were categorized into two groups with and without UP. The dialysis sessions and hours were adjusted according to the patient's residual kidney function. Most of them were dialyzed 2 - 3 times a week. None of the individuals had received ultraviolet (UV) phototherapy within six months preceding the research. A single dermatologist conducted a thorough physical examination of all UP patients. Those suffering from UP were requested to score the severity of their present itch based on a visual analog scale (VAS). The VAS spans from 0 for no itch to 10 for the most severe imaginable itch (8). The different characteristics of pruritus were asked in a precise interview. The same dermatologist gathered data and evaluated the inclusion and exclusion criteria.

3.2. Experimental Methods

In both groups, 10 mL of blood was taken after a long dialysis-free weekend immediately before starting HD. In addition to the routine laboratory measurements, we also assessed FGF23, 25-hydroxyvitamin D3 (25[OH] D3), albumin, calcium, phosphate, and C-reactive protein (hsCRP).

An enzyme-linked immunosorbent assay measured FGF23 (C-terminal, ELISA, Biomedica Austria) (ELISA). The KT/V was adjusted between 1.2 and 1.4.

3.3. Statistical Analysis

SPSS version 20.0 software was used for statistical analysis. The frequency, median, and means $\pm$ standard deviation (SD) were reported using descriptive statistics. The non-parametric Mann-Whitney U test or the χ2-test (for nominal variables) was used to examine differences between patients with and without UP. Pearson's univariate correlation analysis, followed by stepwise and multiple linear regression approaches, was utilized to discover the correlations. P-values of less than 0.05 were considered statistically significant.

4. Results

Among 237 patients who remained in the study, 134 were male with a mean age of 57.09 $\pm$ 15.35 years (range 19 - 94), and 103 were female with a mean age of 61.90 $\pm$ 13.57 years (range 25 - 86). In total, 128 patients had UP, while 109 patients on HD did not report UP at least within the last six months.

The median itch intensity of patients with UP was 5.47 $\pm$ 2.46. The most dermatologic sign of HD patients with pruritus was dryness (n = 116, 91%).

There were no significant differences between the two groups in mean FGF23 (P = 0.85). The phosphorous and hemoglobin levels were not significantly different between the two groups (Table 1).

There were no differences between the two groups regarding their end-stage renal disease (ESRD) etiology. Of note, hyperlipidemia patients were more non-UP than UP; however, this difference was not statistically significant (n = 11 vs. n = 5, P = 0.07). The mean level of FGF23 was higher in urban than rural patients (P = 0.002). Comparing UP and non-UP groups showed that the difference was only within the UP group (0.004), and non-UP patients had no difference in this regard (P = 0.143) (Table 2). Spearman correlation showed that among 237 participants, FGF23 levels had a negative correlation with age and positive correlations with dialysis duration and serum creatinine ($P < 0.05$). We detected a borderline correlation between FGF23 and PTH levels (P = 0.085). This correlation was only among the UP subgroup ($P < 0.05$).

Among non-UP patients, there were correlations between FGF23 levels and age, skin dryness, dialysis duration, serum creatinine, and calcium ($P < 0.05$) (Table 3).

Among demographic factors, sex, smoking, and occupation had no relationship with FGF23 levels.

5. Discussion

The prevalence of UP in our study was estimated at 54.01%. Several studies reported a range of 10% to 85% for UP. This broad range may explain the different used measures; for example, some studies evaluated the lifetime prevalence of UP, while others only evaluated the current prevalence of UP. We estimated the current prevalence of UP in our study. The burden and prevalence of UP are often undervalued. Since the increase in the survival of ESRD will increase the number of patients on HD, UP is highly important. The high prevalence of UP in our study may be explained by improper cooperation of HD patients with

Table 1. Comparison of Quantitative Variables Among Two Groups with and Without Uremic Pruritus

