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Correlation of FGF-23 with Serum Calcium, Phosphate, PTH, Vitamin D and Urinary Phosphate in Different Stages of CKD Patients

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Abstract

Background: Chronic kidney disease (CKD) has been recognized as a leading public health problem worldwide. The global estimated prevalence of CKD is 13.4% (11.7-15.1%). Fibroblast Growth Factor-23(FGF-23) is the bone-derived phosphatonin that has been extensively studied and was found to play a critical role in normal physiology and results in altered mineral metabolism in CKD. **Aim**: To see the correlation of FGF-23 with serum calcium, phosphate, PTH, Vit D and urinary phosphate in different stages of CKD patients. **Methods**: This cross-sectional study was conducted at the Department of Nephrology and Department of biochemistry of National Institute of Kidney Diseases and Urology (NIKDU), Dhaka. A total of 152 patients were included for the study, during July 2018 to June 2019. Among them 112 were patients of CKD from stage 1 to 5 and 40 were healthy individuals. They were assigned in Group I and Group II, respectively. Statistical analysis of the results was done by using computer based statistical software, SPSS (SPSS Inc, Chicago, IL, USA). Prior to the commencement of the study, the thesis protocol was approved by the ethical committee of NIKDU, Dhaka. **Results:** Mean age was 52.0 ±10.2 years and 48.0 ±10 years in Group I and Group II, respectively. Among the 112 CKD patients 8% presented in stage 1 and 2, 27.7%, 35.7% and 28.6% presented in stage 3, 4, 5 respectively. Vit D level was low in both group I and group II and further deterioration of the levels was observed in all stages of CKD, especially in stage 5. S.FGF23 (pg/ml) level were 31.6±22.9, 38.4±27.8 and 53.8±46.5 for CKD stage 3, stage 4 and stage 5 respectively. S.phosphate was significantly raised in group I patient compared to group II. The level of s.phosphate in CKD stage 3 was 3.5±1.1, 4.0±1.2 for stage 4, 5.0±1.6 in stage 5. S.phosphate levels were found to be within normal range in stage 3 and 4 but raised in stage 5. In group I, s. FGF23 level was positively correlated with s.phosphate and urinary phosphate negatively correlated with S.FGF23 level in CKD stage 3,4,5 without any statistical significance. **Conclusions:** Laboratory parameters for different variables with cut off values in CKD patients revealed, S. FGF23 was found raised and S. calcium decreased in stage V.

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Keywords:- Kidney Disease, FGF-23, Vitamin D, Hypertension, eGFR.

INTRODUCTION

Chronic kidney disease (CKD) has been recognized as a leading public health problem worldwide. The global estimated prevalence of CKD is 13.4% (11.7-15.1%).[1] Diabetes, hypertension and obesity are the leading risk factors of chronic kidney disease in all developed and many developing countries however, glomerulonephritis and unknown causes are more common in countries of Asia and sub-Saharan Africa. In healthy individuals, kidneys play an important role in regulating calcium and phosphorus homeostasis through different mechanisms. Chronic kidney disease (CKD) is associated with the inability to control normal mineral homeostasis, resulting in changes in serum levels of calcium, phosphorus, parathyroid hormone (PTH), vitamin D and fibroblastic growth factor-23.[2] Fibroblast Growth Factor-23(FGF-23) is the bone-derived phosphatonin that has been extensively studied and was found to play a crucial role in normal physiology. Additionally, it alters the mineral metabolism in CKD.[3] FGF-23 is predominately expressed in osteocytes and osteoblasts in the skeleton. However, low levels of this factor can be found in pericyte like cells that surround the venous sinusoids of the bone marrow, ventrolateral thalamic nuclei, heart, thymus, and small intestine but its' significance remain unclear. Phosphate retention begins at an early stage of chronic kidney disease, due to a gradual decline in filtered phosphate load. Serum phosphate is maintained within normal limits until the GFR falls to less than approximately 30 mL/min.[4,5] Hyperphosphatemia is delayed until the later stages of CKD by the rise in serum concentration of PTH and FGF-23. In the early course of kidney disease, phosphorus retention stimulates FGF-23 and PTH secretion, which in turn suppress tubular phosphate reabsorption, causing increased renal phosphate excretion. FGF-23 suppresses the production of 1, 25 (OH) 2D at the same time, which limits intestinal phosphate absorption. High FGF23 levels are more strongly associated with kidney disease progression, left ventricular hypertrophy, vascular disease, and mortality than serum phosphate level.[6] Although these results are promising, the role of FGF23 in mineral metabolism remain unresolved.[7] The purpose of our study is to characterize FGF23 levels at NIKDU, a national tertiary center with racially and ethnically diverse population of CKD patients who are still not on dialysis. The study also aims to compare the relationships of FGF23 versus PTH with declining GFR. Additionally, the paper seeks to describe the relationship between FGF-23, dietary phosphorus intake, and other measures of calcium and phosphorus metabolism across the spectrum of GFR.

