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Effect of Dialysis Modality and Membrane Permeability on FGF 23 Level and Cardiovascular Calcification in ESRD Patients.

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ABSTRACT

Background: End-stage renal disease (ESRD) is frequently accompanied by cardiovascular complications, in part due to elevated levels of fibroblast growth factor 23 (FGF-23) and vascular calcification. Hemodiafiltration (HDF), with its superior middle-molecule clearance, may offer advantages over conventional high-flux hemodialysis (HD) in reducing FGF-23 and cardiovascular risk.

Objective: To evaluate the effect of dialysis modality and membrane permeability on serum FGF-23 levels and cardiovascular calcification in ESRD patients.

Methods: This cross-sectional study included 50 ESRD patients on dialysis for ≥6 months, divided into two groups: 25 on high-flux HD and 25 on post-dilution online HDF. Pre- and post-dialysis FGF-23 levels were measured via ELISA. Cardiovascular calcification was assessed using echocardiography, carotid intima-media thickness (IMT), and carotid duplex ultrasonography.

Results: HDF patients demonstrated significantly lower pre- and post-dialysis FGF-23 levels and a greater reduction ratio ($p < 0.001$). While echocardiographic and carotid duplex scores showed no significant difference, carotid IMT was significantly reduced in the HDF group ($p = 0.035$). Post-dialysis FGF-23 positively correlated with IMT in HDF patients ($r = 0.579$, $p = 0.008$) and with calcium, phosphorus, PTH, and CRP in both groups.

Conclusions: Online HDF significantly reduces FGF-23 levels and carotid IMT compared to high-flux HD, suggesting a potential benefit in mitigating cardiovascular risk among ESRD patients.

KEYWORDS: FGF-23, ESRD, Hemodiafiltration, Hemodialysis, Cardiovascular Calcification, Intima-Media Thickness, Phosphate Metabolism.

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INTRODUCTION

End-stage renal disease (ESRD) represents the final stage of chronic kidney disease (CKD), where kidney function is severely compromised, requiring either dialysis or a kidney transplant to sustain life [1]. Patients with ESRD often experience a range of systemic complications, including disturbances in mineral and bone metabolism, chronic inflammation, and cardiovascular (CV) events. This heightened vulnerability stems from progressive vascular calcification, whose severity directly correlates with CV events and their associated mortality. Arterial calcification, along with its downstream results, such as ventricular hypertrophy and micro-embolic disease, plays a pivotal role in this dangerous cascade [2].

FGF-23, a 251-amino acid protein manufactured by bone cells, serves as the master regulator of phosphate balance in the body. It operates as an endocrine hormone, teaming up with α-klotho as its crucial partner. FGF-23 exerts its effect by blocking phosphate reabsorption in the kidneys, ultimately driving down phosphate levels. When this fine-tuned system goes awry, excessive FGF-23 unleashes havoc, triggering phosphate-wasting syndromes like autosomal recessive hypophosphatemic rickets, X-linked hypophosphatemic rickets, and fibrous dysplasia [3]. Our understanding of how FGF23 levels are controlled remains incomplete. While factors like high dietary phosphate, 1,25-dihydroxy vitamin D, and potentially parathyroid hormone (PTH) are identified to influence it, the precise mechanisms remain enigmatic. Emerging evidence suggests inflammation may also play a role in regulating FGF23 production, adding another layer of complexity to this intricate puzzle [4].

α-Klotho, a versatile co-receptor found in the kidney, choroid plexus, and parathyroid glands, is the key partner that unlocks FGF-

23's role in regulating phosphate (Pi) and calcium (Ca) levels. Without this crucial partner, the delicate balance is disrupted, leading to hyperphosphatemia (elevated Pi levels) in Klotho deficiency. The culprit? Uncontrolled calcitriol (vitamin D3 hormone) production, fueled by Klotho's absence. This surge in calcitriol boosts Pi reabsorption in the kidney and intestine, tipping the scales toward hyperphosphatemia [5].

A fascinating interplay emerges between inflammation and FGF23 levels. Diseases marked by both heightened inflammation and elevated FGF23, like CKD, offer compelling evidence. Independent studies further reveal a direct link, suggesting that inflammation might act as a potent trigger for FGF23 production [6]**.** Despite consistent evidence linking FGF-23 excess to poor outcomes in CKD, its precise role in driving the critical complication of vascular calcification remains elusive. Studies attempting to unravel this intricate relationship have presented a confusing tapestry of findings, demanding further investigation to untangle the true nature of this potentially crucial link [7].