	Pruritus				P
	Yes (n = 128)		No (n = 109)		
	Mean ± SD	Med	Mean ± SD	Med	
FGF23	413.17 ±416.97	240.35	410.81 ± 444.49	225.00	0.85
Age	59.80 ± 15.47	60.50	58.45 ± 13.94	62.00	0.63
Duration of ESRD	4.03 ±5.88	1.00	4.11 ± 5.59	1.00	0.40
Duration of dialysis	44.69 ± 43.24	36.00	38.87 ± 50.73	22.00	0.02
WBC	7354.26±2819.9	6900.00	7023.59 ± 2017.63	6900.00	0.89
RBC	3.87 ± 0.68	3.80	3.91 ± 0.70	3.85	0.38
Hb	10.86 ± 1.86	10.75	11.12 ± 2.00	11.20	0.19
HCT	34.19 ± 5.49	33.80	35.11 ± 5.73	35.20	0.13
MCV	89.41 ± 9.36	91.30	89.71 ± 8.99	91.40	0.81
ESR	45.22 ± 38.24	30.00	39.24 ± 26.72	37.00	0.84
CRP	10.22 ± 17.41	2.00	8.44 ± 12.20	4.00	0.53
FBS	125.74 ± 83.01	96.00	122.42 ± 68.66	92.00	0.94
BUN	60.15 ± 18.51	58.90	60.63 ± 16.93	60.00	0.98
CR	7.99 ± 2.94	7.88	7.84 ± 3.06	7.90	0.82
URR	0.67 ± 0.12	0.67	0.69 ± 0.09	0.69	0.21
Kt/V	1.34 ± 0.32	1.30	1.36 ± 0.28	1.31	0.42
SGPT	18.18 ± 9.78	16.00	17.46 ± 9.79	15.00	0.55
SGOT	19.24 ± 15.57	15.50	17.79 ± 9.96	16.00	0.65
AlkP	302.65 ± 187.66	221.00	325.60 ± 223.29	253.00	0.38
Ca	8.88 ± 1.31	8.80	8.77 ± 0.88	8.70	0.69
P	5.60 ± 1.75	5.30	5.48 ± 1.80	5.40	0.58
PTH	393.55 ± 38.41	271.00	404.54 ± 477.80	129.70	0.75
iPTH	231.15 ± 244.18	130.30	218.36 ± 240.82	119.60	0.42
Vitamin D	33.48 ± 18.46	30.50	34.14 ± 15.74	32.00	0.64
Albumin	3.85 ± 0.40	3.90	3.91 ± 0.48	4.00	0.26
Uric Acid	6.52 ± 1.85	6.30	6.60 ± 1.51	6.40	0.81
Ca_P	49.52 ± 16.43	44.77	47.84 ± 15.85	46.97	0.70

their physicians, inadequate therapy, and inappropriate response to treatment.

The results of our study demonstrated that HD patients experienced a moderate itch, which may, to some extent, clarify why UP is underestimated among HD patients. The pathophysiology of pruritus in ESRD is poorly identified. Based on several observational and clinical trials, there are rising data that UP is a systemic rather than an isolated cutaneous disorder (4, 9). It is assumed to be due to the imbalance of Th1 cytokines and the presence of a proinflammatory state. Also, the C-reactive protein level is much higher in ESRD patients. Kimmel et al. found that HD patients had a prominent increased level of IL-6 and Th1 cytokines (4). Peripheral neuropathy is common in ESRD. One hypothesis is that the itch in ESRD could be related to neuropathy. However, other studies do not support it.

Many other pathways were postulated in the pathophysiology of ESRD pruritus. Another possible reason for ESRD itch was the inadequate removal of medium molecular weight uremic toxins (10). Recently, it was found that the removal of small molecular toxins with greater efficiency by standard assessment of Kt/V was related to ESRD itch (3).

The main strength of our investigation is that, to the

Table 2. Comparison of FGF23 Levels by Qualitative Variables in Two Groups with and Without Uremic Pruritus [a]

