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Original

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Correlation of fibroblast growth factor 23 in chronic kidney disease patients with biochemical parameters and outcomes

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Abstract

Introduction: Fibroblast growth factor 23 (FGF23) is a phosphatonin that increases the rate of urinary excretion of phosphate and inhibits renal production of 1,25-dihydroxyvitamin D, hence helping to mitigate hyperphosphatemia in patients with chronic kidney disease (CKD).

Objectives: As there is a paucity of data in Indian CKD patients about the relevance of FGF23 levels, this study was undertaken at a tertiary care centre to correlate with various biochemical parameters and clinical outcome including mortality.

Patients and Methods: A cross-sectional study was done in 76 CKD patients, with 58 males, 18 females, mean age 58.21 ± 14.08 years, ranging from 25 to 91 years, in 36 chronic renal disease on dialysis (CKD-stage 5 dialysis; CKD-5D) and 40 non-dialysis chronic kidney disease (ND-CKD) patients.

Results: Intact FGF23 levels were higher in vegetarians than non-vegetarians, with mean FGF23 in vegetarians 378.72 ± 76.6 pg/ml, whereas in non-vegetarians 100.41 ± 41.3 pg/ml ($P=0.007$). Higher values of intact FGF23 were associated with low EF ($P=0.008$), high left ventricular (LV) mass index (g/m^2) ($P=0.037$) and high interventricular septal (IVS) thickness (mm) ($P=0.033$).

Conclusion: Patients with low ejection fraction, higher interventricular septal thickness and higher LV mass index on 2-dimensional echocardiogram (2D-Echo) had a higher FGF23 level. On follow up of the patients who had cardiovascular death, we found a higher FGF23 than the survived patients.

Keywords: Fibroblast growth factor 23, Chronic kidney disease, Diabetes mellitus

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Introduction

Fibroblast growth factor 23 (FGF23) is a bone-derived phosphatonin, which acts in the kidney to induce urinary phosphate excretion and suppress 1,25-dihydroxyvitamin D synthesis, in the presence of FGF receptor 1 (FGFR1) and its co-receptor Klotho (1), thus helping to mitigate hyperphosphatemia in patients with chronic kidney disease (CKD) (2). CKD patients are at increased risk for cardiovascular events compared with persons with normal renal function (3). In addition to traditional cardiovascular risk factors, disturbances in calcium-phosphate metabolism are strong contributing factors of higher cardiovascular mortality in CKD (4). Hyperphosphatemia and low 1,25-dihydroxyvitamin D levels are associated with mortality among patients with CKD, but the contribution of FGF23 on mortality is not well known (2).

Objectives

As there is a paucity of data in Indian CKD patients about the relevance of FGF23 levels, this cross-sectional study was undertaken at a tertiary care centre to correlate with various biochemical parameters and clinical outcome including mortality.

Patients and Methods

A cross-sectional study was done in 76 CKD patients, with 58 males,18 females, mean age of 58.21 ± 14.08 years (25-91years), in 36 CKD-dialysis (CKD-stage 5 dialysis; CKD-5D) and 40 non-dialysis chronic kidney disease (ND-CKD) patients. The demographic profile of patients such as age, sex, diabetic status, Hypertension (HTN), residual renal function (urine ml/day) and blood pressure (BP) were looked at. In CKD-5D, vintage and frequency of dialysis were assessed. Hemodialysis was done using polysulfone membrane, with surface area 1.3/m^2, 1.7/m^2 and 1.8/m^2 depending upon the body size. Estimated glomerular filtration rate (eGFR) in all ND-CKD were calculated using isotope dilution mass spectrometry (IDMS)-traceable MDRD formula. We

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Implication for health policy/practice/research/ medical education

In a cross-sectional study on 76 chronic renal failure patients, we found as association between high fibroblast growth factor 23 (FGF23) levels increased mortality in a group of chronic renal disease on dialysis and non-dialysis chronic kidney disease patients. Therapeutic strategies should address elevated FGF23 and hyperphosphataemia simultaneously to reduce cardiovascular morbidity and mortality.

