# Study Of Fibroblast Growth Factor 23 (Fgf23) And Anemia In Hemodialysis Patients And Ckd Patients Stages 3 & 4

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**Abstract: Background**: Over the past decade, our under-standing of phosphate homeostasis has increased through the identification of phosphatonins. First case of Iron – induced hyphosphatemic osteomalacia associated with significant FGF23 elevation was reported in 2009. **Patients and Methods:** 47 patients on regular HD (Group A) and 12 CKD patients stages 3 & 4 (Group B) were included in the study.For each patient the following was done: serum calcium, serum phosphorus, calcium – phosphorus product, serum alkaline phosphatase, PTH, FGF23, serum Iron, serum ferritin, Hb, Hct, TSAT, and TIBC. **Results**: PTH was higher than recommended range in both Group A and Group B. FGF23 was also higher than normal in the two groups, and it was affected by serum creatinine in Group A in Multiple Regression Analysis ($P$ = 0.03136). FGF23 didn`t have any relationship to phosphate or PTH in our study. PTH had a positive correlation to Hb ($P$ = 0.052) and serum ferritin ($P$ = 0.009) in HD patients group A but not in CKD group B patients. Iron, Hb & TSAT had an inverse correlation to FGF23 in CKD patients group B ($P$ = 0.028, $P$ = 0.044, $P$ = 0.025 respectively), but not in HD patients group A. **Conclusion**: PTH and phosphate are not the only factors affecting FGF23 in CKD and HD patients, but also Iron and Iron parameters have a great impact on FGF23 serum level.

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## 1. Introduction

Traditionally, the parathyroid hormone (PTH)/Vitamin D axis provided the conceptual framework to understand mineral metabolism. FIBROBLAST GROWTH FACTOR 23 (FGF23) is a recently discovered hormone, predominantly functions are to inhibit renal tubular reabsorption and suppress circulating 1, Dihydroxycholecalciferol levels by decreasing Cyp 27 b1- mediated formation and stimulating Cyp 24 – mediated catabolism of 1, Dihydroxycholecalciferol.

FGF23 participates in a new bone / kidney axis that protects the organism from excess vitamin D and coordinates renal phosphate handling with bone mineralization / turnover. Abnormalities of FGF23 production underlie many inherited and acquired disorders of phosphate homeostasis. Abnormalities of FGF23 production underlie many inherited and acquired disorders of phosphate homeostasis. (Martin *et al.,* Braithwaite *et al.* (2012 b), found a relationship between Iron and FGF23, metabolic pathways have been proposed. Iron deficiency anemia is prevalent in the Gambia and concentrations of FGF23 are elevated in a large percentage of Gambian children with rickets-like bone deformity. Authors speculated that low iron status may be involved in the etiology of Gambian rickets. They also found that circulating concentrations of FGF 23 were inversely proportional with hemoglobin concentration. This study provided support for the contention that iron may be involved in FGF23 metabolic pathways.

**Imel** *et al.* **(2011),** found that low serum iron was associated with elevated FGF23 in autosomal dominant hypophosphatemic rickets (ADHR).

Parenteral iron administration has been associated with hypophosphatemia and osteomalacia (Sato *et al.* (1997) ; Sato and Shikari, Okada *et al.*(1982); Okada *et al.*(1983), Schouten *et al.,* a).

This complication is neither widely appreciated nor acknowledged in reviews on iron therapy or in product information sheets. The condition is characterized by reduced renal phosphate reabsorption and inhibition of 1- hydroxylation of vitamin D. (Sato *et al.,* Sato and Shikari, Chronic kidney disease (CKD) is a public health epidemic that affects millions of people worldwide. Presence of CKD predisposes individuals to high risk ESRD, cardiovascular disease and premature death. Disordered phosphate homeostasis with elevated circulating levels of FGF23 is an early and pervasive complication of chronic

kidney disease (CKD). CKD is likely the most common cause of chronically elevated FGF 23 levels and the clinical condition in which levels are most markedly elevated (Wolf).

**Patients**

This study was performed in Theodor Bilharz Institute between January 2012 and July 2013. Fifty nine patients were included in the study. Group A comprised 47 patients on prevalent hemodialysis and Group B comprised 12 patients with chronic kidney disease (CKD) stages 3 & 4, under treatment.

ELIGIBILITY CRITERIA for group A patients were being adult (age more than 18 years), receiving hemodialysis sessions of four hours duration each, three times per week, for least 6 months, using bicarbonate dialysate and polysufone hollow-fiber with surface area 1.3 to 1.6 meter square.

ELIGIBILITY CRITERIA for Group B patients were being above 18 years and having CKD stages 3 & 4 as determined by having glomerular filteraion rate (eGFR) of 15 -59 ml / mn / 1.73 $m^2$ surface area.

EXCLUSION CRITERIA included patients with co-morbid diseases, acute anemia, chronic liver disease, terminal illness, malignancy and other chronic inflammatory states. We excluded from the study patients using temporary central venous catheters, arteriovenous grafts, patients receiving blood transfusion in the last three months or having occult blood gastrointestinal bleeding (determined by occult blood in stool test). Complete clinical examination was done for all patients with hemodialysis data for all patients and emphasis on drug doses. Serum calcium, serum phosphate, serum parathyroid hormone, serum alkaline phosphatase, serum creatinine, blood urea, Hemoglobin (Hb) level, Hematocrit (Hct) level, Iron profile serum iron, serum ferritin, Transferrin Saturation Ratio (TSAT), Total Iron Binding Capacity (TIBC), and serum Fibroblast Growth Factor (FGF23) were all done.

All samples were withdrawn predialysis.

**2.Methods**

Serum Calcium: " Quantichrom TM Calcium Assay Kit " quantitative determination of calcium ion $Ca^{++}$ by calorimetric method (612 nm), Bio Assay ") systems, Serum Phosphorus: " Quantichrom TM Phosphate Assay Kit " quantitative determination of phosphate by colorimetric method (620 nm), Bio Assay systems (2007)

Parathyroid Hormone: The intact PTH Immuno-Assay a two-side ELISA, PTH (human) ELISA Kit ]. Catalog Number 0924 KA, Kruger *et al.,* Alkaline Phosphatase (ALP): " Alkaline Phosphatase Kit " (Biomed diagnostics, Germany), Normal level ranges between 39 to 117 U/L. (Kochmar and Moss, Serum Creatinine: " Enzy - Chrom TM Creatinine Assay Kit " Quantitative determination of Creatinine by Colorimetric or fluorimetric methods (Bio-Assay Systems, Blood Urea: " Quuanti-Chrom TM Urea Assay Kit ".Quantitative determination of urea by chemical colorimetric method, nm. (Bio - Assay Systems, Hemoglobin Level (Hb): is usually measured as a part of the CBC from a blood sample (Webmd, Hematocrit Level (Hct): is typically measured from a blood sample by an automated machine that makes several other measurements at the same time (Webmd, Normal level for females is 37- 47 % and for males is 45 -54 %.