FGF23	Pruritus			
	Yes	P	No	P
Sex		0.868		0.368
Male	406.37 ± 398.55		323.64 ± 318.87	
Female	422.20 ± 443.82		521.59 ± 549.35	
Place		0.004		0.143
Urban	452.58 ± 441.62		437.01 ± 456.22	
Rural	250.81 ± 238.84		322.80 ± 398.48	
Occupation		0.686		0.393
Currently works	439.93 ± 452.18		526.83 ± 554.07	
Currently does not work	394.27 ± 392.22		322.86 ± 316.31	
Smoking		0.864		0.825
Yes	513.16 ± 514.27		430.64 ± 555.10	
Never	396.59 ± 405.30		421.22 ± 450.76	
Quitted	399.26 ± 344.39		267.65 ± 119.46	
Background disease number		0.469		0.259
0.00	1042.04 ± 760.08		0	
1.00	395.57 ± 360.38		406.71 ± 429.42	
2.00	291.31 ± 245.45		311.69 ± 338.60	
3.00	386.80 ± 418.67		551.81 ± 584.83	
4.00	555.37 ± 589.43		625.10 ± 571.67	
5.00	457.35 ± 431.55		149.83 ± 56.50	
Etiology of ESRD		0.371		0.603
Primary GN	288.81 ± 217.42		373.34 ± 304.00	
PCKD	646.76 ± 553.42		772.35 ± 496.67	
DM	344.45 ± 368.46		385.10 ± 394.87	
HTN	407.33 ± 464.02		369.85 ± 396.50	
Not known	444.21 ± 416.51		468.36 ± 491.49	
Reflux nephropathy	317.57 ± 232.13		287.59 ± 224.33	
UO	428.57 ± 599.78		146.95 ± 25.95	
DM & HTN	425.15 ± 416.94		340.26 ± 326.99	
Other	855.50 ± 749.00		855.50 ± 749.00	
DM and OU	361.32 ± 261.69		391.57 ± 340.73	
Total	412.09 ± 428.93		413.17 ± 416.97	

[a] Values are expressed as mean ± SD.

best of our knowledge, this is the first study to evaluate a large HD population regarding FGF23 levels and UP. Previously, a letter evaluated 18 cases of UP and could not find any association between UP and FGF23 levels (11). The small number of cases in that study was a notable limitation. Other studies evaluated FGF23 in CKD patients.

FGF23, a novel disease biomarker in nephrology, is a significant player in regulating calcium, phosphate, and mineral bone homeostasis (12, 13). FGF23 is constructed and secreted in bone by osteocytes. However, the primary target tissues are the distal nephron and the parathyroid gland. The FGF23 receptor complex consists of two components

of FGF receptor 1c (FGFR1c) and membrane-bound αKlotho, both expressed in target tissues (14-16). When FGF23 binds to its receptor, signal transduction occurs in the cytoplasm by activating tyrosine kinases 9 - 11. FGF23 regulates phosphate reabsorption in the kidney, PTH secretion, and vitamin D metabolism.

Therefore, FGF23 prevents positive phosphate balance and hyperphosphatemia. Consequently, observations showed that CKD patients have a substantial increase in serum FGF23 levels through their compromised renal phosphate clearance (14).

Remarkably, epidemiological studies in both the general population and patients with kidney disease demonstrated an association of FGF23 with significant medical results related to inflammation, cardiovascular disease, and mortality (17-19). The association between FGF23 and mortality enrolled patients on dialysis; FGF23 was unlikely to impact tubular function in that population, indicating another mechanism of action14.

Also, after adjusting for potential confounders, including phosphate concentrations, the association between FGF23 and mortality was not attenuated. Thus, adjustment only supported the link between FGF23 concentrations and mortality. 14ver aside from its impact on renal phosphate, FGF23 influences vitamin D metabolism, which also occurs in the convoluted tubule.

The conversion of 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol is prevented by inhibiting the 1-hydroxylase enzyme, which is responsible for this metabolic step13ver. On the other hand, FGF23 endorses vitamin D catabolism by up-regulating 24-hydroxylase, which inactivates 1,25-dihydroxycholecalciferol. So, a decrease in circulating active vitamin D is essential in the phosphate-lowering effects of FGF23. Also, the decrease in active vitamin D diminishes the gastrointestinal uptake of phosphate (20, 21).

In our study, the mean vitamin D level was 33.82 $\pm$ 17.06, and the median FGF23 level was 412.09 $\pm$ 428.93. Obviously, the balance was distorted in our HD patients. The increased FGF23 level and phosphate secretion were expected since the kidneys' filtration function was decreased.