looked at other comorbidities – HIV, HBs Ag, HCV, previous TB, previous cardiovascular disease, type of diet (vegetarian/non-vegetarian), Hb (g/dl), serum creatinine (mg/dl), serum albumin (g/dl), corrected calcium (mg/dl), phosphorous (mg/dl), 25(OH) Vitamin D (ng/ml), iPTH (pg/ml), bicarbonate (meq/l), 2-dimensional echocardiogram (2D-Echo) showing concentric left ventricular hypertrophy (LVH), calcification of aortic and mitral valve, LV mass index (g/m^2), interventricular septal (IVS) thickness (mm), posterior wall thickness (mm). Intact FGF23 (pg/ml) levels were obtained from a 12-hour fasting serum sample using ELISA kit by Immunotopics and correlations were analysed. Current use of vitamin D and dosage and frequency of phosphate binders were also looked at. The primary outcome which was looked at was death or survival after 6 months.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. Informed consent was obtained and the research was approved by the Ethics Committee of Madras Medical Mission Hospital, Chennai, India.

Data analysis

Continuous variables were reported as mean and standard deviation. Independent sample t test was used to compare 2 means. Pearson correlation was used to study the correlation between two continuous variables. Kaplan-Meier survival curve was used to compare the survival of CKD patients having FGF23 above 100 pg/ml and below 100 pg/ml. A *P* value less than 0.05 were considered significant.

Results

Clinical and demographic details are given in Table 1. Of 76 patients, mean intact FGF23 was 159.01 ± 37.85 pg/ml (5.41 pg/ml to 2313.9 pg/ml). Intact FGF23 levels were higher in vegetarians than non-vegetarians, with mean level of 378.72 ± 76.6 pg/ml in vegetarians and 100.41 ± 41.3 pg/ml ($P = 0.007$) in non-vegetarians as shown in Figure 1.

Out of 76 patients, mean ejection fraction (EF) (%) on 2D-Echo was 49.92 ± 11.09%, with 53.61 ± 9.31% in CKD-5D and 46 ± 11.61% in ND-CKD patients. Patients with low EF (%) were associated with higher intact-FGF23 ($P = 0.008$) as shown in Figure 2. Mean LV mass index was 122.72 ± 18.16 g/m^2 (90 g/m^2 to 150 g/m^2) and mean IVS thickness was 13.93 ± 2.88 mm, with a range from 7 mm to 20 mm. High LV mass index (g/m^2) ($P = 0.037$) and high IVS thickness (mm) ($P = 0.033$) were associated with higher values of Intact FGF23 as shown in Figure 3 and Figure 4 respectively.

ND-CKD patients had a higher corrected serum calcium (mg/dl), mean 8.816 ± 0.928 mg/dl than CKD-5D patients, mean 8.203 ± 0.920 mg/dl ($P = 0.005$). CKD-5D patients had a higher 25(OH) vitamin D (ng/ml), mean 21.698± 12.736 ng/ml, than ND-CKD patients, mean 16.170 ± 8.434 ng/ml ($P = 0.04$). Mean serum phosphorous was 5.59 ± 1.75 mg/dl, in ND-CKD 5.79 ± 1.92 mg/dl and CKD-5D 5.41 ± 1.58 mg/dl. Mean serum intact-PTH in our study was 330.95 ± 27.03 pg/ml.

This cross-sectional study looked at the FGF23 in the prevalent patients who were on dialysis for over 15 years. A total of 7 patients died, 5 were in the CKD-5D group, whose FGF23 levels were 85 pg/ml, 84.95 pg/ml, 166 pg/ml, 122 pg/ml and 147 pg/ml at the cross-section, who died 2, 5, 5, 4 and 5 months later respectively. Two patients who died in the ND-CKD group with FGF23 levels of 199.2 pg/ml and 2313.9 pg/ml, died after 6 and 5 months later respectively. Patients who had cardiovascular death had a higher intact FGF23 than the patients who survived ($P = 0.03$) as shown in Figure 5. The probability of survival of patients with FGF23 >100 pg/ml was found to be less comparative to the patients with FGF23 <100 pg/ml as

Table 1. Clinical and demographic details

Parameter	Group	No.
Gender	Male	58
	Female	18
Mode of treatment	Dialysis	36
	Non dialysis	40
DM	Yes	47
	No	29
HTN	Yes	67
	No	9
Diet	Vegetarian	16
	Non-vegetarian	60
Previous CVD	Yes	42
	No	34
Mitral valve calcification	Yes	29
	No	47
Aortic valve calcification	Yes	42
	No	34
Concentric LVH	Yes	51
	No	25