Serum Iron: Qantitative colorimetric determination of iron (STAMBIO Laboratory, Normal Iron level is 50 - 150 ug /dl.

Serum Ferritin: Immuno-enzymometric Sequential Assay type 4 (Ferritin Test System, Normal ferritin level is 15 - 200 ug/l for males and 30-300 ug/l for females.

Transferrin Saturation Ratio (TSAT): Calculated from total iron level and Iron Binding Capacity. TSAT = (S. IRON / TIBC) X 100, Johnson and Catherine). Normal TSAT IS 20 - 50 %.

Total Iron Binding Capacity (TIBC): Quantitative colorimetric determination of unsaturated Iron Binding Capacity in serum (STAMBIO Laboratory, Normal level is 250 - 410 ug /dl.

Fibroblast Growth Factor (FGF23): ELISA Kit FGF23: This assay recognizes recombinant and natural human FGF23.

**Statistical Methods**

IBM SPSS statistics (2012), was used for data. Data was expressed as Mean $\pm$ SD for quantitative parametric measures in addition to median percentiles for quantitative non-parametric measures and both number and percentage for categorized data.

**The following tests were done:**

- Student t-test: to compare between two independent mean groups for parametric data.
- Wilcoxon Rank Sum test: to compare between two independent groups for non-parametric data.
- Ranked Spearman test: to study the possible association between each two variables among each group for non- parametric data.
- Chi-square test: to study the association between each 2 variables or comparison between two independent groups as regards the categorized data.
- Logistic Multi-regression analysis was used to search for a panel (independent parameters), that can predict the target parameter (dependent variable). By using logistic stepwise multi-regression analysis, we can get the most sensitive ones that can predict the dependent variable. They can be sorted according to their P-value.

- Calculated Relative Risk Assessments (Relative Risk Ratio or RRR): that measure how many times the risk was present among diseased individuals as that among non-diseased ones. They were calculated as absolute figures and as a Standar Error of Estimate (95P).

P-value at or less than 0.05 was considered to be significant value, *P* value between 0.06 and 0.09 was considered to be borderline significant, *P* value of 0.1 or more was considered to be non-significant, *P* value of 0.01, and 0.000 was considered highly significant.

**3.Results**

**Descriptive Statistics in our study has shown the following results:**

Mean age in HD patients (group A) was (51.89 ±14.51) years. In CKD stages 3 & 4 (group B), the mean age was (47.16 ± 12. 87) years.

Re**garding** causes of primary kidney disease in HD patients (Group A), hypertension affected 42.5 % of patients (20 / 47), DM 12.7 % (6 / 47), hypertension & DM together 23.4 % **(**11/47), glomerulonephritis 6.3 % (3 /47), polycystic kidney disease 2.1 % (1/ 47), obstructive uropathy 2.1 % (1 / 47), chronic pyelonephritis 2.1 % (1 /47), vesicoureteric reflux 2.1 % (1 /47), and unknown etiology 6.3 % (3 / 47).

Regarding causes of primary kidney disease in CKD patients stage 3 & 4 (Group B), hypertension affected 16.6 **% (2** / 12), DM 25 **% (**3 /12), hypertension & DM together 25 **% (3/** 12), and glomerulonephritis 33.3 % (4 / 12).

Primary kidney disease duration in patient**s** on HD had a mean value of (10.61 ±6.49) years and in CKD stages 3 & 4 (Group B), it showed a mean of (8.91 ±5.99) years.

Dura**tion** of HD in Group A patients was found to have a mean of (2.56 ± 1.92) years.

Serum creatinine in HD patients (Group A) showed a mean of (7.02 ± 2.27) mg / dl.and in chronic kidney disease stages3 & 4 (Group B), it had a mean of (3.16 ± 1.59) mg / dl.

Blood urea in HD patients (Group A), showed a mean level of (114.29 ± 27.76) mg/dl and in CKD patients stages 3 & 4 (Group B), it had a mean of (102.69 ± 29.94) mg /dl.

In HD patients (Group A), calcium - phosphorus product (Ca x P) showed a mean value of (46.61 ± 15.86) mg $^{2}$/ dl $^{2}$ and in CKD patients stages 3 & 4 (Group B), it had a mean level of (42.48 ± 10.49) mg $^{2}$/ dl $^{2}$.

The parathyroid hormone in HD patients (Group A) had a mean level of (437.581 ± 116.72) pg /dl and in CKD patients stages 3 & 4 (Group B) it had a mean level of (200.58 ± 52.39) pg / dl.

Serum alkaline phosphatase in HD patients (Group A) showed a mean value of (119.19 ± 27) U/l, and in CKD patients stage 3 & 4 (Group B) it was (122.59 ± 39.04) U/l.

FGF23 normal level is estimated to be up to 71 pg / ml. FGF23 level in HD patients (Group A) had a mean value of (111.80 ± 37.62) pg /ml and in CKD patients stages 3 & 4 (Group B) it was (103.90 ± 39.29) pg /ml.

As HD patients (Group A) was mainly formed of males and CKD stages 3 & 4 (Group) was mainly formed of females, FGF23 mean level in females of Group A was (94. 35 ± 25.21) pg / ml. FGF23 in HD male patients of Group A had a mean level of (115.38 ± 38.32) pg / ml. Serum FGF23 in females of CKD stages 3 & 4 (Group B)had a mean level of (99.5 ± 28.92) pg / ml. Serum FGF23 in male patients of Group B had a mean level of(117.13 ± 25.65) pg / ml.On comparing serum FGF23 level in females and males HD patients (Group A), we didn`t find any significant difference, *P* = 0.119). We didn t also find any significant difference in serum FGF23 levels of female and male patients of CKD (Group B), *P* = 0.926).

HD male patients of Group A were found to have a significantly higher Hb level than HD female patients (*P*= 0.031).

On comparing female and male patients with CKD stages 3 & 4 (Group B), we didn t find any significant difference as regards Hb level (*P* = 0.834).

Serum Iron in HD patients (Group A) had a mean value of (53.44 ± 16.55) ug /dl and in CKD stages 3 & 4 patients (Group B), it showed a mean value of (52.25 + 28.32) ug / dl.