PTH secretion is also influenced by FGF23 (20, 21). In CKD, the role of constantly increasing FGF23 levels in the progression of hyperparathyroidism opens a discussion. The FGF receptor is down-regulated in the parathyroid gland in uremic situations, thus bringing to mind FGF23 resistance (22).

Our study showed no significant difference between the two groups of HD patients regarding serum-calcium, serum-phosphate, and 25(OH) D3 values (11, 23).

In our study, FGF23 levels were not significantly different between patients with and without UP and did not show any association with pruritus in HD patients. Thus, the role of this protein in the pathogenesis of UP in HD remains questionable.

Notably, epidemiological research found a statistically significant relationship between FGF23 levels and C-reactive protein (CRP) and IL-6 levels in CKD patients (24). The fact that inflammation is a significant inducer of FGF23 release from bone cells may help to explain the previously reported association (25-27).

In our study, HD patients with UP did not exhibit significantly higher CRP levels than those without UP. This is in line with other observational studies (23). But, some previous experimental studies did not find such associations (4, 5, 11). More research is needed to identify whether inflammation is a cause of persistent pruritus in hemodialysis patients and determine the specific involved pathways.

The mean FGF23 level in our study was correlated with the duration of dialysis (42.00 $\pm$ 46.84 months). Also, Negishi et al. found that the serum FGF23 level in dialysis patients was 1171 $\pm$ 553 pg/mL. The mean dialysis duration was 5.8 $\pm$ 5.0 years, and the concentration of FGF23 increased with the duration of dialysis (28).

Concerning the present study's limitations, we did not evaluate FGF23 levels at the beginning and end of one dialysis session for each patient. We could not assess the changes in PTH, calcitriol, and other minerals. In this study, residual kidney function was also not evaluated due to the administration limitations and the lack of cooperation of patients for 24-hour urine collection. The level of cooperation of patients could be a limitation.

In conclusion, UP needs serious attention because of its increasing frequency and subsequent burden. This study found no linear correlation between UP and FGF23 levels.

Footnotes

Authors' Contribution: A Z and R E had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. Acquisition and interpretation of data were made by all authors. Drafting of the manuscript was done by A Z and R E. Critical revision of the manuscript for important intellectual content was done by A N and M A. Administrative and technical support was done by A Z and R E. All authors were involved in study supervision.

Conflict of Interests: The authors declared no potential conflicts of interest concerning the research and authorship of this publication.

Ethical Approval: The study protocol was approved by the Guilan University of Medical Sciences ethics committees (No. IR.GUMS.REC.1396.237).

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Informed Consent: Written informed consent was obtained from the patients for publishing this article.

