Fibroblast growth factor-23 levels in maintenance hemodialysis patients in India

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ABSTRACT

Fibroblast growth factor-23 (FGF-23) levels start rising early in patients with chronic kidney disease and is implicated in cardiovascular and overall mortality of hemodialysis patients. We conducted a prospective observational cohort study in stable dialysis patients looking into the levels of FGF-23 in hemodialysis patients and its association with various demographic and biochemical variables and mortality. A total of 91 patients were enrolled in the study. The mean FGF-23 levels were very high (1152.7 pg/ml). FGF-23 levels were significantly associated with serum phosphorus and parathyroid hormone (PTH) levels in univariate and multivariate analysis. No significant association between FGF-23 and cardiovascular comorbidities and overall mortality was seen. FGF-23 levels rise exponentially in maintenance hemodialysis patients. There is a strong association between FGF-23 and phosphorus and PTH levels. No association between FGF-23 and mortality was noted in our patients.

Key words: Fibroblast growth factor-23, hemodialysis, mortality, parathyroid hormone, phosphorus

Introduction

Fibroblast growth factor-23 (FGF-23) is a hormone secreted by the bone cells - osteocytes and osteoblasts.[1] It is increasingly recognized as intimately connected to the uremic state and its complications. Its levels increase as the stage of chronic kidney disease (CKD) advances,[2] reaching very high levels in CKD Stage 5. It is also believed to be involved in cardiovascular and endothelial dysfunction in CKD.[3]

Many studies over the last decade have reported FGF-23 as a factor of prognostic significance in CKD.[4] Very little data about the significance of this biomarker exists in Indian scientific literature and our study report the results of the levels of FGF-23 in stable maintenance hemodialysis patients.

Materials and Methods

All patients who were continuing in our maintenance hemodialysis program in January 2012 were enrolled as a prospective observational cohort. This group was longitudinally followed for 2 years till January 2014.

At the beginning of the study, the demographic profile, native kidney disease, and comorbidities were noted. Left ventricular hypertrophy and ischemic heart disease where defined based on standard criteria. The dialysis details were also recorded. The hematochemical parameters and serum FGF-23 levels were tested at the beginning of the study. Routine hematological and biochemical parameters were tested as per dialysis protocols.

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FGF-23 levels were measured in our biochemistry laboratory using the kit EZHFGF-23-32 K human FGF-23 Elisa kit (Merck–Millipore Corporation, Billerica, MA 01821, USA). It is a colorimetric fluorescent assay. For the analysis of the association of FGF-23 with various studied variables, the levels were divided into two groups (Group I, FGF 23 <300 pg/ml and Group II FGF-23 ≥300 pg/ml). All statistical analysis was performed using the Statistical Software for windows version 20.0 SPSS Version 20.0 (IBM Corp. Armonk, NY, 2011).

Results

A total of 91 patients were enrolled in the cohort study. No patient dropped out of the study.

The mean ± standard deviation (SD) age of 91 patients (females 34) was 60.6 ± 10.8 years. During follow-up, in the next 48 months, five patients were transplanted and are doing well. Two patients were shifted to peritoneal dialysis who are also alive and healthy until till the end of the study period. There were six deaths during the study period. Fifty-six of these patients had type 2 diabetes mellitus as the cause of their CKD. The body mass index (BMI) of the group is shown in Table 1a.

The mean ± SD duration of dialysis in months was 47.2 ± 24.8 months. Majority of patients were on thrice weekly dialysis [Table 1b].

The mean ± SD and the range of the major biochemical and hematological parameters are given in Table 2. The serum calcium and phosphorus levels were reasonably well controlled. Serum parathyroid hormone (PTH) level was consistently high, and the Vitamin D level was low in general for the whole cohort.