Hemodiafiltration (HDF) combines diffusive and convective transport mechanisms to facilitate the elimination of both small- and middle-molecular-weight solutes from the blood, addressing limitations of conventional hemodialysis. Notably, online HDF procedures utilize the ultrapure dialysate to substitute the old fluid, eliminating the need for separate infusion solutions. Dialysis machines have been adapted to perform online HDF, incorporating comprehensive safety filters to ensure the quality and sterility of the ultrapure dialysate [8].

The study aimed to investigate the interplay between membrane permeability, hemodialysis modality, and FGF-23 levels, aiming to elucidate their combined influence on cardiovascular calcification.

METHODS

This cross-sectional investigation was carried out on 50 individuals aged >18 years, both sexes, with ESRD who were receiving prevalent haemodialysis for at least 6 months on the same modality before the time of study.

The study was done in the duration from June 2021 to September 2021 after approval from the Ethical Committee Ain Shams University Specialized Hospitals, Egypt (approval code: 335/2018). Participants were recruited from Ain Shams University Specialized Hospitals in Egypt and Qutor Central Hospital in Gharbia Governorate. An informed consent was obtained from all patients. I certify that this research complied with ethical standards, following the Helsinki Declaration (1975, revised in 2013) and relevant national regulations.

Exclusion criteria were those with severe infection within the past 3 months, actively diagnosed cancer, presence of acute or chronic inflammatory conditions, advanced or decompensated chronic liver disease and advanced or severe heart failure.

The study employed a two-group design: Group 1 (n=25): Received regular conventional hemodialysis for at least 6 months, using high-flux dialyzers (Platinum H, 1.8 m² surface area) on Fresenius 4008S or Gambro AK96 machines. 4 hours/session, 3 times/week. Group 2 (n=25): Underwent hemodiafiltration therapy >23 liters post-dilution substitution fluid/session, for at least 6 months, using high-flux dialyzers (Platinum H, 2.0 m² surface region) on Fresenius 5008S machines. Both groups kept the dialysate flow rate of 500 mL/min and blood flow rate of 300-350 mL/min. All dialyzers were made of polysulfone and sterilized via autoclave.

The two groups were matched for age, sex, dialysis vintage, and in the use of phosphate binders and vitamin D analogs.
All participants underwent interviews regarding their: ESRD cause, comorbidities, dialysis duration and vascular access type (e.g., fistula, graft, catheter).

Physical examination: Vital signs (blood pressure) and body weight were measured.

Blood Sampling: Timing: Pre-dialysis blood samples (5ml) were collected during the mid-week session. Collection method: Samples were drawn aseptically from the dialysis bloodline into tubes containing EDTA anticoagulant, clot activator, and serum separation gel. Centrifugation: separation the plasma and stored it at -80°C after centrifuging the tubes at 2000-3000 rpm for five minutes.

Laboratory Testing: Pre-dialysis: (Complete blood count (CBC) , C-reactive protein (CRP), Serum creatinine, blood urea nitrogen (BUN), sodium (Na), potassium (K), calcium, phosphate, parathyroid hormone (PTH), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and albumin.

Post-dialysis: BUN only.
FGF-23: pre-and post-dialysis FGF-23 levels were evaluated using commercial ELISA kits (Cat. No. E0059HU) to Find out the reduction ratio in each category Separate blood samples (5ml) were collected from the dialysis line into tubes with clot activator and serum separating gel, followed by centrifugation at 2000-3000 rpm for 20 minutes. Kits and samples were warmed to room temperature before use.

Kt/V was measured for all the patients before the Study.
All echocardiographic assessments in this study were performed by a single experienced radiologist with over 10 years of expertise in cardiovascular imaging.

Echocardiography and carotid duplex were done for all patients and following scores were used:
1- This study employs a semi-quantitative echocardiographic method to assess coronary artery calcification (CACS). Utilizing two-dimensional (2D) echo images, the extent of calcification is evaluated in four specific locations: aortic valve (AVC), mitral annulus (MAC), aortic root, and papillary muscles. Scoring criteria involve defining each area based on echo brightness and thickening, with each location graded on a scale of 0-3 (severest). The summed score, ranging from 0 to 8, provides an overall assessment of cardiac and aortic root calcification [9].