References

1. Weiss M, Mettang T, Tschulena U, Passlick-Deetjen J, Weisshaar E. Prevalence of chronic itch and associated factors in haemodialysis patients: a representative cross-sectional study. *Acta Derm Venereol*. 2015;**95**(7):816–21. [PubMed: 25740325]. https://doi.org/10.2340/00015555-2087.
2. Momose A, Kudo S, Sato M, Saito H, Nagai K, Katabira Y, et al. Calcium ions are abnormally distributed in the skin of haemodialysis patients with uraemic pruritus. *Nephrol Dial Transplant*. 2004;**19**(8):2061–6. [PubMed: 15187190]. https://doi.org/10.1093/ndt/gfh287.
3. Duque MI, Thevarajah S, Chan YH, Tuttle AB, Freedman BI, Yosipovitch G. Uremic pruritus is associated with higher kt/V and serum calcium concentration. *Clin Nephrol*. 2006;**66**(3):184–91. [PubMed: 16995341]. https://doi.org/10.5414/cnp66184.
4. Kimmel M, Alscher DM, Dunst R, Braun N, Machleidt C, Kiefer T, et al. The role of micro-inflammation in the pathogenesis of uraemic pruritus in haemodialysis patients. *Nephrol Dial Transplant*. 2006;**21**(3):749–55. [PubMed: 16249205]. https://doi.org/10.1093/ndt/gfi204.
5. Virga G, Visentin I, La Milia V, Bonadonna A. Inflammation and pruritus in haemodialysis patients. *Nephrol Dial Transplant*. 2002;**17**(12):2164–9. [PubMed: 12454228]. https://doi.org/10.1093/ndt/17.12.2164.
6. Hanks LJ, Casazza K, Judd SE, Jenny NS, Gutierrez OM. Associations of fibroblast growth factor-23 with markers of inflammation, insulin resistance and obesity in adults. *PLoS One*. 2015;**10**(3). e0122885. [PubMed: 25811862]. [PubMed Central: PMC4374938]. https://doi.org/10.1371/journal.pone.0122885.
7. Yosipovitch G, Zucker I, Boner G, Gafter U, Shapira Y, David M, et al. A questionnaire for the assessment of pruritus: validation in uremic patients. *Acta Derm Venereol*. 2001;**81**(2):108–11. [PubMed: 11501646]. https://doi.org/10.1080/00015550152384236.
8. Yosipovitch G. Methodological Approaches for Testing Anti-itch and Related Substances. In: Gabard B, Surber C, Elsner P, Treffel P, editors. *Dermatopharmacology of Topical Preparations*. Berlin/Heidelberg: Springer; 2000. p. 231–9. https://doi.org/10.1007/978-3-642-57145-9_15.
9. Mettang T, Pauli-Magnus C, Alscher DM. Uraemic pruritus–new perspectives and insights from recent trials. *Nephrol Dial Transplant*. 2002;**17**(9):1558–63. [PubMed: 12198205]. https://doi.org/10.1093/ndt/17.9.1558.
10. Patel TS, Freedman BI, Yosipovitch G. An update on pruritus associated with CKD. *Am J Kidney Dis*. 2007;**50**(1):11–20. [PubMed: 17591521]. https://doi.org/10.1053/j.ajkd.2007.03.010.
11. Mettang T, Kunzmann K, Roth HJ, Weisshaar E. Fibroblast Growth-factor 23 and Calcium-binding Proteins are not Associated with Chronic Itch in Patients on Haemodialysis. *Acta Derm Venereol*. 2017;**97**(3):381–2. [PubMed: 27671605]. https://doi.org/10.2340/00015555-2536.
12. Olauson H, Vervloet MG, Cozzolino M, Massy ZA, Urena Torres P, Larsson TE. New insights into the FGF23-Klotho axis. *Semin Nephrol*. 2014;**34**(6):586–97. [PubMed: 25498378]. https://doi.org/10.1016/j.semnephrol.2014.09.005.
13. Isakova T, Wahl P, Vargas GS, Gutierrez OM, Scialla J, Xie H, et al. Fibroblast growth factor 23 is elevated before parathyroid hormone and phosphate in chronic kidney disease. *Kidney Int*. 2011;**79**(12):1370–8. [PubMed: 21389978]. [PubMed Central: PMC3134393]. https://doi.org/10.1038/ki.2011.47.