Table 1a: Body mass index of the cohort

Body mass index	Number of patients (%) (*n*=91)
<20	13 (14.3)
20-25	47 (51.7)
26-30	22 (24.1)
>30	9 (9.9)

Table 1b: Dialysis details of the cohort

	Number of patients (%) (*n*=91)
Duration of dialysis (months)	
<12	0
12-24	10 (10.9)
>24	81 (89)
Frequency of dialysis (number/week)	
2/week	20 (21.9)
3/week	69 (75.8)
>3/week	2 (2.1)

FGF-23 level was high in the whole cohort. There was a wide range of FGF-23 levels in this group. The mean FGF-23 level was 1152.7 pg/ml. Patients with higher FGF-23 levels tend to be older, have higher BMI and on dialysis for a shorter duration [Table 3a]. The frequency of dialysis and the FGF-23 levels had no significant association. Type 2 diabetes mellitus was more common in the Group II. No significant association was noted with cardiovascular comorbidities and mortality [Table 3b].

There was a strong association between FGF-23 and serum phosphorus levels and PTH levels. There was a trend to an inverse relationship with FGF-23 and Vitamin D levels [Table 4]. A multivariate analysis confirmed the results noted in the univariate analysis [Table 5].

Table 2: Hematological and biochemical parameters of the cohort

Parameter	Mean±SD	Range
Hemoglobin (g/dl)	9.8±1.5	6.2-14.3
Creatinine (mg/dl)	7.0±2.2	2.7-13.5
Blood urea nirogen (mg/dl)	42.9±14.0	14-87
Potassium (mEq/L)	5.0±0.8	2.9-7.5
Albumin (g/L)	3.9±0.5	2.7-5.7
Calcium (mg/dl)	9.3±0.9	6.8-12.7
Phosphorus (mg/dl)	5.1±1.5	2.6-9.5
PTH (IU/ml)	462.7±379.9	24.7-1522
Vitamin D	23.3±8.8	4.8-45.8
FGF-23 (pg/ml)	1152.7±1128.0	66.05-4110.82

SD: Standard deviation, PTH: Parathyroid hormone, FGF-23: Fibroblast growth factor-23

Table 3a: Association between fibroblast growth factor-23 and demographic, and comorbidity details

Parameter	FGF-23 ≤300 pg/ml	FGF-23 >300 pg/ml	*P*
Age (mean±SD) in years	58.8±13.3	61.3±9.8	0.05
BMI (mean±SD)	24.2±3.3	24.9±5.8	0.03
Presence of IHD	-	-	-
Presence of LVH	-	-	-
Presence of HTN (*n*, %)	23 (95.8)	62 (92.5)	0.9
Presence of type 2 DM (*n*, %)	19 (79.1)	37 (55.2)	0.06
Presence of PVD (*n*, %)	9 (37.5)	27 (40.2)	0.9
Mortality (*n*, %)	1 (4.1)	5 (7.4)	0.9

SD: Standard deviation, BMI: Body mass index, HTN: Hypertension, IHD: Ischemic heart disease, LVH: Left ventricular hypertrophy, DM: Diabetes mellitus, PVD: Peripheral vascular disease, FGF-23: Fibroblast growth factor-23

Table 3b: Association of fibroblast growth factor-23 and dialysis

Parameter	FGF-23 ≤300 pg/ml	FGF-23 >300 pg/ml	*P*
Dialysis duration (months)			
12-24	4	6	0.01
>24	20	61	0.4
Frequency (times/week)			
≤2	5	15	0.7
3	19	50	0.9
≥4	0	2	0.8

FGF-23: Fibroblast growth factor-23

Table 4: Association of hematochemical variables and fibroblast growth factor-23 levels

Parameter	FGF-23 ≥300 pg/ml	FGF-23 >300 pg/ml	*P*
Hemoglobin (g/dl)	10.3±1.7	9.6±1.4	0.05
Blood urea nitrogen (mg/dl)	43.1±14.6	42.9±13.9	0.9
Creatinine (mg/dl)	6.9±1.9	7.1±2.4	0.7
Potassium (meq/l)	5.3±0.9	4.9±0.7	0.02
Calcium (mg/dl)	9.2±1.0	9.3±0.9	0.6
Phosphorus (mg/dl)	45±1.2	5.7±1.5	0.0001
Albumin (g/dl)	4.0±0.3	3.9±0.4	0.2
Vitamin D (ng/ml)	25.9±8.2	22.3±8.9	0.08
PTH (pg/ml)	263.4±201.1	535.2±380.9	0.001