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MATERIAL AND METHODS

This cross-sectional study was conducted at the Department of Nephrology and Department of biochemistry of National Institute of Kidney Diseases and Urology, Dhaka. A total of 152 patients were included for the study, during July 2018 to June 2019. Among them 112 were predominantly patients of CKD from stage 1 to 5, who were assigned in Group I and 40 were healthy individuals who enrolled in this study were assigned in Group II. Purposive sampling technique was used as per inclusion and exclusion criteria. Blood sample was collected from both Group I and Group II to detect the level of Serum FGF23, Calcium, Phosphate, PTH, Vitamin D and other biochemical parameters. Also spot urine sample was collected to detect urinary phosphate level. Statistical analysis of the results was done by using computer based statistical software, SPSS (SPSS Inc, Chicago, IL, USA). Prior to the commencement of the study, the thesis protocol was approved by the ethical committee of NIKDU, Dhaka.

- **Inclusion Criteria**

  For group I:
  - CKD stage 1-5 irrespective of drug therapy.
  - Age 18 years and above.
  - Both gender (male and female)

  Group II:
  - Healthy subjects.
  - Age over 18 years
  - Both gender

- **Exclusion Criteria**
  - Acute MI within three months,
  - Acute renal failure.

RESULTS

[Table 1] shows Age, Systolic BP were significantly higher in Group I compared to Group II and BMI was significantly higher in Group II compared to Group I. [Figure 1] shows primary disease of the patients. In this chart, Diabetes Mellitus manifests as the primary disease with 40.2% of CKD patients. In 30.4% cases of CKD patients had Glomerulonephritis, 10.7% cases had Hypertension. In 12.5% cases of CKD patients, primary cause was undetermined. Among the rest of the participants 3.6% cases had renal stone and 2.7% had ADPKD. [Figure 2] shows Distribution of the patients according to CKD stages. According to the data, 35.7% were stage IV, 28.6% were stage V, 27.7% were stage III, 8.0% were stage I and II. [Table 2] shows serum phosphate, serum PTH, S.FGF-23 were significantly higher in Group I compared to Group II. [Table 3] shows S.phosphate, S.PTH, S.FGF23 were found higher in stage V compared to stage III and stage IV. [Table 4] shows s.FGF-23 had negative correlation with S. calcium in stage V and eGFR in stage IV.

Table 1: Baseline clinical parameters of group I and group II (N=152)

Variables	Group I (n=112) (mean ± SD)	Group II (n=40) (mean ± SD)	P Value
Age (year)	52.0 ± 10.2	48.0 ± 10	0.026

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BMI (kg/m2)	25.2 ± 3.6	27.8 ± 5.9	0.016
Systolic BP (mmHg)	131.2 ± 19.6	119.4 ± 13.1	0.013
Diastolic BP (mmHg)	78.3 ± 11.7	74.2 ± 9.0	0.146
Unpaired t test was done to measure the level of significance			