Total Iron Binding Capacity in HD patients (Group A) showed a mean level (`191.68 ± 51.53) ug / dl and in CKD stages 3 & 4 patients (Group B) it had a mean of (218.83 ± 55.79) ug / dl.

In HD patients (Group A), Transferrin Saturation (TSAT) showed a mean level of (29.27 ± 8.82) %.

TSAT in CKD stages 3 & 4 patients (Group B) had a mean of (23.78 ± 9.56) %.

Serum ferritin level in HD patients (Group A) showed a mean level of (60 ± 20.54) ug / l.

Serum ferritin in CKD stages 3 & 4 patients (Group B) had a mean level of (71.83 ± 20.87) ug / l.

Serum ferritin level in female HD patients (Group A) had a mean of (62.25 ± 15.12) ug / l. Serum ferritin levels in males of HD patients (Group A) had a mean value of (58.92 ± 15.72) ug / l. Serum ferritin level in females with CKD stage 3 & 4 patients (Group B) had a mean of (73.11 ± 19.59) ug / l. Serum ferritin level in male patients with CKD stage 3 & 4 (Group B) showed a mean of (68 ± 18.84) ug / l.

On comparing male and female patients on HD (Group A) as regards serum ferritin level, we couldn t find any significant difference between the two groups (*P* = 0.605).On comparing male and female patients

with CKD stage 3 & 4 (Group B) as regards serum ferritin level, we didn t find any significant difference between both groups ($P = 0.852$).

Elemental Calcium dose per day in HD patients (Group A) had a mean value of (1897.87 ± 575.77) mg and in CKD stages 3 & 4 patients (Group B) it had a mean level of (1800 ± 610.55) mg.

One alpha calcidiol dose per day in HD patients (Group A) had a mean value of (2.64 ± 1.13) ug and in CKD stages 3 & 4 patients (Group B) it had a mean level of (1.5 ± 0) ug.

Mean IV Iron dose in HD patients (Group A) was (74.46 ± 14.61) mg.

There was no IV Iron supplementation to CKD stage 3 & 4 (Group B).

As regards EPO dose supplemented to HD patients (Group A), mean dose was (4782.6 ± 1260.86) Units / Week and in CKD stage 3 & 4 patients (Group B) it showed a mean value of (5250 ±957.42) Units / Week.

The mean creatinine clearance of HD patients (Group A) had a value of (8.83 ± 2.87) ml / mn / 1.73 $m^2$ and in CKD stages 3 & 4 patients (Group B) had a mean value of (42.08 ± 11.38)ml/mn/1.73$m^2$.

Estimated GFR value in HD patients (Group A) had a mean of (9.55 ± 2.50) ml /mn and in CKD stages 3 & 4 patients (Group B) it had a mean value of (42.41 ± 11.36) ml / mn.

**Table (1): Comparison of gender distribution in group A and B.**

| Variable | | | Group (A) | Group (B) | Total |
|---|---|---|---|---|---|
| gender | Female | Count (%) | 8 (17.0) | 9 (75.0) | 17 (28.8) |
| | Male | Count (%) | 39 (83.0) | 3 (25.0) | 42 (1.2) |
| Total | | Count (%) | 47 (100) | 12 (100) | 59 (100) |
| | | Value | *P* | | |
| Pearson Chi-square | | 15.666* | 0.000 | | |

* Chi-square test.

**Table (2): Comparison between group A and B as regards age (years), primary kidney disease duration (years), hemodialysis duration (years), serum creatinine (mg/dl) and blood urea (mg/dl).**

| Variable | age | 1ry dis duration | HD duration | Serum creatinine | Blood urea |
|---|---|---|---|---|---|
| Z* | -0.942 | -0.814 | -5.375 | -4.483 | -1.262 |
| *P* | 0.346 | 0.416 | 0 | 0 | 0.27 |
| Sig. | NS | NS | HS | HS | NS |

* Wilcoxon Rank Sum test.

**Table (3): Comparison between group A and B as regards calcium (mg/dl) and phosphorus (mg/dl).**

| Variable | Group | N | Mean | SD | t* | *P* | Sig. |
|---|---|---|---|---|---|---|---|
| **calcium** | Gr A | 47 | 8.445 | 1.1221 | | | |
| | Gr B | 12 | 8.392 | 1.0971 | 0.149 | 0.883 | NS |
| **Phosph.** | Gr A | 47 | 5.517 | 1.601 | | | |
| | Gr B | 12 | 5.142 | 1.3853 | 0.811 | 0.428 | NS |

* Student t-test.

**Table (4): Comparison between group A and B as regards Ca x P product (mg2/dl2) , PTH (pg/dl), Alkaline phosphatase (U/L) and FGF23 (pg/ml).**

| Variable | Ca xP product | PTH | Alk. Phosphat. | FGF23 |
|---|---|---|---|---|
| Z* | -0.574 | -1.977 | -0.961 | -0.226 |
| *P* | 0.566 | 0.048 | 0.337 | 0.821 |
| Sig. | NS | S | NS | NS |

* Wilcoxon Rank Sum test.

**Table (5): Comparison between group A and B as regards Hemoglobin (Hb) (gm/dl) and Hematocrit (Hct0 (%).**

| Variable | Group | N | Mean | SD | t* | *P* | Sig. |
|---|---|---|---|---|---|---|---|
| Hb | Gr A | 47 | 10.215 | 1.215 | 1.4295 | | |
| | Gr B | 12 | 9.9 | 2.366 | 0.441 | 0.666 | NS |
| Hct | Gr A | 47 | 32.37 | 4.7514 | | | |
| | Gr B | 12 | 29.658 | 7.7604 | 1.156 | 0.268 | NS |

* Student t-test.

**Table (6): Comparison between group A and B as regards serum iron(ug/dl), TIBC (ug/dl), TSAT(%) and serum ferritin (ug/dl).**

| Variable | Serum iron | TIBC | TSAT | ferritin |
|---|---|---|---|---|
| Z* | -0.019 | -1.13 | -1.064 | -1.798 |
| P | 0.985 | 0.258 | 0.287 | 0.072 |
| Sig. | NS | NS | NS | BS |

* Wilcoxon Rank Sum test.

**Table (7): Comparison between group A and B as regards calcium dose (mg) , one alpha calcidiol dose (ug), IV iron (mg) and EPO dose (units).**

| Variable | Ca dose | One alpha | IV iron | EPO |
|---|---|---|---|---|
| Z* | -0.593 | -4.593 | -2.985 | -1.856 |
| *P* | 0.553 | 0.000 | 0.003 | 0.063 |
| Sig | NS | HS | HS | BS |

* Wilcoxon Rank Sum Test.

