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**Original Research Paper**

# Study of Fibroblast Growth Factor -23 Levels and its Correlation with Carotid Intima Media Thickness in Chronic Kidney Disease Patients on Hemodialysis

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**Abstract**
**Background**: *CKD is a global public health problem, a leading cause of death and disability worldwide. Patients with CKD is more likely to die of cardiovascular disease than due to end stage renal disease. The cardiovascular mortality in CKD is due to accelerated atherosclerosis and vascular calcification among other factors. Patients with chronic kidney disease (CKD) develop disturbed calcium – phosphate metabolism, the so called mineral bone disease (MBD) which is the primary cause of many adverse effects including cardiovascular diseases.Fibroblast growth factor – 23 (FGF23), a novel hormone secreted primarily by osteoblast is one of the key factors in the development of CKD-MBD.FGF23 level rises early and increases corresponding with the progression of CKD and it acts by increasing the rate of urinary phosphate excretion and suppresses 1,25- dihydroxy vitamin D action. Carotid intima media thickness (CIMT) measurement is considered a valid and reliable surrogate marker for assessment of atherosclerotis. There are conflicting results on association between FGF23 and carotid intima media thickness and paucity of such Indian studies.*
**Aim:** *To study the correlation between serum FGF23 levels with carotid intima media thickness in CKD patients on hemodialysis*
**Materials and Methods:** *A Cross-sectional Observational Study on a total of 70 patients was conducted in patients with chronic kidney disease on hemodialysisas defined by KDIGO guidelines. Serum intact FGF23 was measured using sandwich ELISA technique. The CIMT was measured with B mode ultrasound using hand held transducer at 7.5 mHz. Correlations between the two were analyzed in detail.*
**Results**: *A significant positive correlation was found between FGF23 and CIMT in CKD patients on haemodialysis.FGF23 and CIMT was found to be increased according to the severity of CKD. Both univariate and multivariate regression analysis showed a significant association between FGF23 and CIMT*
**Conclusion:** *Serum FGF23 correlate with significantly increased atherosclerotic burden and cardiovascular disease as measured by CIMT in CKD patients on hemodialysis.*

**Introduction**

Chronic kidney disease is a broad term that encompasses a spectrum of different pathophysiologic process associated with abnormal kidney function and progressive decline in glomerular filtration rate is associated with increased morbidity and mortality, decreased quality of life and increased health expenditures. The incremental risk of cardiovascular disease in those with CKD compared to age and sex matched general population ranges from 10 to 200-fold, depending on stage of CKD.

Much of the vascular disease in CKD is caused by atherosclerosis. CIMT is the surrogate marker of atherosclerosis and is measurement of thickness of inner two layers of vascular wall, tunica intima and media. The first structural change that can be seen in atherosclerosis is increased CIMT. European society of cardiology/hypertension guidelines says CIMT in normal population is 0.5 to 0.6 mm and carotid IMT > 0.9mm as a marker of asymptomatic organ damage.

FGF 23 is a 251 amino acid protein (MW 26kda) synthesized and secreted by bone cells, mainly osteoblasts. In CKD circulating FGF 23 level gradually increases with declining renal function. FGF-23 plays an important role in regulation of phosphate and 1, 25 dihydroxy vitamin D metabolism. It induces urinary phosphate excretion and suppress 1, 25 dihydroxy vitamin D synthesis in the presence of FGF-R1 receptor and its co-receptor klotho. FGF23 is positively regulated by phosphorous, calcitriol, iron and negatively regulated by PHEX gene (a phosphorous regulating gene on X chromosome).