14. Urakawa I, Yamazaki Y, Shimada T, Iijima K, Hasegawa H, Okawa K, et al. Klotho converts canonical FGF receptor into a specific receptor for FGF23. *Nature*. 2006;**444**(7120):770–4. [PubMed: 17086194]. https://doi.org/10.1038/nature05315.
15. Quarles LD. Endocrine functions of bone in mineral metabolism regulation. *J Clin Invest*. 2008;**118**(12):3820–8. [PubMed: 19033649]. [PubMed Central: PMC2586800]. https://doi.org/10.1172/JCI36479.
16. Osuka S, Razzaque MS. Can features of phosphate toxicity appear in normophosphatemia? *J Bone Miner Metab*. 2012;**30**(1):10–8. [PubMed: 22219005]. [PubMed Central: PMC3804315]. https://doi.org/10.1007/s00774-011-0343-z.
17. Vervloet M. Renal and extrarenal effects of fibroblast growth factor 23. *Nat Rev Nephrol*. 2019;**15**(2):109–20. [PubMed: 30514976]. https://doi.org/10.1038/s41581-018-0087-2.
18. Gutierrez OM, Mannstadt M, Isakova T, Rauh-Hain JA, Tamez H, Shah A, et al. Fibroblast growth factor 23 and mortality among patients undergoing hemodialysis. *N Engl J Med*. 2008;**359**(6):584–92. [PubMed: 18687639]. [PubMed Central: PMC2890264]. https://doi.org/10.1056/NEJMoa0706130.
19. Marthi A, Donovan K, Haynes R, Wheeler DC, Baigent C, Rooney CM, et al. Fibroblast Growth Factor-23 and Risks of Cardiovascular and Noncardiovascular Diseases: A Meta-Analysis. *J Am Soc Nephrol*. 2018;**29**(7):2015–27. [PubMed: 29764921]. [PubMed Central: PMC6050929]. https://doi.org/10.1681/ASN.2017121334.
20. Krajisnik T, Bjorklund P, Marsell R, Ljunggren O, Akerstrom G, Jonsson KB, et al. Fibroblast growth factor-23 regulates parathyroid hormone and 1alpha-hydroxylase expression in cultured bovine parathyroid cells. *J Endocrinol*. 2007;**195**(1):125–31. [PubMed: 17911404]. https://doi.org/10.1677/JOE-07-0267.
21. Ben-Dov IZ, Galitzer H, Lavi-Moshayoff V, Goetz R, Kuro-o M, Mohammadi M, et al. The parathyroid is a target organ for FGF23 in rats. *J Clin Invest*. 2007;**117**(12):4003–8. [PubMed: 17992255]. [PubMed Central: PMC2066196]. https://doi.org/10.1172/JCI32409.
22. Galitzer H, Ben-Dov IZ, Silver J, Naveh-Many T. Parathyroid cell resistance to fibroblast growth factor 23 in secondary hyperparathyroidism of chronic kidney disease. *Kidney Int*. 2010;**77**(3):211–8. [PubMed: 20016468]. https://doi.org/10.1038/ki.2009.464.
23. Weisshaar E, Weiss M, Passlick-Deetjen J, Tschulena U, Maleki K, Mettang T. Laboratory and dialysis characteristics in hemodialysis patients suffering from chronic itch–results from a representative cross-sectional study. *BMC Nephrol*. 2015;**16**:184. [PubMed: 26530958]. [PubMed Central: PMC4632673]. https://doi.org/10.1186/s12882-015-0177-3.
24. Munoz Mendoza J, Isakova T, Ricardo AC, Xie H, Navaneethan SD, Anderson AH, et al. Fibroblast growth factor 23 and Inflammation in CKD. *Clin J Am Soc Nephrol*. 2012;**7**(7):1155–62. [PubMed: 22554719]. [PubMed Central: PMC3386678]. https://doi.org/10.2215/CJN.13281211.
25. Ito N, Wijenayaka AR, Prideaux M, Kogawa M, Ormsby RT, Evdokiou A, et al. Regulation of FGF23 expression in IDG-SW3 osteocytes and human bone by pro-inflammatory stimuli. *Mol Cell Endocrinol*. 2015;**399**:208–18. [PubMed: 25458698]. https://doi.org/10.1016/j.mce.2014.10.007.