**Table (8): Comparison between group A and B as regards chronic kidney disease stage, creatinine clearance (ml/mn) and eGFR (ml/mn).**

| Variable | CKDstage | Creat.Clear, | eGFR |
|---|---|---|---|
| Z* | -7.588 | -5.025 | -5.335 |
| *P* | 0.000 | 0.000 | 0.000 |
| Sig. | HS | HS | HS |

* Wilcoxon Rank Sum test.

**Table (9): Correlation between FGF23 (pg/ml), Hb (gm/dl) and S. ferritin (ug/l) versus age (ys), 1ry kid disease duration (ys), HD duration (ys) within group A.**

| Variable | | FGF23 | Hb | ferritin |
|---|---|---|---|---|
| age | [r]* | 0.002\ | -0.202 | -0.512 |
| | [P] | 0.992 | 0.173 | 0.308 |
| | [Sig.] | NS | NS | NS |
| Kid dis duration | [r]* | 0.031 | 0.296 | 0.228 |
| | [P] | 0.844 | 0.051 | 0.137 |
| | [Sig.] | NS | BS | NS |
| HD duration | [r]* | 0.163 | 0.042 | 0.232 |
| | [P] | 0.274 | 0.781 | 0.117 |
| | [Sig.] | NS | NS | NS |

* Ranked Spearman correlation test.

**Table (10): Correlation between FGF23(pg/ml), Hb (gm/dl) and S. ferritin(ug/l) versus S. creatinine(mg/dl) and blood urea (mg/dl) within group A.**

| Variable | | Serum Creat. | Blood urea |
|---|---|---|---|
| FGF23 | [r]* | -0.157 | -0.035 |
| | [P] | 0.292 | 0.813 |
| | [Sig.] | NS | NS |
| Hb | [r]* | 0.12 | 0.007 |
| | [P] | 0.422 | 0.964 |
| | [Sig.] | NS | NS |
| S. ferritin | [r]* | 0.022 | 0.085 |
| | [P] | 0.883 | 0.572 |
| | [Sig.] | NS | NS |

* Ranked Spearman correlation test.

**Table (11): Correlation between FGF23 (pg/ml), Hb(gm/dl) and ferritin(ug/l) versus serum calcium (mg/dl), seum phosphorus (mg/dl), calcium- phosphorus product, PTH (pg/dl) and alkaline phosphatase (U/L) within group A.**

| Variable | | Ca | P | Ca x *P* | PTH | Alk. Phos. |
|---|---|---|---|---|---|---|
| FGF23 | [r]* | 0.113 | 0.114 | 0.155 | -0.181 | -0.128 |
| | [P] | 0.448 | 0.446 | 0.297 | 0.223 | 0.39 |
| | [Sig.] | NS | NS | NS | NS | NS |
| Hb | [r]* | -0.032 | -0.017 | 0.021 | 0.985 | 0.118 |
| | [P] | 0.83 | 0.912 | 0.89 | 0.052 | 0.429 |
| | [Sig.] | NS | NS | NS | BS | NS |
| ferritin | [r]* | -0.016 | -0.094 | 0.097 | 0.377 | 0.003 |
| | [P] | 0.915 | 0.529 | 0.518 | 0.009 | 0.983 |
| | [Sig.] | NS | NS | NS | HS | NS |

* Ranked Spearman correlation test.

**Table (12): Correlation between FGF23 (pg/ml), Hb (gm/dl) and ferritin(ug/l) versus Hct (%), serum iron(ug/dl), TIBC (ug/dl), TSAT(%) within group A.**

| Variable | | Hct (%) | Iron | TIBC | TSAT |
|---|---|---|---|---|---|
| FGF23 | [r]* | -0.205 | -0.057 | -0.04 | -0.063 |
| | [P] | 0.166 | 0.703 | 0.792 | 0.675 |
| | [Sig.] | NS | NS | NS | NS |
| Hb | [r]* | 0.951 | 0.058 | -0.01 | 0.073 |
| | [P] | 0 | 0.698 | 0.946 | 0.624 |
| | [Sig.] | HS | NS | NS | NS |
| ferritin | [r]* | 0.081 | 0.326 | 0.113 | 0.306 |
| | [P] | 0.589 | 0.03 | 0.45 | 0.036 |
| | [Sig.] | NS | S | NS | S |

* Ranked Spearman correlation test.

**Table (13): Correlation between FGF23 (pg/ml), Hb(gm/dl) and ferritin(ug/l) versus calcium dose(mg), one alpha calcidiol dose (ug), IV iron dose(mg) and EPO dose (Units) within group A.**

| Variable | | Ca dose | One alpha | IV iron | EPO dose |
|---|---|---|---|---|---|
| FGF23 | [r]* | 0.217 | -0.065 | -0.119 | -0.002 |
| | [P] | 0.142 | 0.662 | 0.424 | 0.988 |
| | [Sig.] | NS | NS | NS | NS |
| Hb | [r]* | 0.114 | -0.007 | 0.2 | 0.101 |
| | [P] | 0.446 | 0.964 | 0.177 | 0.506 |
| | [Sig.] | NS | NS | NS | NS |
| ferritin | [r]* | 0.066 | 0.026 | -0.149 | 0.094 |
| | [P] | 0.657 | 0.864 | 0.318 | 0.534 |
| | [Sig.] | NS | NS | NS | NS |

* Ranked Spearman correlation test.

**Table (14): Correlation between FGF23(pg/ml), Hb (gm/dl) and ferritin (ug/l) versus creatinine clearance (ml/mn) and eGFR (ml/mn) within group A.**

| Variable | | Creatinine clearance | eGFR |
|---|---|---|---|
| FGF23 | [r]* | 0.058 | -0.248 |
| | [P] | 0.761 | 0.092 |
| | [Sig.] | NS | NS |
| Hb | [r]* | -0.007 | -0.135 |
| | [P] | 0.971 | 0.366 |
| | [Sig.] | NS | NS |
| ferritin | [r]* | -0.099 | -0.105 |
| | [P] | 0.602 | 0.481 |
| | [Sig.] | NS | NS |

* Ranked Spearman correlation test.