Despite the ubiquitous presence of FGFRs, the target organs of FGF23 are limited to the kidney and parathyroid. The main site of action of FGF23 is the FGF receptor-Klotho complex in the kidney. FGF23 induces urinary phosphate excretion by decreasing expressions of the type IIa and IIc sodium-dependent phosphate co-transporters (NPT2a and 2c) in the renal proximal tubule. Furthermore, FGF23 decreases dietary absorption of phosphate through suppression of circulating concentrations of 1, 25(OH)[2] Vitamin D by inhibiting renal expression of the vitamin D-synthesizing CYP27B1,the gene responsible for synthesizing 1-α-hydroxylase, and stimulating expression of CYP24, which produces 24-hydroxylase[1], responsible for breakdown of vit D. FGF23 level increases with worsening of kidney function. FGF23 levels are mildly raised during stage 1(early stages) of CKD and can reach more than 200 times the normal level in cases of advanced CKD.

Increased serum FGF23 levels is independently associated with mortality and cardiovascular disease in CKD. a cohort study by Jean G et al [2] of 219 dialysis patients followed for two years and high level of circulating FGF23 was found despite infrequent hypophosphatemia and high FGF23 level was associated with mortality and vascular calcification regardless of serum phosphate level.

A study by Manar Rafat et al[3] concluded that elevated FGF23 levels were associated with faster progression of CKD, and increased cardiovascular progression in CKD patients Inflammation induces FGF23 transcription[4], conversely FGF23 induces hepatic production of IL6 and CRP via klotho independent mechanism[5], inflammation may increase mortality by inducing atherosclerosis. A study by Munoz Mendoza et al[6] suggested that elevated levels of inflammatory markers and FGF23 increased mortality through seemingly distinct pathways. FGF23 was found to be positively correlated with total body atherosclerosis in the community as measured by MRI angiography in a study by M A I Mirza et a[7] in one more study by Ashikaga E et al [8]FGF23 was negatively correlated with atherosclerosis and CIMT was less elevated in higher FGF23 tertile levels, and FGF23 inversely correlated with cholesterol and a study by Turan et al[9] states that FGF23 levels are associated with vascular calcification but not with atherosclerosis in hemodialysis patients as in this study there was no correlation between FGF23 and CIMT.

There are conflicting results on association between FGF23 and carotid intima media

thickness, a marker of cardiovascular disease. Interventional studies targeting dietary phosphate or phosphate absorption are required to determine if FGF23 can be lowered and if it translates to prevention of cardiovascular diseases[10]. Hence further studies are needed to answer above controversies and with further validation, this study aims to correlate FGF23 with carotid intima media thickness.

**Material and Methods**

A Cross-sectional Observational Study was conducted on a total of 70 patients with chronic kidney disease on hemodialysis as defined by KDIGO guidelines. Serum intact FGF23 was measured using sandwich ELISA technique. The CIMT was measured with B mode ultrasound using hand held transducer at 7.5 mHz. Study was conducted in VMMC and Safdarjung hospital New Delhi during the period 2017-19.

**Inclusion Criteria**

1. Adults (> 18 years) of all genders
2. With a diagnosis of CKD (ESRD) on hemodialysis.

**Exclusion Criteria**

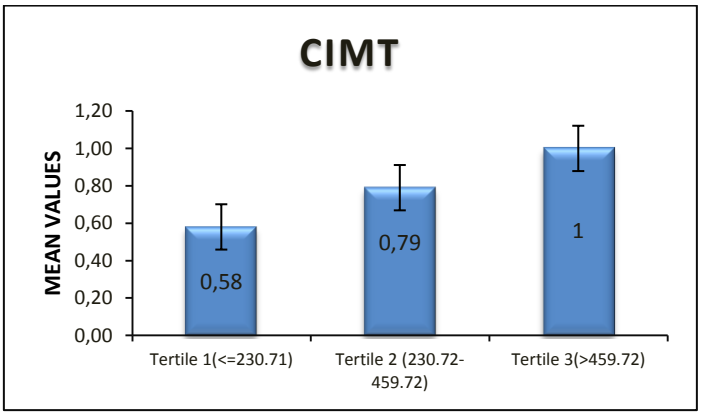
1. Patients with active hepatitis or malignancy
2. Patients on hypolipidemic drugs
3. Patients with acute cardiovascular or cerebrovascular events
4. Patients taking intravenous injection of iron
5. Patients with history of carotid surgery
6. Patients already on phosphate binders
7. Patients with known primary parathyroid disorder

**Observation and Results**

**Results according to FGF23 tertiles**

Patients were divided into 3 tertiles according to FGF23 levels, tertile 1 included patients with FGF23 <230.71pg/ml, tertile 2 included patients with FGF23 between 230.72-459.72 pg/ml and tertile 3 included patients with FGF23 levels >459.72 pg/ml.