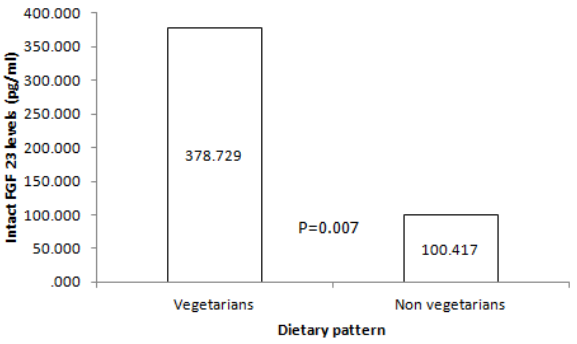

Figure 1. FGF23 and dietary pattern.

shown in the Figure 6.

Intact FGF23 levels did not show any association with patients' age ($P=0.77$), sex ($P=0.78$), diabetic status ($P=0.99$), presence of hypertension ($P=0.66$), residual kidney function (ml/day) ($P=0.23$) and level of blood pressure (mm Hg) ($P=0.99$). In CKD-5D, vintage ($P=0.78$) and frequency ($P=0.45$) of dialysis and serum creatinine value ($P=0.55$) with eGFR ($P=0.12$) in all ND-CKD did not correlate significantly with intact-FGF23 levels. Association of plasma hemoglobin (g/dl) ($P=0.78$), serum albumin (g/dl) ($P=0.66$), corrected calcium (mg/dl) ($P=0.45$), phosphorous (mg/dl) ($P=0.42$), 25(OH) vitamin D (ng/ml) ($P=0.76$), intact-PTH (pg/ml) ($P=0.63$), bicarbonate (meq/l) ($P=0.45$) with intact-FGF23 levels were done using multivariate analysis.

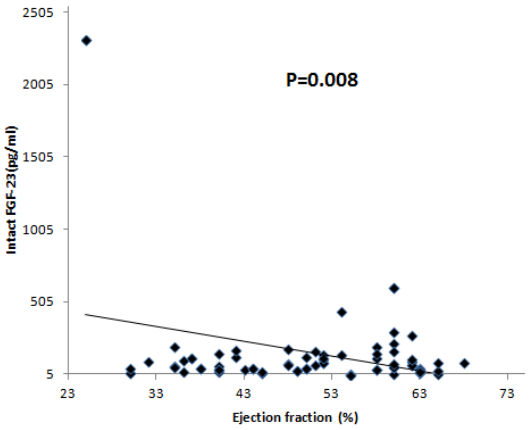

Figure 2. FGF23 and ejection fraction.

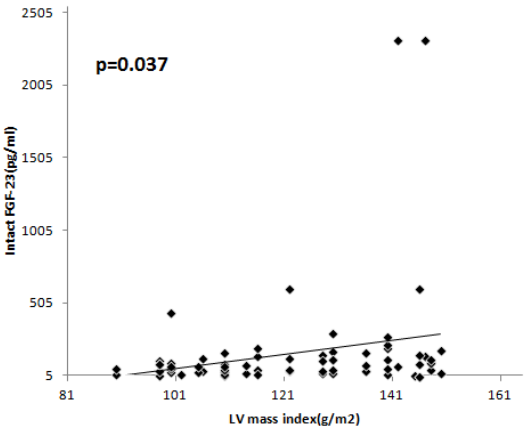

Figure 3. FGF23 and LV mass Index.

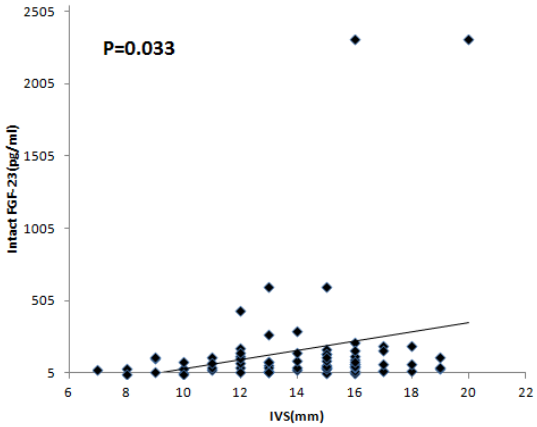

Figure 4. FGF23 and IVS thickness.