**Table (15): Correlation between fgf23(pg/ml), Hb (gm/dl) and ferritin(ug/l) versus FGF23 (pg/ml), Hb (gm/dl) and ferritin (ug/l) within group A.**

| Variable | | FGF 23 | Hb | Ferritin |
|---|---|---|---|---|
| FGF23 | [r]* | | -0.176 | 0.144 |
| | [P] | | 0.236 | 0.334 |
| | [Sig.] | | NS | NS |
| Hb | [r]* | -0.176 | | 0.082 |
| | [P] | 0.236 | | 0.583 |
| | [Sig.] | NS | | NS |
| ferritin | [r]* | 0.144 | 0.082 | |
| | [P] | 0.334 | 0.583 | |
| | [Sig.] | NS | NS | |

* Ranked Spearman correlation test.

**Table (16): Correlation between FGF23(pg/ml), Hb (gm/dl) and ferritin (ug/l) versus age (ys), duration of 1ry kidney disease (ys), serum creatinine (mg/dl) and blood urea (mg/dl) within group B .**

| Variable | | age | 1ry kiddis | creat | urea |
|---|---|---|---|---|---|
| FGF23 | [r]* | -0.137 | -0.095 | 0.481 | 0.473 |
| | [P] | 0.672 | 0.77 | 0.114 | 0.121 |
| | [Sig.] | NS | NS | NS | NS |
| Hb | [r]* | 0.207 | 0.372 | -0.854 | -0.498 |
| | [P] | 0.518 | 0.234 | 0 | 0.099 |
| | [Sig.] | NS | NS | HS | BS |
| ferritin | [r]* | -0.323 | -0.358 | 0.612 | 0.255 |
| | [P] | 0.306 | 0.254 | 0.035 | 0.424 |
| | [Sig.] | NS | NS | S | NS |

* Ranked Spearman correlation test.

**Table (17): Correlation between FGF23(pg/ml), Hb(gm/dl) and ferritin(ug/l) versus serum calcium (mg/dl), serum phosphorus (mg/dl), Ca x P product , PTH (pg/dl) and alkaline phosphatase (U/L) within group B.**

| Variable | | Ca | P | Ca x P | PTH | ALK. PHOS |
|---|---|---|---|---|---|---|
| FGF23 | [r]* | -0.126 | 0.375 | 0.364 | 0.287 | 0.238 |
| | [P] | 0.696 | 0.23 | 0.245 | 0.366 | 0.457 |
| | [Sig.] | NS | NS | NS | NS | NS |
| Hb | [r]* | 0.354 | 0.305 | -0.112 | -0.455 | -0.263 |
| | [P] | 0.258 | 0.335 | 0.729 | 0.137 | 0.409 |
| | [Sig.] | NS- | NS | NS | NS | NS |
| ferritin | [r]* | -0.489 | 0.345 | 0.113 | 0.59 | 0.067 |
| | [P] | 0.107 | 0.272 | 0.726 | 0.043 | 0.836 |
| | [Sig.] | NS | NS | NS | S | NS |

* Ranked Spearman correlation test.

**Table (18): Correlation between FGF23 (pg/dl), Hemoglobin (gm/dl) and ferritin (ug/l) versus Hematocrit (%), serum iron (ug/dl), TIBC (ug/dl) and TSAT (%) within group B.**

| Variable | | Hct | iron | TIBC | TSAT |
|---|---|---|---|---|---|
| FGF23 | [r]* | -0.49 | -0.629 | -0.329 | -0.641 |
| | [P] | 0.106 | 0.028 | 0.297 | 0.025 |
| | [Sig.] | NS | S | NS | S |
| Hb | [r]* | 0.956 | 0.529 | 0.116 | 0.705 |
| | [P] | 0 | 0.077 | 0.72 | 0.01 |
| | [Sig.] | HS | NS | NS | S |
| ferritin | [r]* | -0.77 | -0.35 | -0.085 | -0.48 |
| | [P] | 0.003 | 0.265 | 0.793 | 0.115 |
| | [Sig.] | HS | NS | NS | NS |

* Ranked Spearman correlation test.

**Table (19): Correlation between FGF23 (pg/ml), Hemoglobin (gm/dl) and ferritin (ug/l) versus calcium dose (mg) and EPO dose (Units) within group B.**

| Variable | | Calcium dose | EPO dose |
|---|---|---|---|
| FGF23 | [r]* | -0.015 | -0.105 |
| | [P] | 0.963 | 0.895 |
| | [Sig.] | NS | NS |
| Hb | [r]* | -0.073 | -0.105 |
| | [P] | 0.821 | 0.895 |
| | [Sig.] | NS | NS |
| ferritin | [r]* | 0.009 | 0.316 |
| | [P] | 0.977 | 0.684 |
| | [Sig.] | NS | NS |

* Ranked Spearman correlation test.

**Table (20): Correlation between FGF23 (pg/ml), Hemoglobin (gm/dl) and ferritin (ug/l) versus CKD stage , creatinine clearance (ml/mn) and eGFR (ml/mn) within group B.**

| Variable | | CKD stage | Creat. Clear. | eGFR |
|---|---|---|---|---|
| FGF23 | [r]* | 0.518 | -0.455 | -0.347 |
| | [P] | 0.084 | 0.138 | 0.269 |
| | [Sig.] | NS | NS | NS |
| Hb | [r]* | -0.292 | 0.196 | 0.2 |
| | [P] | 0.357 | 0.541 | 0.532 |
| | [Sig.] | NS | NS | NS |
| ferritin | [r]* | 0.065 | 0.099 | 0.051 |
| | [P] | 0.84 | 0.76 | 0.874 |
| | [Sig.] | NS | NS | NS |

* Ranked Spearman correlation test.

**Table (21): Correlation between FGF23 (pg/ml), Hemoglobin (gm/dl) and ferritin (ug/l) versus FGF23 , Hemoglobin and ferritin within group B.**

| Variable | | FGF 23 | Hb | Ferri tin |
|---|---|---|---|---|
| FGF23 | [r]* | | -0.588 | 0.163 |
| | [P] | | 0.044 | 0.614 |
| | [Sig.] | | S | NS |
| Hb | [r]* | -0.588 | | -0.779 |
| | [P] | 0.044 | | 0.003 |
| | [Sig.] | S | | HS |
| ferritin | [r]* | 0.163 | -0.779 | |
| | [P] | 0.614 | 0.003 | |
| | [Sig.] | NS | HS | |

* Ranked Spearman correlation test.

**Table (22): Odds ratio for FGF23 (pg/ml) in group A and B.**

| Variable | | | Group (A) | Group (B) | Total |
|---|---|---|---|---|---|
| FGF23 | <100 | Count | 21 | 4 | 25 |
| | | (%) | 44.7 | 33.3 | 42.4 |
| | >100 | Count | 26 | 8 | 34 |
| | | (%) | 55.3 | 66.7 | 57.6 |
| Total | | Count | 47 | 21 | 59 |
| | | (%) | 100 | 100 | 100 |
| | | Value | P | | |
| Pearson Chi-square | | 504* | 0.478 | | |

* Chi-square test.

