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RESEARCH ARTICLE
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Association of Fibroblast Growth Factor-23 Level with Carotid Intima Media Thickness in Hemodialysis Patients

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ABSTRACT

Background: One of most prevalent cause of death in patients on hemodialysis (HD) is cardiovascular disease (CVD). Cardiovascular events in HD patients are significantly predicted by ultrasound measurements of carotid intima media thickness (cIMT). The hypothesis that serum fibroblast growth factor-23 (FGF-23) may be independently correlated with cardiovascular risk factor has been suggested because of the substantial correlation between altered mineral metabolism and increased cardiovascular risk in patients with chronic kidney disease (CKD). This study's objective was to assess the plasma FGF-23 level and its correlation to cIMT in patients with kidney failure on HD.

Methods: 100 participants on regular HD participated in the study. Two groups of patients were created based on cIMT; group 1 consisted of 50 participants with increased cIMT ≥ 1 mm, and group 2 consisted of 50 participants with cIMT below 1 mm. Patients with diabetes mellitus, patients on anticoagulant therapy and those with history of parathyroidectomy were excluded from the study. High resolution B-mode ultrasonography was utilized to evaluate cIMT at the common carotid artery.

Results: The study showed that FGF-23 was significantly greater in patient group with increased cIMT, however it wasn't a reliable indicator of increased cIMT on regression analysis. cIMT was in a strong correlation with duration of dialysis, PTH and phosphorus and in a negative correlation with body mass index. FGF-23 was strongly and positively linked with both age and PTH.

Conclusion: Phosphorous level and duration of dialysis and not FGF-23 were the significant independent predictors for increased cIMT.

Keywords: *cardiovascular mortality, carotid intima media thickness, fibroblast growth factor-23, hemodialysis*

INTRODUCTION

Patients with chronic kidney disease (CKD) and those with kidney failure on hemodialysis (HD) commonly die from cardiovascular disease (CVD) (1, 2). In both HD patients and the wider populace, assessing the carotid intima media thickness (cIMT) by ultrasonography is a strong indicator of cardiovascular events (3-5).

Osteocytes and osteoblasts both generate fibroblast growth factor-23 (FGF-23). There is a complex that is formed between this phosphaturic hormone and its co-receptor, Klotho. This complex is crucial for regulating mineral metabolism (6). Early in the evolution of CKD, FGF-23 levels begin to rise and continue to grow as the disease progresses (7, 8).

In HD patients, FGF-23 levels are often considerably raised, and this increase has been independently linked to death in this patient population (9). The study's purpose was to determine the plasma level of FGF-23 as well as its relationship to cIMT in HD patients.

METHODS

The purpose of this cross-sectional observational research was to assess any potential links between elevated cIMT and FGF-23 in patients undergoing HD. Participants who attended Tanta University Hospitals' HD unit between August 2022 and February 2023 were the subjects of the study. 100 patients who were 18 years of age or older, receiving regular HD at least for one year, and receiving adequate dialysis, determined according to a urea reduction ratio (URR) ≥ 65% throughout the six months just before the trial, were included in the study. The research excluded individuals with diabetes mellitus, those on anticoagulant therapy, and those with a history of parathyroidectomy.

High-resolution B-mode ultrasound (Siemens Sono-Line G60F, Germany) was used to measure the cIMT at the common carotid artery (CCA). Used transducer frequencies ranged from 5 to 10 MHz. Within that 4-cm portion before the carotid bifurcation, cIMT was evaluated by scanning the near and far CCA walls. cIMT measurement ≥ 1 mm were considered as thick. For the purpose of detecting plaques, arteries were examined both transversely and longitudinally. When the artery wall was > 50% thicker than the surrounding sites, a localised echostructure that was intruding into the lumen of the vessel was determined to be plaque (10).

Participants were divided into two groups based on cIMT; group 1 had 50 patients with increased cIMT (≥ 1 mm), while group 2 contained 50 patients with cIMT (< 1 mm). Both groups were matched for age and sex.

