**Int J Med. Public Health. 2022; 12(4):165-168**
A Multifaceted Peer Reviewed Journal in the field of Medicine and Public Health
www.ijmedph.org

*Original Article*

# Carotid Intima-media Thickness is a Sequel of Elevated FGF-23 Levels in CKD!

**Upma Narain[1,*], Arvind Gupta[2], Seema Pandey[3]**

## ABSTRACT

**Background:** FGF-23 regulates phosphate homeostasis and has a correlation with morbidity and mortality due to cardiovascular episodes and chronic renal conditions. The risk of subclinical atherosclerosis can be predicted by measurements of the intima-media thickness of the carotid artery. The objective of this studyisto study therelation between serum FGF-23 levels and Carotid intima-media thickness in the early stages of CKD. **Materials and Methods:** This study was conducted at MLN Medical College, SRN Hospital, Prayagraj and Tejas Microdiagnostics. The study design adopted was prospective and observational. A total of 270 newly diagnosed CKD patients were enrolled as cases while 90 patients without CKD were taken as control. High-resolution ultrasonography was utilised to measure Carotid artery intima-media thickening. Serum FGF-23 levels were performed at the beginning of study, along with other baseline investigations and were repeated on 6th and 9th months respectively. **Results:** Among the case group of CKD, the mean age was 54.8+2.1 years with male to female proportions representing 62% and 38%, respectively of the control group consisted mean age distribution of 51.0 + 2.1 years a and male-female proportion of 58% and 42%, respectively. It was observed that FGF-23 levels and Carotid intima-media thickness measurements were high in patients than in controls. A statistically significant correlation at 0.01 levels was observed between FGF-23 and the Carotid intima-media thickness. **Conclusion:** Our study clearly establishes a strong correlation between FGF-23 and CIMT indicating that FGF-23 plays an important role in the development of vascular calcifications in early stages of CKD. Subclinical atherosclerosis in CKD patients can be predicted by monitoring of their FGF-23 and CIMT level.
**Keywords:** FGF-23, Carotid intima-media thickness, CKD, Association.

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**History**
- Submission Date: 13-06-2022;
- Revised Date: 08-08-2022;
- Accepted Date: 16-09-2022;

**DOI : 10.5530/ijmedph.2022.4.30**

**Article Available online**
http://www.ijmedph.org/v12/i4



## INTRODUCTION

Serum phosphorus levels in CKD patients is maintained by Fibroblast growth factor 23 (FGF-23), which is a 251-amino-acid protein produced by osteocytes in adults.[1] The mode of action of FGF-23 is to increasethe urinary phosphate excretion and decrease thedietary phosphorus absorption through inhibition of 1,25-dihydroxyvitamin D (1,25(OH)2D) synthesis.[2] Therefore, it can be assumed that FGF-23 levels are raised to compensate for the phosphate imbalance in CKD patients, keeping into account the diminished capacity of renal phosphate excretion in CKD patients.[3-4] Prior to hyperphosphataemia, FGF-23 level starts rising quite early in CKD patients, and proves to be an important early indicator of disrupted phosphorus metabolism in cases of CKD.[3,5] More the FGF-23 levels, the higher are the chances of further deterioration of renal function and, in turn, higher the mortality rate.

A higher prevalence of mortality due to cardiovascular disease has been observed in patients with CKD. Carotid arterial plaque and intima-media thickness (IMT) more than 0.8 mm have a strong correlation with cardiovascular disease in the population.[6] Similarly, carotid IMT independently affects mortality due to cardiovascular diseases in renal disease patients that are on haemodialysis.[7-8] However, the correlation between FGF-23 and IMT in CKD cases has not been widely studied. Only a handful of studies could be found on this subject,[9] especially taking into consideration stage 3 or more severe CKD. Considering the disease burden and alarming rates of mortality due to cardiovascular disease in CKD cases and the association of FGF-23 as a marker in CKD-MBD, this study aims to examine the correlation between serum FGF-23 levels and IMT in the early phase of chronic kidney disease.