We couldn't find any significant risk difference between Group A and B as regards Odds Ratio for FGF23 (pg/ml) levels (Odd's ratio (95CI) = 1.62 (0.43-6.11, Non risk).

**Table (23): Odds ratio for Hemoglobin (gm/dl) in group A and B.**

| | | | Group(A) | Group (B) | Total |
|---|---|---|---|---|---|
| Hb | <10.5 | Count | 29 | 6 | 35 |
| | | (%) | 62.7 | 50.0 | 59.3 |
| | >10.5 | Count | 18 | 6 | 24 |
| | | (%) | 38.3 | 50.0 | 40.7 |
| Total | | Count | 47 | 12 | 59 |
| | | (%) | 100 | 100 | 100 |
| | | Value | P | | |
| Pearson Chi-square | | 0.542* | 0.461 | | |

* Chi-square test.

We found significant risk difference for Hemoglobin between group A and B using odds ratio [Odd's Ratio (95CJ) = 1.61 (0.45-5.77), non-risk].

**Table (24): Odds ratio for ferritin (ug/l) in group A and B.**

| | | | Group (A) | Group (B) | Total |
|---|---|---|---|---|---|
| ferritin | <40 | Count<br>(%) | 8<br>17.0 | 0<br>0.0 | 8<br>13.6 |
| | >40 | Count<br>(%) | 39<br>83.0 | 12<br>100 | 31<br>86.4 |
| Total | | Count<br>(%) | 47<br>100 | 12<br>100 | 59<br>100 |
| | | Value | P | | |
| Pearson Chi-square | | 2.363* | 0.124 | | |

* Chi-square test.

We couldn't find risk difference between group A and B as regards ferritin using Odd's ratio.

**Table (25): Multiple regression coefficient, STD error and probability for age (years), gender distribution, duration of primary kidney disease (years), duration of hemodialysis (years), serum creatinine (mg/dl), blood urea (mg/dl), and eGFR (ml/mn) versus FGF23(pg/ml) as dependent factor within group A.**

| Variable | Regression coefficient | STD Error | T (DF=21) | *P* |
|---|---|---|---|---|
| age | -0.6115 | 0.6017 | -1.016 | 0.32109 |
| gender | 12.6648 | 21.2438 | 0.596 | 0.55744 |
| 1ry kid dis | 0.0200 | 2.0592 | 9.7296 | 0.99233 |
| HD duration | 5.2446 | 4.5562 | 1.151 | 0.26263 |
| creatinine | -8.4154 | 3.6484 | -2.307 | 0.03136 |
| urea | 0.1203 | 0.3535 | 0.340 | 0.73706 |
| eGFR | -2.2878 | 3.3818 | -0.676 | 0.50611 |

**Table (26):** Multiple regression coefficient, STD error and probability for serum calcium (mg/dl), serum phosphorus (mg/dl), calcium-phosphorus product (mg2/dl2), parathyroid hormone (pg/dl), alkaline phosphatase (U/L), Hemoglobin(gm/dl), Hematocrit (%), serum iron (ug/dl), TIBC (ug/dl), TSAT (%) and ferritin (ug/dl) versus FGF23 (pg/ml) as dependent factor within group A

| Variable | Regression coefficient | STD Error | T (DF=21) | *P* |
|---|---|---|---|---|
| calcium | -36.1937 | 36.7839 | -0.984 | 0.33634 |
| phosphorus | -52.0783 | 48.3024 | -1.078 | 0.29319 |
| Ca x P | 6.1844 | 5.6313 | 1.098 | 0.28455 |
| PTH | -0.0251 | 0.0259 | -0.971 | 0.34243 |
| Alk. Phos. | -0.0733 | 0.0882 | -0.831 | 0.41547 |
| Hb | -15.4663 | 23.9718 | -0.645 | 0.52579 |
| Hct | 4.3606 | 6.6803 | 0.653 | 0.52099 |
| S. iron | -0.7712 | 0.5959 | -1.294 | 0.20963 |
| TIBC | 0.1411 | 0.1431 | 0.986 | 0.33516 |
| TSAT | 0.4801 | 0.9431 | 0.509 | 0.61601 |
| ferritin | 0.2696 | 0.3923 | 0.687 | 0.49955 |

**Table (27): Multiple regression coefficient, STD error and probability of calcium dose(mg), one alpha calcidiol dose (ug), IV iron dose (mg), and EPO dose (Units) versus FGF23 (pg/ml) as dependent factor within group A.**

| Variables | Regression coefficient | STD Error | T (DF=21) | P |
|---|---|---|---|---|
| Ca dose | 0.0212 | 0.0145 | 1.459 | 0.15934 |
| 1-alpha dose | 1.3063 | 6.6577 | 0.196 | 0.84633 |
| IV iron dose | -0.0856 | 0.1061 | -0.807 | 0.42871 |
| EPO dose | 0.0016 | 0.0038 | 0.409 | 0.68674 |

Analysis of variance was done for all variables to show the most dependent variable that affect factor (13) but it didn't show any significant probability, (r ratio = 0.868, P = 0.6282) except for serum creatinine (P=0.03136).

**Table (28): Modified regression coefficient, STD error, and probability of PTH (pg/dl) and TSAT (%) versus ferritin (ug/l) as dependent factor within group A.**

| Variables | Regression coefficient | STD Error | T (DF=21) | *P* |
|---|---|---|---|---|
| PTH | 0.0187 | 0.0066 | 2.634 | 0.00709 |
| TSAT | 0.5942 | 0.1975 | 3.008 | 0.00448 |

Analysis of variance was done for PTH (pg/dl) and TSAT (%) to show the most dependent variable that affect ferritin and it showed highly significant probability for both.

Analysis of variance was done for all variables to show the most dependent variable that affect Hemoglobin within group A, and it showed highly significant P value for duration of primary kidney disease (years), serum calcium (mg/dl), Hematocrit (%), serum iron (ud/dl) significant P value for age (years), duration of hemodialysis (years), calcium-phosphorus product (mg2/dl2), and borderline significance for eGFR (ml/mn), serum phosphorus (mg/dl), TIBC (ug/dl), and calcium dose (mg).

Analysis of variance couldn't be done for all variables versus FGF23 (pg/ml), ferritin (ug/l) and Hemoglobin (gm/dl) within group B because of the too small size of the sample.