FGF-23: Fibroblast growth factor-23, SD: Standard deviation, PTH: Parathyroid hormone

Table 5: Multivariate analysis of association between fibroblast growth factor-23and various clinical variables

Clinical variables	Standardized coefficients beta	*t*	Significant	95% CI	
				Lower	Upper
Constant		−0.534	−0.595	−4711.291	2721.506
BMI	−0.30	−0.304	0.762	−48.548	35.700
Age	0.116	1.213	0.229	−7.725	31.685
Frequency of HD	−0.13	−0.139	0.890	−507.231	441.211
Dialysis vintage	−0.121	−1.212	0.229	−0.471	0.115
Creatinine	0.207	1.860	0.067	−7.331	210.049
Calcium	0.039	0.384	0.702	−183.081	270.388
Phosphorus	0.250	2.554	0.013	39.745	322.378
Albumin	−0.24	−0.260	0.795	−484.130	372.378
Vitamin D	−0.066	−0.726	0.471	−31.504	14.696
PTH	0.567	5561	0.000	1.072	2.272
DM	0.036	0.328	0.744	−420.798	586.717
HTN	0.039	0.382	0.704	−735.480	1083.812
PVD	0.007	0.068	0.946	−482.855	516.923
IHD	−0.083	−0.912	0.365	−627.156	233.490
LVH	−0.011	−0.121	0.904	−477.221	422.727
Mortality	−0.094	−0.988	0.326	−1379.787	465.466

Dependent variable FGF-23. BMI: Body mass index, CI: Confidence interval, PTH: Parathyroid hormone, DM: Diabetes mellitus, HTN: Hypertension, PVD: Peripheral vascular disease, IHD: Ischemic heart disease, LVH: Left ventricular hypertrophy, HD: Hemodialysis

Discussion

Patients with CKD have raised serum FGF-23 levels. These levels start rising in early stages of CKD and have an exponential increment in levels in stage 5 CKD, especially patients on dialysis.[5]

FGF-23 levels rise with rising serum phosphorus levels. Rising FGF-23 levels suppress 1,25-hydroxy Vitamin D levels.[6] The rise in PTH correlated with FGF-23 in CKD patients and this is attributed to the suppressive effect of FGF-23 on Vitamin D levels.[7]

FGF-23 level was independently associated with a higher risk of myocardial infarction, stroke, coronary, carotid, and lower limb revascularization, lower extremity amputation and death.[8] In some studies, a significantly higher rate of congestive heart failure in patients with higher FGF-23 levels was noted.[9]

Our study re-emphasizes the strong association between serum phosphorus and PTH levels in both univariate and multivariate analyses. Simple statistical analyses (both univariate and multivariate) did not show any link between FGF-23 and cardiovascular comorbidities (both the presence of left ventricular hypertrophy and ischemic heart disease). There was also no link between FGF-23 and mortality. This lack of association has been seen in a recent study also.[10]

The strength of our study is that it is the first of its kind which addresses the issue of FGF-23 levels in relativelyhomogenous stable hemodialysis patients.

The limitation of our study is that it is a relatively small study with a short duration (2 years) follow-up. The cohort of patients also is not fully representative of dialysis patients in India as they came from a relatively higher socioeconomic background.

Conclusion

There is a strong positive association between FGF-23, phosphorus and PTH levels. FGF-23 levels in our study continue to remain high despite acceptable control of phosphorus. Our study did not show any link between FGF-23 and cardiovascular morbidity and overall mortality.

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Conflicts of interest
There are no conflicts of interest.

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