Discussion

FGF23 levels increase progressively in early stages of CKD (5). In a prospective study involving white European nondiabetic CKD patients, who were followed-up for a median of 53 months, both serum intact-FGF23 and c-terminal FGF23 levels (cFGF) above optimal cut-off level predicted a doubling of serum creatinine and/or the need for kidney replacement therapy, independent of eGFR and proteinuria (6). In another prospective study from Brazil on patients with diabetes mellitus (DM) and macroalbuminuric diabetic nephropathy, intact-FGF23 was an independent predictor of the composite primary outcome defined as death, doubling of baseline serum creatinine and/or need for dialysis (7). In our study, we measured the intact-FGF23 levels and did not find to correlate significantly with the eGFR nor serum creatinine in ND-CKD patients, however raised intact-FGF23 was associated with cardiovascular mortality.

FGF23 is associated with vascular dysfunction, atherosclerosis, and left ventricular hypertrophy (8). In hemodialysis patients, serum FGF23 levels have been independently associated with peripheral vascular calcification assessed semi-quantitatively on plain radiographs (9) and aortic calcification assessed quantitatively on CT in non-diabetics (10). In primary CKD stages, FGF23 independently predicted the extent of coronary artery disease by angiography (11). FGF23 levels

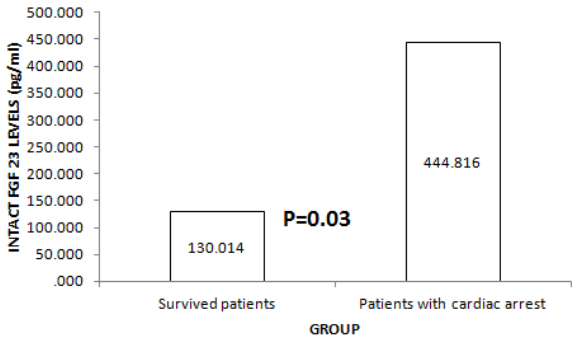

Figure 5. FGF23 and cardiac arrest.

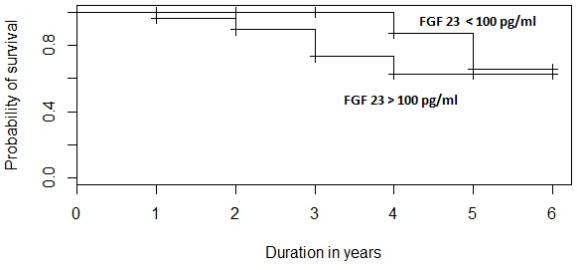

Figure 6. FGF23 and survival.

were associated with vascular dysfunction depicted on the attenuation of flow-mediated dilatation in non-diabetics (12). In hemodialysis patients, FGF23 levels associated with LV mass index and myocardial performance index, which is a surrogate of cardiac failure and increased left ventricle end-diastolic pressures (13). In a study involving individuals with CKD stages 3 and 4, FGF23 associated with high-sensitivity troponin T, an index of cardiomyocyte injury (14). Likewise, in our investigation, low EF, higher LV mass index and thicker IVS were associated with higher FGF23 which in turn was high in patients who died of heart disease on follow up.

Conventionally, people who ingest predominantly vegetarian diet with low phosphorous protein ratio have low intestinal absorption of phosphate and relatively lower serum phosphorous concentration in CKD (15). However we detected a significantly higher level of FGF23 in our vegetarian individuals, which on dietary survey found high phosphorous protein ratio.

Conclusion

This cross-sectional study correlating FGF23 levels with biochemical parameters and cardiovascular status, in ND-CKD and CKD-5D, showed higher cardiac death, which was directly proportional to the rising FGF23 levels. Patients with low ejection fraction, higher IVS thickness and higher left ventricular mass index on 2D-Echo had a higher FGF23.

Limitations of the study

Limitations of our study is the lack of longitudinal estimation of FGF23 levels and small cohort of patients.

Authors' contribution

GA: As the corresponding author, has played a major role in editing the manuscript and guiding me. AY: As the first author, I have compiled all the required information, edited the manuscript and have submitted the same. MV: has played a major role in statistics and data analysis. JJ: Blood bank in charge who had helped us to run the ELISA kit and give us appropriate values required for the manuscript. SK: Nephrologist who has played a major role in data collecting and compiling them. SN: Nephrologist who has played a role in editing the manuscript.

Conflicts of interest

The authors declared no competing interests.

Ethical considerations

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

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