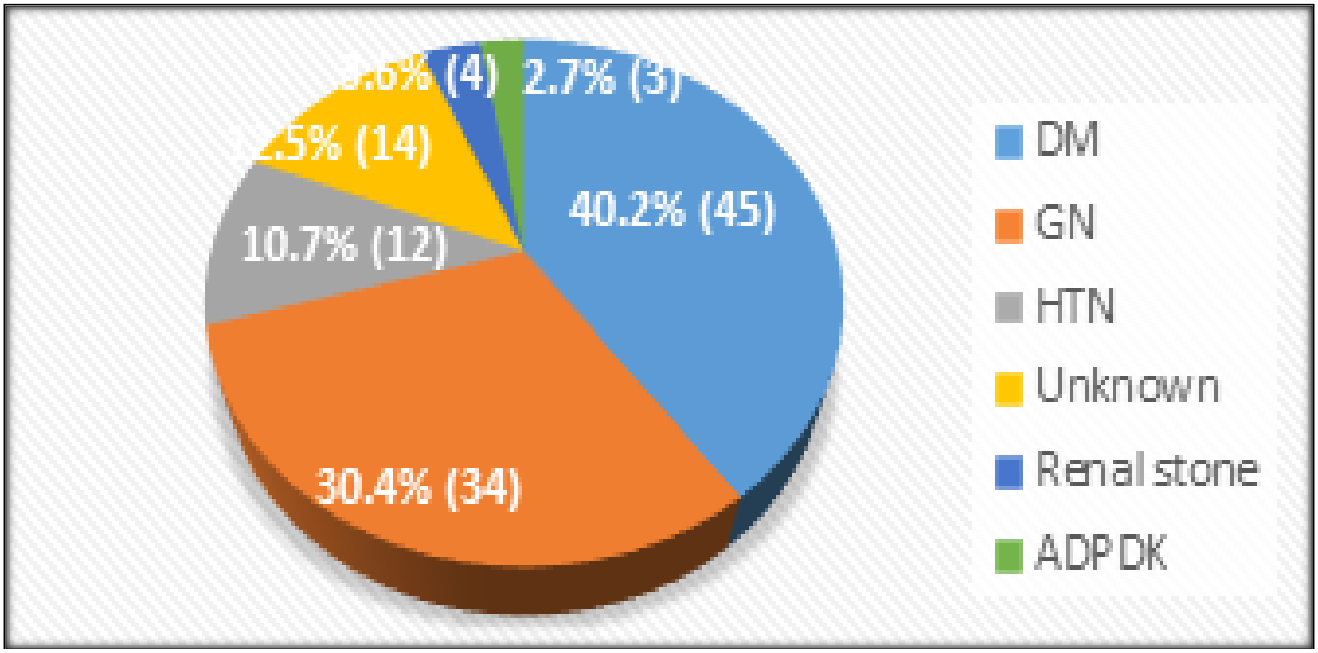

Figure 1: Primary disease of the patients

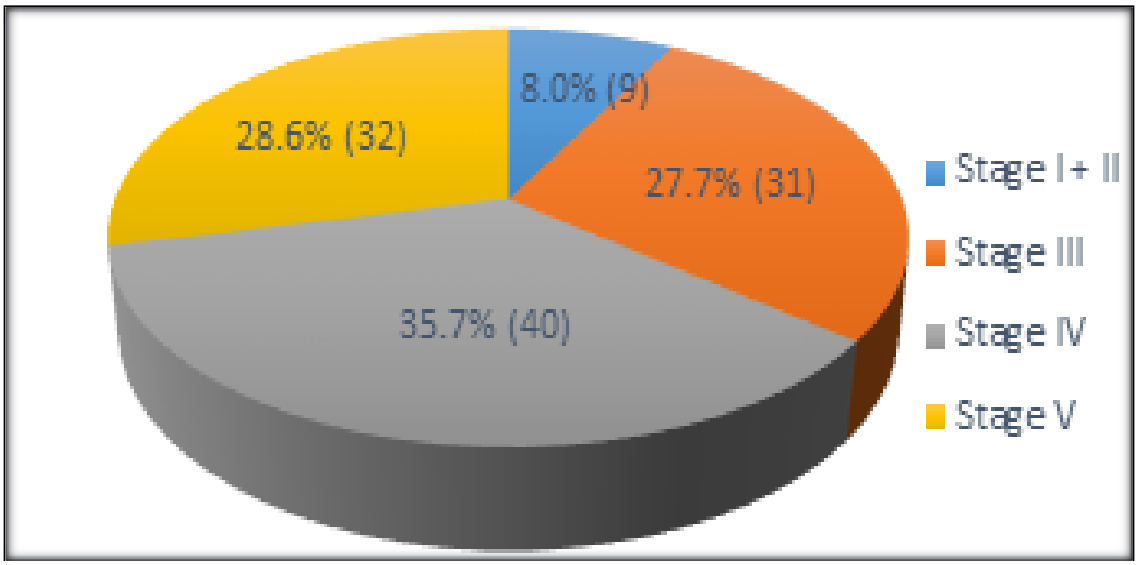

Figure 2: Distribution of the patients according to CKD stages

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Table 2: Baseline biochemical characteristics of group I and group II (N=152)

Variables	Group I (n=112) (mean ± SD)	Group II (n=40) (mean ± SD)	P Value
Serum Calcium(mg/dl)	8.8 ± 1.1	9.2 ± 0.8	0.503
Serum Phosphate(mg/dl)	4.3 ± 1.2	3.4 ± 0.7	0.001
iPTH(pg/ml)	184.1 ± 154.7	19.4 ± 8.0	0.001
Vit D(ng/ml)	17.9 ± 6.6	17.1 ± 10.4	0.583
FGF-23(pg/ml)	40.9 ± 33.5	26.7 ± 16.9	0.011
Urinary phosphate(mg/dl)	32.5 ± 32.3	35.2 ± 34.2	0.663
Unpaired t test was done to measure the level of significance			

Table 3: Baseline Biochemical parameters of the study subjects according to different CKD stage (N=103)

Variables	Stage III (n=31)	Stage IV (n=40)	Stage V (n=32)	p-value
Serum Calcium(mg/dl)	9.2 ± 1.1	8.7 ± 2.1	8.4 ± 1.5	0.139
Serum Phosphate(mg/dl)	3.5 ± 1.1	4.0 ± 1.2	5.0 ± 1.6	0.001
iPTH(pg/ml)	145.1 ± 107.4	150.9 ± 88.2	280.4 ± 220.2	0.001
Vit D(ng/ml)	18.4 ± 6.8	18.9 ± 7.1	15.6 ± 5.5	0.095
FGF-23(pg/ml)	31.6 ± 22.9	38.4 ± 27.8	53.84± 46.5	0.028
Urinary phosphate(mg/dl)	26.63 ± 20.34	34.57 ± 37.02	35.65 ± 37.69	0.485