All study population underwent thorough history taking focusing on possible causes of kidney disease, dialysis duration, vascular access and current medications. Complete clinical examination was performed with special focus on blood pressure measurement, signs of volume overload and body mass index (BMI). Mean arterial pressure (MAP) was calculated from the mean of three measurements taken at various times while the patient was seated. (11).

Investigations (during the non-dialysis day) included total calcium, phosphorous, blood urea, serum albumin, total cholesterol, triglyceride (Synchron CX5, Beckman, USA), full blood count (ERMA, Tokyo, Japan), intact PTH (using ELISA technique) (12) and FGF-23. Using an enzyme-linked immunosorbent technique with two sites (C-terminal/NH2-terminal), the plasma levels of the intact FGF-23 molecules had been measured. (Shanghai Sunred Biological Technology Co., Ltd) based on the instructions provided by the manufacturer. All parameters' serum samples were taken at the same time.

Data were entered into the computer, and SPSS version 23 was used to analyze them (SPSS Inc., Chicago, IL, USA). Number and percentage were used to describe qualitative data. Quantitative data was presented using the mean, SD, and/or median, as well as the range (minimum and maximum). The acquired findings were considered significant at the 5% level. (13).

RESULTS

This cross-sectional observational research was carried out on 100 regular HD patients at our hemodialysis unit. 50 patients in group 1 had cIMT ≥ 1 mm, whereas 50 patients in group 2 had cIMT that was less than 1 mm. The most

prevalent causes of kidney disease in the study population were hypertension, chronic pyelonephritis, and glomerulonephritis (Table 1).

Relevant medications received by our study population included calcium carbonate (77 patients), calcium acetate (7 patients), alfacaclcidiol (62 patients), cinacalcit (18 patients), sevelamer (12 patients), and statins (23 patients) (Table 2).

There was also no statistically substantial variation in either group's age (p=0.460), sex (p=0.636), BMI (p=0.725), dialysis duration (p=0.179), or smoking status (p value=0.806). Group 1 had a higher MAP (p value<0.001) (Table 3).

Regarding laboratory parameters, URR and serum albumin did not significantly vary between the two groups (p values 0.757 and 0.626 respectively). Calcium and hemoglobin levels in group 1 were substantially lower (p values 0.016 and < 0.001, correspondingly), whereas group 2 had substantially greater levels of cholesterol (p < 0.001), triglyceride (p = 0.001), phosphorus (p = 0.001), parathyroid hormone (p = 0.001), and FGF-23 (p = 0.001) (Table 4).

cIMT was significantly higher in group 1 (p value = 0.001) (Table 5). Age and PTH were significantly and positively linked with FGF-23 in the study group (Table 6). There was a substantial positive link between cIMT and duration of dialysis, phosphorus, smoking and PTH but negative correlation with BMI (Table 7). For other measured parameters we found no statistically significant correlation. Multiple regression analysis of variables predicting cIMT showed that phosphorous level and duration of dialysis were the significant independent predictors for cIMT (Table 8)

TABLE 1: Possible causes of kidney disease in the study population

Cause of kidney disease	Group 1 [n (%)]	Group 2 [n (%)]
Hypertension	18(36%)	17 (34%)
Pyelonephritis	10 (20%)	11 (22%)
Glomerulonephritis	8 (18%)	7 (14%)
Obstructive uropathy	6 (12%)	7 (14%)
Unknown	8 (16%)	8 (16%)

TABLE 2: Relevant medications received by study group patients

Type of medication	Group 1 [n (%)]	Group 2 [n (%)]	Total
Calcium carbonate	38 (76%)	39 (78%)	77
Calcium acetate	2 (4%)	5 (10%)	7
Alfacalcidiol	31 (62%)	31 (62%)	62
Cinacalcit	10 (20%)	8 (16%)	18
Sevelamer	7 (14%)	5 (10%)	12
Statins	12 (24%)	11 (22%)	23

TABLE 3: Comparison of clinical and demographic characteristics between both groups.