**4.Discussion**

The first reports on phosphatonins date back to 1994 (Cai *et al.,* In studies of patients with tumor – induced osteomalacia, cultures of tumor cells revealed the presence of 10 to 30 Kda thermosensitive factor that inhibited the Na – dependent tubular transportation of phosphate but not that of other substances, such as glucose and amino – acids. That thermosensitive factor was named phosphatonin. (Yamashita *et al.,* Healthy individuals are able to maintain their serum phosphate in a relatively narrow range regardless of dietary phosphate intake, because FGF23 levels rise and fall in parallel with the amount of dietary phosphate. High FGF23 levels in response to high phosphate intake induce greater urinary fractional excretion of phosphate, and by lowering 1, dihydroxyvitamin D levels, reduce the efficiency of phosphate absorption in the gut (Ferrari *et al.,* Burnett *et al.,* and Antoniucci *et al.,* Fibroblast Growth Factor (FGF23) has recently been shown to have a key role in the " bone – parathyroid – kidney " axis and the regulation of phosphate / calcium / vitamin D metabolism (Liu and Quarles, Yamazaki *et al.,* Yoshiko *et al.,* Baccheta *et al.,* FGF23 can also act outside the kidney. FGF23 decreases synthesis of parathyroid hormone in parathyroid gland. (Krajisnik *et al.,* Ben-Dov *et al.,* Baccheta *et al.,* FGF23 appears to be an independent predictor of both CKD progression and mortality in adults with predialysis CKD. (Isakova *et al.*, Baccheta *et al.,* High FGF23 circulating levels have been shown to be a risk factor for cardiovascular morbidity and mortality in general adult and dialysis populations (Fukagawa *et al.,* Gutierrez *et al.,* Nakanishi *et al.,* Mirza *et al.,* a ; Mirza *et al.,* b ; Baccheta *et al.,* Age didn t show any significant correlation to each of serum FGF23, Hb and serum ferritin in both HD patients (Group A) and CKD stages 3 & 4 patients (Group B).

The idea of presence of high turn – over bone disease in Group A and secondary hyperparathyroidism in Group B was reinforced by finding serum alkaline phosphatase levels above normal in the two groups.

Serum FGF23 levels were higher than normal level determined by assay kit (71 pg / ml) in the two groups of our study. Multiple Regression Analysis for all parameters included in the study showed that serum creatnine was the only dependent factor affecting FGF23 serum level in HD patients of Group A, $P = 0.03136$, regression coefficient = -8.4154).

Wolf 2012, stated that higher FGF23 level on a continuous scale was consistently associated with lower estimated GFR. Fliser *et al.,* and Prats *et al.,* confirmed this result.

Over the past decade, numerous studies have documented that FGF23 levels are increased in patients with chronic kidney disease and that this hormone is related to the development of secondary hyperparathyroidism. (Razzaque 2009 ; Shimada *et al.,* Lafage – Proust 2010 ; Juppner *et al.,* Yuan *et al.,* and Baccheta *et al.,* Razzaque *et al.,* Prie *et al.*, Juppner *et al.,* and Baccheta *et al.,* reported that increase in FGF23 levels in patients with CKD may be due, in part, to decreased renal FGF23 clearance but increased synthesis of FGF23 by osteocytes also occurs as early as CKD stage 2, perhaps in an attempt to maintain renal phosphate excretion in the context of declining renal mass.

Health Professionals Follow-up Study was the first to confirm a direct correlation between phosphate intake and FGF23 levels in the population level. This finding is noteworthy given the imprecise ascertainment of dietary phosphate in nutritional epidemiology studies(Gutierrez and Wolf, A clinical experiment performed by Burnett – Bowie *et al.,* demonstrated that infusion of PTH into healthy humans can increase serum FGF23 levels.

Liu *et al.,* Burnett *et al.,* and Lavi – Moshayoff *et al.,* reported that cultured osteoblasts increase FGF23 expression in response to 1, dihydroxyvitamin D and PTH but not phosphate.

Deger *et al.,* and Hasegawa *et al.,* didn't find any correlation between serum phosphorus and iPTH and serum FGF23 in dialysis patients. Hasegawa *et al.,* also demonstrated that FGF23 production occurs regardless of the serum phosphate level in CKD patients, especially those on dialysis.

Studies from transgenic mice suggested that FGF23 - induced phosphaturia is not PTH dependent (Kurosu *et al.,* Yuan *et al.,* in their study demonstrated for the first time that FGF23 / Klotho signaling is not essential for the phosphaturic and anabolic effects of intermittent PTH (1 -34) Marsell *et al.,* and Larsson 2010, reported that the expression of FGF-R and Klotho in the parathyroid glands supports a regulatory effect of FGF23 on PTH secretion. FGF23 has an inhibitory effect on PTH secretion.

This was not the case in our study as FGF23 was above normal and also PTH was very much higher than recommended range in K/DOQI guidelines, in the two groups of the study.

Prats *et al.,* found no correlation between FGF23 and PTH in non-dialysis CKD patients.

Fugakawa and kazama, Komaba and Fugakawa, Yuan *et al.,* stated that the action of PTH and FGF23 was suggested in the effects of Chronic Kidney Disease, where both serum PTH and FGF23 levels are markedly elevated. Krieger *et al.,* found that metabolic acidosis increased FGF23 in neonatal bone.

Canalejo *et al.,* reported that elevated FGF23 reduced PTH secretion in normal rat parathyroid glands, but FGF23 failed to inhibit uremic parathyroid gland.

Interestingly, parathyroidectomy prevented an increase in FGF23 levels in experimental kidney failure rats (Lavi – Moshayoff *et al.,* Yuan *et al.,* Marsell *et al.,* reported that high serum FGF23 in chronic kidney disease is a predictor of secondary hyperparathyroidism.

Sliem *et al.,* stated that data with regard to the role of PTH in FGF23 regulation were conflicting.However, there was growing evidence that PTH may stimulate FGF23 expression and secretion by bone tissue. They found that FGF23 was a central factor in the early pathogenesis of secondary hyperparathyroidism.

We found a borderline significant positive correlation between PTH and Hb within HD patients of Group A. This relationship didn t exist in CKD patient of Group B.

PTH had a highly significant positive correlation with serum ferritin level in HD patients of Group A. ($P$ = 0.009). Such a significant positive correlation also existed in CKD patients of Group B. ($P$ = 0.043). In Multiple Regression Analysis, PTH was the most influencing factor affecting ferritin level.($P$ = 0.024).