## MATERIALS AND METHODS

The study was conducted at a Government Medical College Hospital (SRN Hospital, Allahabad) between July 2017 to August 2019 by prospectively observing a cohort of 270 CKD cases that had been reported during this period. After ruling-out diabetes mellitus and pre-existing cardio-vascular or cerebro-vascular conditions, these 270 CKD cases were enrolled from amongst the regular out-patients visiting the

**Cite this article :** Narain U, Gupta A, Pandey S. Carotid Intima-media Thickness is a Sequel of Elevated FGF-23 Levels in CKD!. Int J Med Public Health. 2022;12(4):165-8.

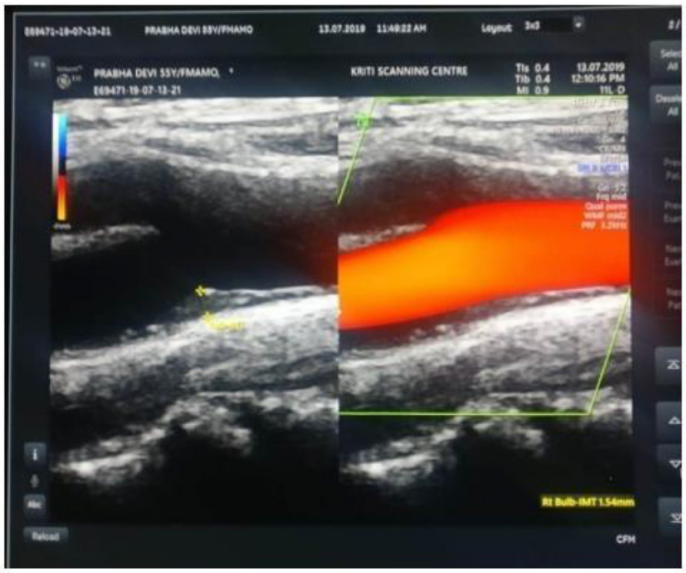


**Figure 1:** IMT 1.54 mm (Case).

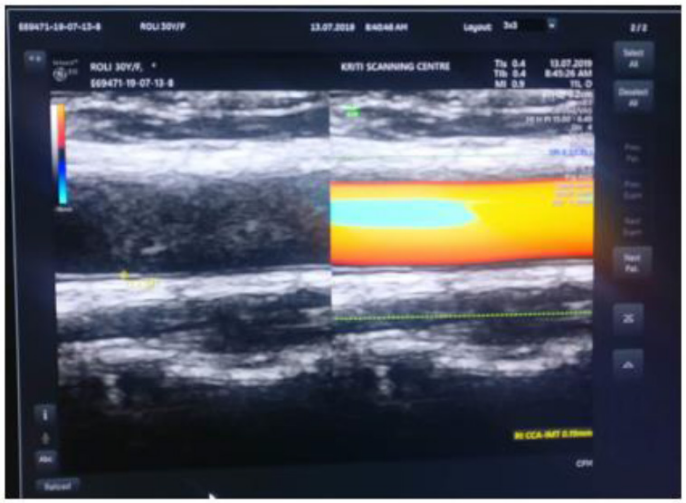


**Figure 2:** IMT 0.19 mm (Control).

nephrology OPD at this tertiary-care hospital. Another group of ninety persons with no acute or chronic illness attending the general medicine OPD were taken as the control group. Both, the study and control groups were subjected to bases-line investigations, including serum levels of FGF-23 at the inception of the study, which were combined with clinical follow-ups on a monthly basis. The same set of investigations was again conducted at 6 and 9 months. FGF-23 levels were assessed using an ELISA kit for human FGF-23 (code number EZH FGF-23 32 K) while ultrasonography was used to measure carotid artery intima-media thicknesses (IMT) as an indicator of atherosclerosis as shown in Figure 1 (case) and Figure 2 (control) in all 270 patients with CKD stage 3–4 and all 90 controls.

The data was subjected to statistical analysis employing descriptive statistics including mean and standard deviation.

## RESULTS

Among the case group of CKD, mean age was 54.8+2.1 years with male to female proportions representing 62% and 38%, respectively the control group consisted mean age distribution of 51.0 + 2.1 years and male-female proportion of 58% and 42%, respectively. In the parameters and values of baseline, investigations have been depicted in Table 1.