		Groups		p value
		Group 1	Group 2	
Age (years)	Min.	20	32	0.460
	Max.	80	72	
	Mean (±SD)	46.84 ± 13.62	44.35 ± 13.85	
Sex [n(%)]	Male	33 (66%)	30 (60%)	0.636
	Female	17 (34%)	20 (16%)	
BMI (kg/m2)	Min.	18	21	0.725
	Max.	43	34	
	Mean (±SD)	28.32 ± 5.21	27.87 ± 3.58	

MAP (mmHg)	Min.	69.9	73	< 0.001*
	Max.	123	111	
	Mean (±SD)	94.50 ± 12.15	90.60 ± 5.92	
Dialysis duration (months)	Range	17.0 - 180.0	15.0 - 120.0	0.179
	Median (IQR)	48.0 (24.0-84.0)	36.0 (12.0 - 55.0)	
Smoking, n(%)		26 (54)	24 (48)	0.806
* statistically significant BMI: body mass index, MAP: mean arterial pressure, Max.: maximum, Min.: miniumum, n: number, SD: standard deviation.				

TABLE 4: Comparison of laboratory parameters between both groups.

		Groups		p value
		Group 1	Group 2	
URR (%)	Min.	0.65	0.65	0.757
	Max.	0.9	0.88	
	Mean (±SD)	0.7 ± 0.1	0.7 ± 0.2	
Serum albumin (gm/dl)	Min.	2.0	2.2	0.626
	Max.	3.8	4.5	
	Mean (±SD)	3.4 ± 0.4	3.4 ± 0.5	
Hemoglobin (gm/dl)	Min.	5.6	6.5	< 0.001*
	Max.	13.5	15.7	
	Mean (±SD)	9.2 ± 2.1	10.9 ± 3.0	
Serum cholesterol (mg/dl)	Min.	130.0	120.00	< 0.001*
	Max.	230.00	185.00	
	Mean (±SD)	187.90 ± 25.6614	164.80 ± 21.	
Serum triglyceride (mg/dl)	Min.	85	90	0.001*
	Max.	326	150	
	Mean (±SD)	187.3 ± 66.41	113 ± 25.73	
CRP (mg/dl)	Min.	2	2.1	0.521
	Max.	24	23.2	
	Mean (±SD)	12.25 ± 6.79	12.1 ± 6 .74	
Calcium (mg/dl)	Min.	5.70	9.10	0.016*
	Max.	11.58	11.00	
	Mean (±SD)	9.25 ± 1.29	9.99 ± 0.59	
Phosphorous (mg/dl)	Min.	2.90	3.50	0.001*
	Max.	6.30	4.50	
	Mean (±SD)	5.68 ± 0.7	3.90 ± 0.308	
PTH (pg/ml)	Min.	15.0	63.0	0.009*
	Max.	1720.0	815.0	
	Median (IQR)	589 (254.5 - 871.0)	238.5 (102.5- 380.0)	
FGF-23 (pg/ml)	Min.	413.2	123.13	0.001*
	Max.	968.9	435.11	
	Mean (±SD)	696.39 ± 139.85	281.83 ± 121.83	
* statistically significant Ca: calcium, FGF-23: fibroblast growth factor-23, PTH: parathyroid hormone, Max.: maximum, Min.: minimum, n: number, SD: standard deviation.				

TABLE 5: Comparison of cIMT between both groups.

cIMT (mm)	Groups		p value
	Group 1	Group 2	
Min.	1.1	0.6	0.001*
Max.	1.9	0.95	
Mean (±SD)	1.41 ± 0.23	0.77 ± 0.11	
Max.: maximum, Min.: minimum, n: number, SD: standard deviation.			

TABLE 6: Correlation of FGF-23 with various parameters in the study groups.