2-**Carotid intima-media thickness (IMT)** is typically measured using ultrasound. This technique involves analyzing a double-line pattern on the screen, which corresponds to the interface between the inner lining (lumen-intima) and the middle layer (media) of the carotid artery wall. Importantly, measurements obtained through this method closely match those derived from tissue samples (histological specimens). Thickening of the artery wall, as indicated by an increased IMT, is a key indicator of both atherosclerosis and vascular calcification [10]. Also**,** color Doppler ultrasound to assess calcification and stenosis levels in the carotid arteries. Narrowing of the internal carotid artery was quantified using the established NASCET formula, calculating the percentage reduction in blood flow diameter compared to the normal distal segment. Based on this calculation, carotid artery stenosis (CAS) was categorized into four severity levels: mild (<30% narrowing), moderate (30-69% narrowing), severe (70-99% narrowing), and complete occlusion (100% narrowing) [11].

Sample size:
The sample size calculation was done by G*Power 3.1.9.2 (Universitat Kiel, Germany). We performed a pilot study (five cases in each group), and we found that the mean (± SD) of FGF23 was 270 ± 109.54 pg/mL in group 1 and 176 ± 66.93 pg/mL in group 2. The sample size was based on the following considerations: 0.99 effect size, 95% confidence level, 90% power of the study, group ratio 1:1, and four cases were added to each group to overcome dropout. Therefore, we recruited 25 patients in each group.

Statistical Analysis:
Statistical analysis was done by SPSS v26 (IBM Inc., Chicago, IL, USA). Quantitative variables were presented as mean and standard deviation (SD) and compared between the two groups utilizing unpaired Student's t-test. Qualitative variables were presented as frequency and percentage and analyzed using the Chi-square or Fisher's exact test when appropriate. Pearson correlation was used to how the correlation between tow quantitative variables. A two-tailed P value < 0.05 was considered statistically significant.

RESULTS

Patient demographics and characteristics
Dialysis efficiency: Hemodiafiltration patients achieved significantly higher clearance per unit blood volume (Kt/V) than hemodialysis patients ($p < 0.012$), indicating more efficient removal of waste products while Both groups underwent dialysis for similar durations, suggesting no difference in treatment time required. Most laboratory results, which included hemoglobin, white blood cell count, platelets, blood urea nitrogen (BUN), calcium, phosphorus, parathyroid hormone (PTH), creatinine, and albumin, did not exhibit any significant differences. among the categories. However, CRP, inflammatory marker, was significantly lower in the hemodiafiltration category ($p < 0.032$). Pre-dialysis FGF-23 levels were significantly low in the hemodiafiltration category in comparison to the hemodialysis category, furthermore the FGF 23 reduction ratio is significantly high in the hemodiafiltration category in comparison to the hemodialysis category ($p = 0.015$, < 0.001 respectively). **Table 1, 2**
Although there were no significant differences in cardiac calcification assessed by echocardiography (ECHO score) or overall plaque burden in the carotid arteries (carotid duplex score), hemodialysis patients exhibited a significantly greater thickening of the inner and middle layers of the carotid artery walls (carotid intima-media thickness, IMT) compared to those on hemodiafiltration ($p = 0.035$). This suggests a potential increased risk of cardiovascular complications in hemodialysis patients despite similar levels of overall arterial plaque. **Table 3**

In hemodialysis (HD) and hemodiafiltration (HDF) patients, higher FGF-23 levels were significantly connected to thicker carotid artery walls (IMT) for HDF patients ($r=0.579$, $p=0.008$). This correlation wasn't seen in HD patients or for other measures like the heart ultrasound (ECHO score) or overall carotid artery plaque burden (carotid duplex score). Furthermore, both HD and HDF groups showed positive associations among post-treatment FGF-23 levels and: Serum calcium: stronger in HD ($r=0.659$, $p=0.002$) than HDF ($r=0.474$, $p=0.035$). Serum phosphorus: similar strength in both ($r=0.462$, $p=0.04$ for HD; $r=0.478$, $p=0.033$ for HDF). Parathyroid hormone (PTH): stronger in HDF ($r=0.547$, $p=0.013$) than HD ($r=0.485$, $p=0.03$). CRP: stronger in HDF ($r=0.707$, $p<0.001$) than HD ($r=0.646$, $p=0.002$). **Table 4.**