A statistically significant difference was recorded between various physical and biochemical parameters in cases and controls. Table 2 revealed the serum FGF-23 levels, CIMT and other base line investigations of cases at interval of 0, 6th and 9 months respectively.

A statistically significant correlation was observed analysis was done between 0 month to 6 months interval and 0 to 9 months interval. Spearman's correlation was undertaken between FGF-23 levels and CIMT as shown in Table 3.

Significant 2-tailed correlation was observed between FGF-23 levels and CIMT at 0.01 levels in early stages of CKD.

## DISCUSSION

Chronic Kidney Disease is a precursor to cardiac malfunction by causing structural and functional abnormalities to the heart as well as the vascular system, which leads to significant morbidity in these cases.[10] Laboratory assessment of FGF-23 and ultrasonography for those patients was the main scope of our study to detect if there is a relation between FGF-23 and CIMT for detection of preclinical atherosclerosis.[11]

The data in the present study revealed that the prevalence of CKD was higher in males (58%) than in females (42%). This finding is consistent with several other reports that the incidence and prevalence of CKD are greater in males than females.

We noticed a significant difference between cases (427.08±124.82) and controls (92.08±24.82) with regard to FGF-23. Yelmaz *et al.* also found that FGF-23 was significantly higher in CKD cases than in controls.[12] The present study showed that measurements of CIMT were significantly high in cases (1.10±0.40) than the control group (0.70±0.20) similar findings were also reported by Tiwari *et al.* and Kumar *et al.*[11,13]

**Table 1: Comparison of various physical and biochemical parameters in cases and controls.**

| Sl. No. | Parameter | Cases ($n$ = 270) | | Control ($n$ = 90) | | Significance of difference | |
|---|---|---|---|---|---|---|---|
| | | Mean | SD | Mean | SD | "t" | "p" |
| 1 | SBP | 140.38 | 22.12 | 108.2 | 7.2 | 8.233 | <0.001 |
| 2 | DBP | 84.85 | 12.02 | 68.9 | 6.7 | 7.211 | <0.001 |
| 3 | Total cholesterol | 202.5 | 58.2 | 189.6 | 44.0 | 1.234 | 0.220 |
| 4 | LDL | 123.2 | 47.9 | 116.7 | 40.8 | 0732 | 0.465 |
| 5 | HDL | 43.7 | 10.8 | 40.5 | 7.1 | 1.705 | 0.091 |
| 6 | Triglyceride | 138.6 | 53.1 | 140.1 | 54.5 | -0.223 | 0.824 |
| 8 | Ionized calcium (mmol/L) | 1.06 | 0.13 | 1.11 | 0.08 | -2.472 | 0.015 |
| 9 | Phosphate (mg/dL) | 5.9 | 1.7 | 3.4 | 0.7 | 8.992 | <0.001 |
| 10 | Urea (mg/dL) | 136.0 | 85.0 | 39.0 | 14.8 | 7.149 | <0.001 |
| 11 | Creatinine (mg/dL) | 7.7 | 5.7 | 0.9 | 0.2 | 7.494 | <0.001 |
| 12 | iPTH (pg/ml) | 385.7 | 287.7 | 30.8 | 13.4 | 7.780 | <0.001 |
| 13 | Vitamin D (ng/ml) | 27.4 | 17.6 | 34.8 | 16.0 | -2.067 | 0.041 |