Parameter	FGF-23 (pg/ml)	
	r	p
Age	0.382	0.006*
Duration	0.074	0.609
BMI	0.261	0.067
MAP	0.128	0.393
URR	0.017	0.906
Albumin	- 0.048	0.746
Hb.	0.078	0.593
Cholesterol	0.194	0.178
CRP	0.410	0.499
Ca	0.188	0.191
P	0.096	0.506
PTH	0.315	0.026*
* statistically significant BMI: body mass index, Ca: calcium, Ca*P: Calcium*phosphorous product, CCA-IMT: common carotid artery intima-media thickness, FGF-23: fibroblast growth factor-23, Hb: hemoglobin, MAP: mean arterial pressure, PTH: parathyroid hormone.		

TABLE 7: Correlation of cIMT with various parameters in the study groups.

Parameter	cIMT (mm)	
	r	p
FGF-23 (pg/ml)	0.059	0.513
Age	0.105	0.469
Duration	0.977	0.001*
BMI	- 0.393	0.005*
MAP	0.101	0.501
URR	0.156	0.278
Albumin	0.041	0.784
Hb.	0.169	0.241
Cholesterol	0.166	0.248
CRP	0.086	0.596
Calcium	0.179	0.215
Phosphorous	0.328	0.020*
PTH	0.395	0.005*
Smoking, pack/year	0.312	0.005*
* statistically significant BMI: body mass index, Ca: calcium, Ca*P: Calcium*phosphorous product, cIMT: carotid intima-media thickness, FGF-23: fibroblast growth factor-23, Hb: hemoglobin, MAP: mean arterial pressure, PTH: parathyroid hormone,		

TABLE 8: Predictors of increased cIMT using multiple regression analysis.

	β	Significance
Age	0.914	0.369
Hemodialysis duration	2.191	0.037*
BMI	- 1.108	0.278
MAP	0.857	0.399
URR	1.058	0.289
Albumin	0.659	0.516
Hb.	1.517	0.141
Cholesterol	0.708	0.485
CRP	0.501	0.187
Ca	0.212	0.834
P	2.328	0.028*
PTH	0.595	0.557
FGF-23	0.535	0.597

* statistically significant
BMI: body mass index, Ca: calcium, Ca*P: Calcium*phosphorous product, CCA-IMT: common carotid artery intima-media thickness, FGF-23: fibroblast growth factor-23, Hb: hemoglobin, MAP: mean arterial pressure, PTH: parathyroid hormone

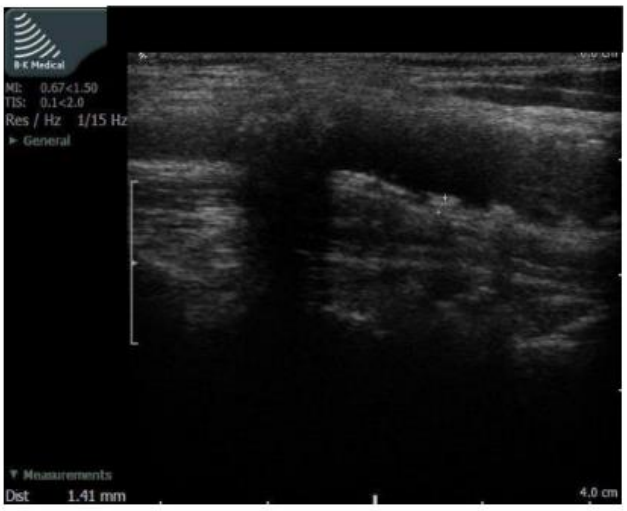

FIGURE 1: cIMT with increased thickness (1.4 mm)

DISCUSSION

An essential method for evaluating vascular atherosclerosis that represent the extent of arterial damage in other body parts is high-resolution carotid ultrasonography (14). In HD patients, presence of left ventricular hypertrophy (LVH) and elevated cIMT are related with an increasing risk of cardiovascular fatality (15). FGF-23 has been linked to LVH (16), cardiovascular and overall causes of mortality in CKD patients (17). In some studies, this association was independent of kidney function (18, 19).

The current study's goal was to determine if FGF-23 is related to elevated cIMT in HD patients. Study participants were classified into two groups; 50 patients in group 1 had cIMT ≥1 mm, while 50 patients in group 2 had cIMT less than 1 mm.