There was no correlation between carotid duplex score and IMT in group1 ($r=0.262$, $p=0.204$). There was a positive correlation carotid duplex score and IMT in group 2 ($r=0.592$, $p=0.001$) **(Table 5).**

Table 1: Patient's characteristics and demographic data and aetiology of ESRD between both groups

		Group 1 (n = 25)	Group 2(n = 25)	P value
Age (years)	**Mean ± SD**	50.44 ± 12.24	57.68 ± 13.99	0.057
	Range	25 - 80	22 - 72	
Sex	**Male**	14 (56.0%)	18 (72.0%)	0.239
	Female	11 (44.0%)	7 (28.0%)	
Weight (kg)	**Mean ± SD**	66.92 ± 8.74	67.90 ± 13.76	0.765
	Range	54 - 83	49 - 90	
Aetiology of ESRD	**DM**	5 (20%)	4 (16%)	0.785
	HTN	7 (28%)	7 (28%)	
	Obstructive uropathy	0 (0%)	2 (8%)	
	Analgesic abuse	2 (8%)	3 (12%)	
	ADPKD	3 (12%)	4 (16%)	
	Neurogenic bladder	2 (8%)	1 (4%)	
	Unknown	6 (24%)	4 (16%)	

Data is presented as Mean ± SD, (n = 25)

Table 2: Laboratory investigations , Kt/v and duration of dialysis between both groups

		Group 1 (n = 25)		Group 2 (n = 25)		P value
Kt/v	**Mean ± SD**	1.36 ± 0.06		1.42 ± 0.10		**0.012***
	Range	1.3 - 1.5		1.3 - 1.6		
Duration of dialysis (years)	**Mean ± SD**	5.80 ±3.25		5.12 ± 3.18		0.458
	Range	2 - 14		1 - 15		
		Mean	**±SD**	**Mean**	**±SD**	
Hemoglobin (gm/dL)		10.36	1.53	11.08	1.49	0.101
Serum BUN (mg/dl)		55.048	18.05	55.05	22.12	0.870
Serum Cr (mg/dL)		9.12	1.51	9.12	1.77	1.00
Serum Ca (mg/dL)		8.25	1.93	8.84	0.78	0.074
Serum PO4 (mg/dL)		5.58	2.06	5.32	1.52	0.652
PTH (pg/mL)		459.45	322.2	377.85	246.97	0.374
CRP (mg/L)		21.58	16.98	11.75	10.05	**0.032***
Serum Albumin (g/dL)		3.65	0.33	3.67	0.29	0.856
FGF23 (pg/mL)		**Group 1**		**Group 2**		**P value**
Pre	**Mean ± SD**	944±316.33		775.2±297.7		**0.015***
	Range	650 - 1750		350 - 1500		
Post	**Mean ± SD**	373.6±79.16		176.4±91.19		**<0.001***
	Range	250 - 500		100 - 500		
Reduction ratio (%)	**Mean ± SD**	58.28% ± 15.60%		79.98% ± 8.28%		**<0.001***
	Range	20.00% - 80.00%		54.55% - 89.57%		

Cr: creatinine, Ca: calcium, Po_4 phosphorus, CRP C reactive protein, FGF 23 fibroblast growth factor 23 *: significant as p value < 0.05.

Table 3: ECHO score, carotid duplex score (%) and carotid intima-media thickness between both groups.

		Group 1	Group 2	P value
ECHO score	**Mean ± SD**	2.6 ± 1.12	2.16 ± 1.7	0.285
	Median	3	2	
	Range	1 - 5	0 - 8	
Carotid duplex score (%)	**Mean ± SD**	6.07% ± 12.95%	3.89% ± 11.25%	0.529
	Median	0.00%	0.00%	
	Range	0.0% - 43.0%	0.0% - 44.0%	
Carotid intima-media thickness (mm)	**Mean ± SD**	0.89 ± 0.19	0.78 ± 0.18	**0.035***
	Median	0.9	0.8	
	Range	0.4 - 1.2	0.5 - 1.3	

*: significant as p value <0.05.