ANOVA test was done to measure the level of significance.				

Table 4: Correlation of FGF-23 with serum calcium, phosphate, PTH, Vit D, urinary phosphate and eGFR in different stages of CKD patients.

	Stage III		Stage IV		Stage V	
	r value	p value	r value	p value	r value	p value
Serum Calcium	0.117	0.524	0.036	0.827	-0.564	0.001
Serum Phosphate	0.049	0.788	0.151	0.352	0.206	0.258
PTH	-0.274	0.129	0.247	0.125	0.208	0.262
Vit D	-0.093	0.625	-0.173	0.307	-0.313	0.087
Urinary phosphate	-0.035	0.851	-0.101	0.536	-0.332	0.064
Pearson correlation test was done to measure the level of significance.						

DISCUSSION

In this study, mean age of the participants was 52.0 ±10.2 years and 48.0 ±10 years in Group I and Group II, respectively. In the study of Sedighi and Abediankenari,[8] they found mean age of the CKD patients was 65.0 ± 12.6 years and 61.0± 8.2 in healthy people. Menon et al,[9] found mean age 52.0±12.0 years in CKD patients. In our study 40.2% of our CKD patients had Diabetes Mellitus as a primary cause. Just above thirty percentwas cases of CKD had Glomerulonephritis, 10.7% cases had Hypertension. In 12.5% cases of CKD patient, the primary cause was undetermined.3.6% cases had renal stone and 2.7% had ADPKD.