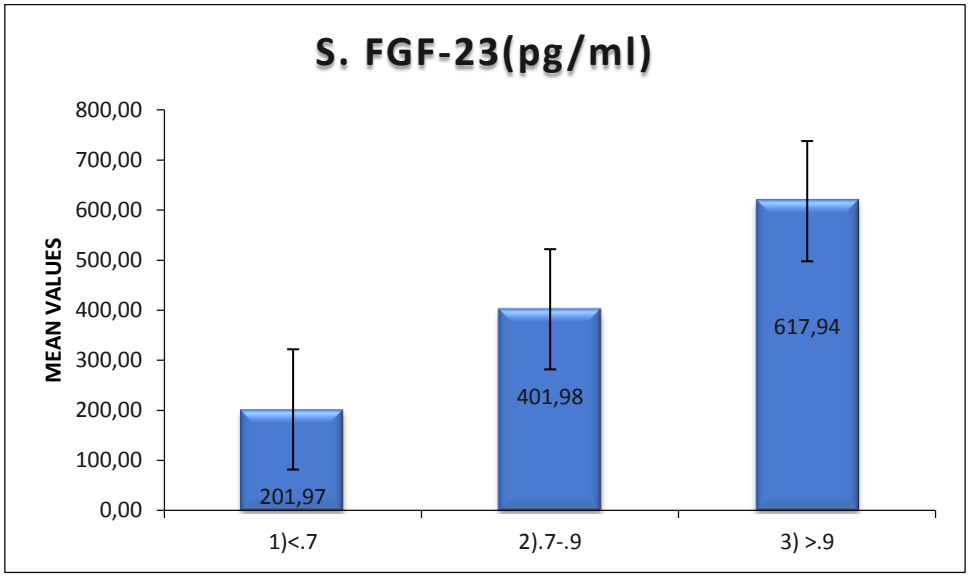
CIMT values increased significantly with higher FGF23 tertiles (p<0.0001)




**Results according to CIMT tertiles**

Patients were divided according to CIMT values into three tertiles, tertile 1 had CIMT level of <0.7mm, tertile 2 had CIMT of 0.7-0.9mm and tertile 3 had CIMT of >0.9mm

Mean S.FGF23 increased significantly with higher CIMT tertiles (p<0.0001)