26. Pathak JL, Bakker AD, Luyten FP, Verschueren P, Lems WF, Klein-Nulend J, et al. Systemic Inflammation Affects Human Osteocyte-Specific Protein and Cytokine Expression. *Calcif Tissue Int*. 2016;**98**(6):596–608. [PubMed: 26887974]. https://doi.org/10.1007/s00223-016-0116-8.
27. David V, Martin A, Isakova T, Spaulding C, Qi L, Ramirez V, et al. Inflammation and functional iron deficiency regulate fibroblast growth factor 23 production. *Kidney Int*. 2016;**89**(1):135–46. [PubMed: 26535997]. [PubMed Central: PMC4854810]. https://doi.org/10.1038/ki.2015.290.
28. Negishi K, Kobayashi M, Ochiai I, Yamazaki Y, Hasegawa H, Yamashita T, et al. Association between fibroblast growth factor 23 and left ventricular hypertrophy in maintenance hemodialysis patients. Comparison with B-type natriuretic peptide and cardiac troponin T. *Circ J*. 2010;**74**(12):2734–40. [PubMed: 21041973]. https://doi.org/10.1253/circj.cj-10-0355.

Table 3 . Correlation of FGF23 with Quantitative Variables in the General Uremic Population of Study and Groups with and Without Uremic Pruritus

		Corrected FGF23		
		All the Participants n = 237	UP	Non-UP
Age				
	Correlation coefficient	-0.134	-0.078	-0.201
	Sig. (2-tailed)	0.039	0.380	0.036
	N	237	128	109
Duration of ESRD				
	Correlation coefficient	-0.052	-0.035	-0.058
	Sig. (2-tailed)	0.434	0.699	0.554
	N	232	126	106
Duration of dialysis				
	Correlation coefficient	0.163	0.149	0.190
	Sig. (2-tailed)	0.012	0.095	0.048
	N	236	127	109
WBC				
	Correlation coefficient	-0.136	-0.186	-0.058
	Sig. (2-tailed)	0.042	0.040	0.559
	N	225	122	103
RBC				
	Correlation coefficient	0.051	0.048	0.085
	Sig. (2-tailed)	0.442	0.603	0.391
	N	225	122	103
HB				
	Correlation coefficient	0.014	-0.011	0.051
	Sig. (2-tailed)	0.835	0.905	0.607
	N	227	124	103
HCT				
	Correlation coefficient	0.004	-0.019	0.054
	Sig. (2-tailed)	0.953	0.838	0.586
	N	226	123	103
MCV				
	Correlation coefficient	-0.079	-0.010	-0.162
	Sig. (2-tailed)	0.235	0.910	0.103
	N	226	123	103
ESR				
	Correlation coefficient	-0.027	-0.174	0.140
	Sig. (2-tailed)	0.765	0.172	0.278
	N	125	63	62
CRP				
	Correlation coefficient	-0.041	-0.082	-0.036
	Sig. (2-tailed)	0.618	0.488	0.762
	N	148	73	75
FBS				
	Correlation coefficient	-0.072	0.018	-0.241
	Sig. (2-tailed)	0.408	0.875	0.083
	N	133	80	53
BUN				
	Correlation coefficient	0.073	-0.010	0.170
	Sig. (2-tailed)	0.276	0.910	0.085
	N	226	123	103
CR				
	Correlation coefficient	0.218	0.132	0.314
	Sig. (2-tailed)	0.001	0.148	0.001
	N	225	122	103

URR				
	Correlation coefficient	-0.058	-0.092	-0.004
	Sig. (2-tailed)	0.428	0.363	0.973
	N	191	99	92
KTV				
	Correlation coefficient	-0.127	-0.164	-0.091
	Sig. (2-tailed)	0.076	0.099	0.382
	N	196	102	94
SGPT				
	Correlation coefficient	-0.042	-0.146	0.073
	Sig. (2-tailed)	0.590	0.191	0.506
	N	166	82	84
SGOT				
	Correlation coefficient	-0.046	-0.181	0.108
	Sig. (2-tailed)	0.554	0.105	0.326
	N	166	82	84
AlkP				
	Correlation coefficient	-0.019	0.005	-0.036
	Sig. (2-tailed)	0.814	0.964	0.747
	N	163	82	81
Ca				
	Correlation coefficient	-0.026	0.135	-0.232
	Sig. (2-tailed)	.699	0.144	0.019
	N	221	119	102
P				
	Correlation coefficient	-.039	-0.114	0.036
	Sig. (2-tailed)	0.573	0.235	0.726
	N	210	111	99
PTH				
	Correlation coefficient	0.232	0.414	0.017
	Sig. (2-tailed)	0.086	0.021	0.935
	N	56	31	25
iPTH				
	Correlation coefficient	0.025	-0.082	0.136
	Sig. (2-tailed)	0.787	0.537	0.297
	N	120	59	61
Vitamin D				
	Correlation coefficient	0.053	0.230	-0.148
	Sig. (2-tailed)	0.545	0.067	0.233
	N	131	64	67
Albumin				
	Correlation coefficient	0.101	0.117	0.082
	Sig. (2-tailed)	0.216	0.313	0.478
	N	153	76	77
Uric acid				
	Correlation coefficient	-0.002	0.046	-0.055
	Sig. (2-tailed)	0.982	0.682	0.632
	N	160	81	79