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Yuvaraj A et al,[10] found majority of the patients had Diabetes Mellitus (47%) as primary cause of CKD based on clinical presentation and other supporting investigations. Among them 92% presented in stage 3, stage 4 or stage 5 of CKD. Ghonemy et al,[12] found 17.0% DM and 14.0% hypertension in their study. In our study, among 112 CKD patients 8% presented in stage 1 and 2, 27.7%, 35.7% and 28.6% presented in stage 3,4,5 respectively. Jonsson KB et al,[11] stated that excess activity of s.FGF23 resulted in low Vit D level and osteomalacia. In our study, Vit D level was low in both group I and group II. It was found to be low in all stages of CKD, and most reduced in stage V. S.FGF23 negatively correlated with Vit D level with no statistical significance. It has been postulated that the elevated s.FGF levels observed in early stages of CKD Wolf M.[12] In our study s.FGF23 (pg/ml) level were 31.6±22.9, 38.4±27.8 and 53.8±46.5 for CKD stage III, stage IV and stage V respectively. Additionally, this study found s. phosphate was significantly raised in group I patient compared to group II. The rise was incremental according to the stage of CKD. In stage III, s.phosphate (mg/dl) was 3.5±1.1, 4.0±1.2 for stage IV and 5.0±1.6 for stage V. S.phosphate levels were found to be within normal range in stage 3 and 4 but raised in stage 5. In group I, s.FGF23 level was positively correlated with s. phosphate level in stage III, IV and V but was not statistically significant. Block GA et al,[13] stated that disturbed calcium phosphate metabolism is occurred in CKD patients. Fliser D et al,[6] showed that s.calcium was not significantly decreased. In our study, s.calcium level was not significantly changed between group I and group II. S.calcium mildly decreased in stage III and stage IV, and negatively correlated with s.FGF-23 level in stage V. In our study, S. PTH level was 184.1±154.7 in group I, 19.4 ± 8.0 in group II and significantly higher in group I. S.PTH level was 145.1±107.4, 150.9±88.2, 280.4±220.2 in stage III, IV and stage V respectively. S.PTH increased progressively. S.FGF-23 level positively correlated with S.PTH level in stage IV and V but not significantly. Isakova T et al,[14] found that prevalence of abnormally high s.FGF-23 versus s.PTH levels, they calculated the proportions of participants with normal or high s.FGF-23 and s.PTH levels. Panichi V et al,[15] stated that in the presence of progressive CKD, serum FGF-23 levels increase in parallel with the deterioration of renal function and the increase of serum phosphate and PTH concentrations. Isakova T et al,[14] plotted serum phosphate and urinary phosphate excretion in using fitted splines and tested whether there was a statistically significant change in their slopes. In our study, urinary phosphate excretion was less in group I comparing to group II but was not significant. Urinary phosphate negatively correlated with S.FGF-23 level in stage III, IV, V but not significantly.

Limitations of the study

The sample size of participants was relatively small. The present study was conducted with in a short period of time. The study subjects were selected from single center, so the study result may not represent the exact picture of the country.

CONCLUSIONS

Laboratory parameters for different variables with cut off values in CKD patients revealed. S. FGF23 was found raised and S. calcium decreased in stage V. Serum phosphate was

significantly raised in stage V. But there is no correlation of Serum FGF-23 with S. phosphate and S.PTH in CKD patients. S. FGF-23 was not significantly correlated with vitamin D. Further studies could be carried out involving multiple centers and with greater number of participants.