In CKD patients of Group B, serum Iron showed an inverse significant correlation to serum FGF23 ($P$ = 0.02). This relationship didn t exist in HD patients of Group A, although there was a non – significant inverse relationship between FGF23 and serum Iron. This may be due to the more preserved renal function in CKD patients, although serum FGF23 level and serum Iron were nearly at the same level in the two groups.This inverse correlation was confirmed by other studies (Imel *et al.,* Farrow *et al.,* Hb had an inverse significant correlation to FGF23 in CKD of Group B, and this relationship didn t exist in HD patients of Group A, may be due to the same reasons as for serum Iron. Hb level in both HD patients of Group A and CKD patients of Group B, was around the recommended range by K/DOQI guidelines. Braithwaite *et al.,* b, in their study have confirmed this relationship.

TSAT had also an inverse significant correlation to FGF23 in CKD of Group B ($P$ = 0.025). This same finding was present in a study conducted by Prats *et al.,* on 47 non-dialysis CKD patients with Iron deficiency anemia. This relation didn t also exist in HD patients of Group A of our study.

None of the three parameters: serum Iron, Hb and TSAT, have shown to affect FGF23 serum level as dependent factors in Multiple Regression Analysis.

A study done by Schouten *et al.,* b, showed that a single infusion of Iron Polymaltose predictably causes significant and prolonged FGF23 elevation. The same inverse correlation between Iron level and iFGF23 level were obtained by Deger *et al.* (2013), on administrating Iron therapy to dialysis patients, whether hemodialysis or peritoneal dialysis.

Lack of IV Iron infusion was accompanied by elevation of FGF23 in our CKD patients of Group B, and phosphorus level was around the recommended range by K/DOQI guidelines and it didn t show any significant relationship to FGF23 serum level in our study, while IV infusion in HD patients of Group A could explain elevation of FGF23 serum level in this group.

Furrow *et al.,* showed that a diet low in Iron can induce elevated FGF23 concentration in an ADHR mouse model.

Both Iron deficiency and excess are associated with altered skeletal metabolism (Merkel *et al.,* Iron overload in hereditary hemochromatosis, even without hypogonadism, is associated with osteoporosis (Valenti *et al.,* Because FGF23 is expressed in osteoblast / osteocyte lineage cells, iron may have a direct or indirect impact on FGF23 metabolism (Takeda *et al.,* Imel *et al.,* in their study found that serum Iron was negatively correlated to both C-terminal FGF23 ($P$ < 0.05) and intact FGF23 ($P$ < 0.0001) in Autosomal Dominant Hypophosphatemic Rickets. However, healthy controls also demonstrated a negative relationship of serum Iron with C- terminal FGF23 ($P$ < 0.001) only.

Imel *et al.,* reported that one week after parenteral Iron, all patients in their study having tumor – induced osteomalacia had FGF23 level above the previously established assay reference range. Imel *et al.,* stated that the degree of elevation was dramatic, with levels similar to those seen in autosomal dominant hypophosphatemic rickets.

Durham *et al.,* Schouten *et al.,* b, and Imel *et al.,* reported that the mechanism underlying the changes in circulating FGF23 levels may involve upregulation of synthesis or secretion, reduction in clearance of the intact molecule, post-translational modification affecting the cleavage site, or possibly inhibition of

proteolytic cleavage. This suggested that Iron may regulate the rate of enzymatic cleavage of intact FGF23, with increased levels inhibiting, and iron deficiency increasing protease activity, besides the direct proximal tubulotoxicity of Iron therapy itself (Schouten *et al.,* a ; Schouten *et al.,* b ; Shimizu *et al.,* and Deger *et al.,* Sanai *et al.* 2005 ; and Shimizu *et al.,* stated that not all iron preparations are associated with renal wasting and osteomalacia in mice and humans.

Prats *et al.,* demonstrated a decrease in FGF23 serum level after a single 1000 mg dose of ferric carboxymaltose in non-dialysis CKD patients. They suggested that iron – induced hypophosphatemia might be due to increased cellular uptake of phosphate during erythropoeisis, as suggested by Van Wyck *et al.,* Hb had a significant positive correlation to serum ferritin in CKD patients of Group B ($P = 0.003$). This relationship didn t exist in HD patients of Group A, may be due to factors related to malnutrition and biochemical reactions taking place in uremic milieu transforming many substances into abnormal ones no more capable of performing their normal physiological functions and the presence of many toxic substances interfering with Iron storage in HD patients of Group A bodies.

Serum ferritin had a significant positive correlation to serum creatinine in CKD patients of Group B ($P = 0.035$), but this relationship didn t exist in HD patients of Group A may be due to the more complex situation of HD dialysis affected by many factors related to ESRD, HD vintage, oxidative stress factors and drug intake, rather than the more simple situation of chronic inflammatory state and partially preserved renal function of CKD patients.

Serum ferritin didn t have any significant relationship with FGF23 serum level in both HD patients of Group A and CKD patients of Group B as ferritin was below recommended range by K/DOQI guidelines, although it is a well known acute phase reactant.

Durham *et al.,* Schouten *et al.,* and Imel *et al.,* reported elevated C-terminal FGF23 (Immunotopics, San Clemente, CA) in patients with low serum ferritin, but not with the intact FGF23 assay used in their study. This was confirmed by Prats *et al.,* In contrast to our study, Braithwaite *et al.,* a, found that ferritin was the strongest independent inverse predictor of FGF23 in subjects with and without elevated CRP, and that improved Iron status (including Hb and ferritin) was associated with increased FGF23 concentration in univariate and multivariate analysis.

Serum ferritin was positively correlated to serum Iron and TSAT in HD patients of Group A ($P = 0.03$ and $P = 0.036$), respectively. But these relationships didn t exist in CKD patients of Group B, may be due to presence of IV Iron and EPO supplementation in HD patients.

Imel *et al.,* stated that the low ferritin concentration were consistent with iron deficiency. This was exactly the case in our patients

We couldn`t perform a Multiple Regression Analysis for all studied parameters affecting FGF23, Hb and ferritin in CKD patients of Group B due to the small number of patients (Only 12).

ALL our drugs supplemented to HD patients of Group A and CKD patients of Group B, didn t affect FGF23, Hb and ferritin in our study except for calcium dose affecting Hb level.

**Conclusion**

We did find a strong impact of Iron deficiency in our patients on FGF23 serum levels in our patients. Also, we had a strong impact of high levels of PTH on parameters of Iron profile in our patients.Iron profile seemed to be, at least in our study, one of the most important factors affecting serum FGF23 levels.

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