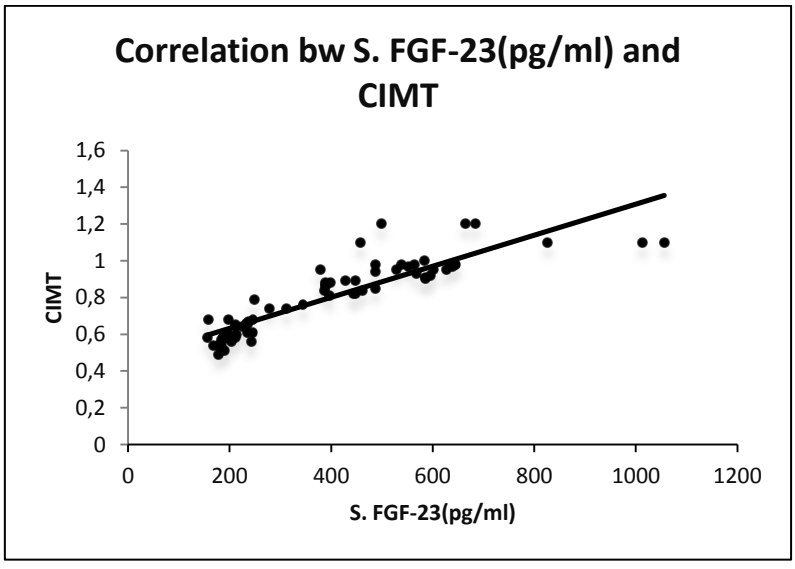

After univariate regression analysis, male sex (p=0.035), smoking (p=0.001), haemoglobin (p=0.007), platelets (p=0.003), eGFR (p=0.0001p), s. creatinine (P<0.0001), s. calcium (p<0.0001), s. vit D (p<0.0001), s. phosphate (p<0.0001), S.FGF23 (p<0.0001) were significantly correlated with CIMT. But after Multivariate regression analysis, only smoking (p=0.012), s. creatinine (p=0.006), s. calcium (p=0.0001) and FGF23 (p=0.033) were significantly associated with CIMT.

**Correlation between FGF23 and CIMT**

Spearman rank correlation coefficient was used to find out the correlation between CIMT and FGF23. Correlation coefficient was 0.926 with a p value of <0.0001.

**Correlation table**

| | | S. FGF-23(pg/ml) |
|---|---|---|
| CIMT | Correlation Coefficient | 0.926 |
| | P value | <0.0001 |
| | n | 70 |




**The graph depicts significant positive correlation between FGF23 and CIMT (p <0.0001)**

**Discussion and Conclusion**

1. The mean value of s.FGF23 in CKD patients on hemodialysis was found to be 387.22±206.35pg/ml. Also as the severity of CKD increased FGF23 levels increased accordingly.
2. Serum FGF23 levels is found to have a significant negative correlation with eGFR ($p<0.0001$)
3. CIMT also increased proportionately, with the severity of CKD
4. Hence CIMT also varied inversely and statistically significantly with eGFR ($p<0.0001$)
5. Serum FGF23 levels increased irrespective of age, diabetes, hypertension, dyslipidemia, BMI but was significantly positively associated with smoking, s. calcium and s. phosphate levels and CIMT
6. After multivariate regression analysis, FGF23 had a statistically significant association only with serum phosphate and CIMT levels with a p value of 0.0002 and 0.033 respectively.
7. Serum FGF23 levels had a significant positive correlation with increased CIMT levels, with a p value of <0.0001 and a correlation coefficient of 0.926.
8. FGF23 is a risk factor for atherosclerosis in CKD patients on maintenance haemodialysis.
9. Monitoring of FGF23 levels may be recommended to predict the possibility of vascular atherosclerosis and hence improve outcomes in these patients.
10. The mean serum calcium in our study population was low i.e,7.28±0.74.But, correlated significantly and positively with increased CIMT($p<0.0001$) and the mean serum calcium in patients with CIMT of >0.9mm was 8.13±0.2
11. The mean serum phosphate in our study population was high i.e, 5.39±1.16 .It correlated significantly with increased CIMT levels ($p<0.0001$) and the mean s.phosphate levels in patients with CIMT of >0.9mm is 6.76±0.74.
12. CIMT levels also increased irrespective of age, diabetes, hypertension, dyslipidemia and BMI, but was significantly positively associated with male sex, smoking, reduced haemoglobin, s. creatinine, s. calcium and s. phosphate and FGF23 levels
13. After multivariate regression analysis, CIMT correlated significantly only with s.FGF23 ($p=0.033$), smoking ($p=0.021$), s. creatinine ($p=0.006$) and s. calcium ($p=0.0001$) in increasing order of significance.
14. Additional investigations are further required to confirm whether lowering FGF23 translates into prevention of cardiovascular diseases in CKD patients on hemodialysis, and help them reduce the risk of cardiovascular morbidity and mortality.

FGF23 is an interesting link between mineral metabolism and atherosclerosis, forming the basis of so called “bone –vascular axis”. More research is required in this regard to confirm whether anti FGF23 therapy causes mortality benefits in CKD patients by altering the cardiovascular burden

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