REFERENCES

1. Lv JC, Zhang LX. Prevalence and Disease Burden of Chronic Kidney Disease. Adv Exp Med Biol. 2019; 1165.3-15. doi:10. 1007/978-981-13-8871-2_1. PMID:31399958
2. Keung L, Perwad F. Vitamin D and kidney disease [published correction appears in Bone Rep. 2021;14:101084]. Bone Rep. 2018;9:93-100. doi:10.1016/j.bonr.2018.07.002
3. Liu S, Guo R, Simpson LG, Xiao ZS, Burnham CE, Quarles LD. Regulation of fibroblastic growth factor 23 expression but not degradation by PHEX. J Biol Chem. 2003;278(39):37419-26. doi: 10.1074/jbc.M304544200.
4. Craver L, Marco MP, Martínez I, Rue M, Borràs M, Martín ML, et al. Mineral metabolism parameters throughout chronic kidney disease stages 1-5--achievement of K/DOQI target ranges. Nephrol Dial Transplant. 2007;22(4):1171-6. doi: 10.1093/ndt/gfl718.
5. Levin A, Bakris GL, Molitch M, Smulders M, Tian J, Williams LA, et al. Prevalence of abnormal serum vitamin D, PTH, calcium, and phosphorus in patients with chronic kidney disease: results of the study to evaluate early kidney disease. Kidney Int. 2007;71(1):31-8. doi: 10.1038/sj.ki.5002009.
6. Fliser D, Kollerits B, Neyer U, Ankerst DP, Lhotta K, Lingenhel A, et al. Fibroblast growth factor 23 (FGF23) predicts progression of chronic kidney disease: the Mild to Moderate Kidney Disease (MMKD) Study. J Am Soc Nephrol. 2007;18(9):2600-8. doi: 10.1681/ASN.2006080936.
7. Wolf M. Forging forward with 10 burning questions on FGF23 in kidney disease. J Am Soc Nephrol. 2010;21(9):1427-35. doi: 10.1681/ASN.2009121293.
8. Sedighi O, Abediankenari S. Relationship between plasma adiponectin level with inflammatory and metabolic markers in patients with chronic kidney disease. Nephrourol Mon. 2013;6(1):e11743. doi:10.5812/numonthly.11743
9. Yuvaraj A, Abraham G, Vijayan M, Jayapal J, Kulanthaipandian S, Nair S. Correlation of fibroblast growth factor 23 in chronic kidney disease patients with biochemical parameters and outcomes. J Parathyr Dis. 2015;4(1):7-10.
10. Ghonemy TA, Farag SE, Soliman SA. Risk factors of progression of chronic kidney disease patients under conservative treatment. Int J Res Med Sci. 2015;3(10):2734. https://dx.doi.org/10.18203/2320-6012.ijrms20150823
11. Larsson T, Nisbeth U, Ljunggren O, Jüppner H, Jonsson KB. Circulating concentration of FGF-23 increases as renal function declines in patients with chronic kidney disease, but does not change in response to variation in phosphate intake in healthy volunteers. Kidney Int. 2003;64(6):2272-9. doi: 10.1046/j.1523-1755.2003.00328.x.
12. Wolf M. Update on fibroblast growth factor 23 in chronic kidney disease. Kidney Int. 2012;82(7):737-747. doi:10.1038/ki.2012.176
13. Goodman WG, London G, Amann K, Block GA, Giachelli C, Hruska KA, et al; Vascular Calcification Work Group. Vascular calcification in chronic kidney disease. Am J Kidney Dis. 2004;43(3):572-9. doi: 10.1053/j.ajkd.2003.12.005.
14. Isakova T, Xie H, Yang W, Xie D, Anderson AH, Scialla J, et al; Chronic Renal Insufficiency Cohort (CRIC) Study Group. Fibroblast growth factor 23 and risks of mortality and end-stage renal disease in patients with chronic kidney disease. JAMA. 2011;305(23):2432-9. doi: 10.1001/jama.2011.826.
15. Panichi V, Mantuano E, Paoletti S, Santi S, Manca Rizza G, Cutrupi S, et al. Effect of simvastatin on plasma asymmetric dimethylarginine concentration in patients with chronic kidney disease. J Nephrol. 2008;21(1):38-44.

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