Many studies showed that FGF-23 levels increase with CKD progression (20, 21) and that levels are higher in patients on HD patients (7, 22) and those on peritoneal dialysis (23). According to Imanishi Y et al., HD patients had considerably greater levels of FGF-23 than CKD

patients and healthy participants had. Moreover, CKD patients' FGF-23 levels were greater than those of healthy participants. (7).

FGF-23 was considerably greater in group 1 in the current investigation (p = 0.001), whereas FGF-23 wasn't an important indicator of elevated cIMT. Balci M et al. found, in contrast to our investigation, that elevated FGF-23 levels were linked to carotid artery atherosclerosis in HD patients. Also, they found a strong association between cIMT and plasma levels of FGF-23 in their investigation (24).

On the reverse hand, another study found that FGF-23 level was an independently a negative predictor of peripheral but not aortic vascular calcification independent of serum phosphorous level (25). Higher FGF-23 tertiles were linked to lesser increase in IMT levels in a cross-sectional study of 196 individuals, and this connection remained after adjusting for phosphorus. (26). Variation in findings across studies may be related to study sample and variation in duration of HD as well as medications related to CKD-mineral bone disease (CKD-MBD) management.

The conflicting relationship between FGF-23 and cIMT was also evident in studies that included patients with CKD. In agreement with our results, according to Kaya B et al., levels of FGF-23 did not correlate with cIMT in CKD patients (27). However, Yilmaz G et al. discovered that level of FGF-23 was an independent indicator for IMT (28).

In this research, there was a substantial and positive correlation between FGF-23 with PTH and patient age. No significant correlation was found with serum phosphorous. In several investigations, patients with CKD were shown to have an inverse correlation between serum level of FGF23 and serum phosphorus (27, 29, 30). Similar findings were shown in patients on HD (16, 31), suggesting that phosphaturic effect of FGF23 still persists. Similar to our findings, Ashikaga E et al. found that FGF-23 level was correlated with age and PTH but in contrast to our findings, FGF-23 was correlated to phosphorous (26). Sliem et al. found that though FGF-23 was positively correlated to PTH, but neither age nor PTH were found to be independent predictors for FGF-23 (22).

In this research, cIMT had a negative correlation with BMI and a positive correlation with the duration of dialysis, PTH, and phosphorus. No statistically significant correlation was found with FGF-23, age, hemoglobin, albumin, CRP, total calcium, cholesterol or triglyceride. The negative correlation between cIMT and BMI in our study was an example of inverse biology in HD patients (32). The positive correlation between cIMT and duration of dialysis found in our study, was also reported by other studies (33, 34). Other studies also found a positive correlation of cIMT with serum phosphorous (24, 35, 36).

Diversity in study results may be related to variation of serum phosphorous level in different studies. Another explanation could be that variations in metabolism of phosphorus across time cannot be determined by a single test of blood phosphorus (37).

Our research has a number of limitations. This research examined a small cohort cross-sectionally. We used a single measurement of biomarkers and cIMT. A cause/effect relationship can't be concluded; only association data were presented.

CONCLUSIONS

FGF-23 was considerably greater in the patient group with higher cIMT, however on regression analysis, it wasn't an important indicator for increased cIMT. Phosphorous level and dialysis duration were the significant independent predictors for increased cIMT which was in a strong correlation with duration of dialysis, PTH and phosphorus and in a negative correlation with BMI. FGF-23 was strongly and positively associated to both PTH and age.

Ethical considerations

The Faculty of Medicine at Tanta University in Egypt's Research Ethics Committee gave its approval to the research.(approval code: 35925/10/22). All participants had s written informed consent before study inclusion.

Conflict of Interest

There was no conflicting interests. There was no particular funding for this study.

Author Contributions

The conception, design, analysis, and interpretation of the data were significantly influenced by the contributions of all authors. All agreed to submit the manuscript to the current journal after critically editing it or writing it. All agreed to be responsible for all aspects of the work.

Data Availability Statement

The study data will be made available by the corresponding author on reasonable request.

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