**Table 2: Serum FGF-23 levels, CIMT and base line investigations of cases at 0, 6th and 9th months.**

| Sl. No. | Groups | Time period (*n*=270) | | | Mean change, *p*- value[1] | |
|---|---|---|---|---|---|---|
| | | 0 month | 6 month | 9 month | 0 to 6 month | 0 to 9 month |
| 1 | SBP | 140.38±22.12 | 149.85±20.52 | 154.62±19.02 | 9.46, 0.003* | 14.23, 0.0001* |
| 2 | DBP | 84.85±12.02 | 86.31±9.76 | 91.92±12.01 | 1.46, 0.47 | 7.07, 0.006* |
| 3 | Calcium | 1.06±0.13 | 0.96±0.08 | 0.91±0.08 | -0.09, 0.001* | -0.14, 0.001* |
| 4 | Phosphorus | 4.81±1.59 | 5.19±1.55 | 5.70±1.45 | 0.37, 0.001* | 0.88, 0.001* |
| 5 | Urea | 103.29±51.69 | 111.00±47.11 | 120.00±47.34 | 7.70, 0.001* | 16.70, 0.0001* |
| 6 | Creatinine | 3.39±1.31 | 3.89±1.47 | 4.72±1.64 | 0.49, 0.001* | 1.32, 0.0001* |
| 7 | iPTH | 148.15±64.07 | 184.58±82.02 | 245.96±98.72 | 36.42, 0.0001* | 97.80, 0.0001* |
| 8 | FGF-23 | 427.08±124.82 | 530.62±108.96 | 606.96±109.57 | 103.53, 0.0001* | 179.88, 0.0001* |
| 9 | GFR | 23.35±10.75 | 20.45±10.18 | 16.46±6.54 | 2.89, 0.001* | 6.88, 0.0001* |
| 10 | CIMT | 0.84±0.60 | 0.98±0.10 | 1.10±0.40 | 0.04, 0.001 | 0.19, 0.001 |

**Table 3: Spearman's correlation was done between FGF-23 levels and CIMT.**

| Spearman's rho | | | | | |
|---|---|---|---|---|---|
| | | Fibroblast Growth 00 | Fibroblast Growth 06 | Fibroblast Growth 09 | CIMT |
| Fibroblast Growth 00 | Correlation Coefficient | 1.000 | .860** | .779** | 0.096 |
| | Sig. (2-tailed) | . | .000 | .000 | 0.014 |
| | N | 270 | 270 | 270 | 270 |
| Fibroblast Growth 06 | Correlation Coefficient | .860** | 1.000 | .893** | 0.055 |
| | Sig. (2-tailed) | .000 | . | .000 | 0.002 |
| | N | 270 | 270 | 270 | 270 |
| Fibroblast Growth 09 | Correlation Coefficient | .779** | .893** | 1.000 | 0.023 |
| | Sig. (2-tailed) | .000 | .000 | . | 0.018 |
| | N | 270 | 270 | 270 | 270 |
| CIMT | Correlation Coefficient | 0.96 | 0.055 | 0.023 | 1.000 |
| | Sig. (2-tailed) | 0.014 | 0.002 | 0.018 | . |
| | N | 270 | 270 | 270 | 270 |

**. Correlation is significant at the 0.01 level (2-tailed).

A statistically significant 2-tailed correlation at 0.01 levels was observed between FGF-23 and the CIMT in our study. Yelmaz *et al.* also noticed a positive correlation between FGF-23 and CIMT[12] while Bulent *et al.* could not seen such a relationship between FGF-23 and the CIMT.[14]

Our findings revealed that CKD patients having high mean BP was having high mean CIMT in comparison to the control group as shown in Table 1. Similar results were also reported by Kim *et al.*, and they suggested that the main cause of atherosclerosis in non-diabetic CKD patients was age and hypertension which were the main determinants of increased CIMT.[15] Though the vascular calcification is seen in all the stages of CKD, some studies have reported higher CIMT in later stages of CKD.[16]

We found significantly higher mean CIMT in all stages of CKD, but there was no significant difference among them. Similar results were observed by Querfeld *et al.*, who they noted CIMT was significantly increased in all stages of CKD and after transplantation.[17]

The limitation of our study was that we did not study the various other parameters responsible for atherosclerosis. Further larger studies are needed focusing on all the other parameters of atherosclerosis.

## CONCLUSION

The presentstudy clearly establishes a significant correlation between FGF-23 and CIMT indicating the role that FGF-23 plays in the development of vascular calcifications in the early stages of Chronic Kidney Disease. Thus, monitoring of serum FGF-23 may prove to be a useful non-invasive indicator of subclinical atherosclerosis in patients with CKD and CIMT can be used as an important tool to assess this risk in patient with CKD.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## ABBREVIATIONS

**FGF-23:** Fibroblast growth factor 23; **CIMT:** Carotid intima-media thickness.

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**Cite this article :** Narain U, Gupta A, Pandey S. Carotid Intima-media Thickness is a Sequel of Elevated FGF-23 Levels in CKD!. Int J Med Public Health. 2022;12(4):165-8.