Table 4: Correlation between serum level of FGF23 post-dialysis and ECHO score, carotid intima-media thickness, carotid duplex score and (serum calcium, phosphorus and PTH) in the studied groups

	FGF post HD		FGF post HDF	
	Group 1		Group 2	
	r	P value	r	P value
ECHO score	0.505	0.158	0.043	0.856
Carotid intima-media thickness	0.201	0.395	0.579	**0.008***
Carotid duplex score	0.106	0.656	0.148	0.534
Serum Ca (mg/dL)	0.659	**0.002***	0.474	**0.035***
Serum Po4 (mg/dL)	0.462	**0.04***	0.478	**0.033***
PTH (pg/mL)	0.485	**0.03***	0.547	**0.013***
CRP (mg/L)	0.646	**0.002***	0.707	**<0.001***

Ca: calcium, po4: phosphorus, PTH: parathyroid hormone. CRP: C reatctive protein r: correlation coefficient, *: significant as P value ≤ 0.05.

Table 5: Correlation between IMT and carotid duplex score in the studied groups

	IMT		IMT	
	Group 1		Group 2	
	r	P value	r	P value
Carotid duplex score	0.262	0.204	0.592	**0.001***

IMT: Intima media thickness, r: correlation coefficient, *: significant as P value ≤ 0.05.

DISCUSSION

We assessed the effectiveness of different dialysis modalities in controlling FGF-23 levels by measuring pre- and post-dialysis FGF-23 in both hemodialysis and hemodiafiltration patients. Notably, pre-dialysis FGF-23 levels were significantly reduced in the hemodiafiltration category in comparison to the haemodialysis category. The percentage reduction in FGF-23 (reduction ratio) was significantly more elevated in the hemodiafiltration group compared to the hemodialysis group, highlighting the potentially superior ability of hemodiafiltration to remove this key mediator of cardiovascular complications in ESRD patients.

Several mechanistic pathways may underlie the association between elevated FGF-23 levels, inflammation, and vascular calcification in patients with ESRD. FGF-23, primarily secreted by osteocytes, is known to rise early in CKD and has been implicated in promoting left ventricular hypertrophy and endothelial dysfunction. Recent evidence suggests that FGF-23 may also play a pro-inflammatory role by stimulating hepatic production of inflammatory cytokines such as IL-6 and TNF-α via FGFR4-mediated pathways [12].

Chronic systemic inflammation, in turn, accelerates vascular smooth muscle cell transformation into osteoblast-like cells, promoting medial vascular calcification. Additionally, FGF-23 may indirectly contribute to calcification by modulating phosphate retention and impairing vitamin D metabolism, further disturbing mineral balance. These interconnected processes highlight the multifactorial nature of vascular damage in dialysis patients and suggest that FGF-23 is not only a biomarker but potentially a mediator of vascular pathology [13].

Donate-Correa et al. [14] linked the calcification of the vascular tissue with the expression of FGF23 in the vessels and with the elevation of circulating levels this hormone.

Dohuim et al. [15] revealed that there was a significant correlation linking circulating FGF23 and serum aldosterone levels among CKD cases, suggesting their potential as independent predictors of CKD progression. Both circulating FGF23 level was considerably elevated in CKD cases in comparison with normal controls, highlighting their predictive performance.

In agreement with our results, Bouma-de Krijger et al. [16] compared the effectiveness of online HDF and low-flux HD in controlling mortality and cardiovascular events in ESRD patients and found that FGF-23 levels significantly lowered over time in the HDF group due to its superior clearance capacity, while remaining stable in the HD group. Also, revealed that the median FGF-23 was in HDF group is significantly lower [3691 RU/mL (IQR 1826–12 293)] than in HD group [4983 RU/mL (IQR 1815–12 265)].

Choo et al. [17] compared two dialysis regimens (8-hour hemodialysis vs. 4-hour hemodiafiltration) in stable HD patients and showed that better clearance of small molecules like urea and creatinine, hemodiafiltration was more effective in removing FGF-23, a key player in cardiovascular health, by a statistically significant margin at 8-hour hemodialysis.

Contrasting our findings, Kim et al. [18] carried out a small observational investigation comparing the efficacy of different dialysis modalities in six stable HD patients. Using a single midweek treatment for each of three modalities (MCO HD, High-flux HD, and pre-dilution OL-HDF), and observed no significant differences in FGF-23 reduction ratios (55.5%, 34.6%, and 35.8% respectively). This discrepancy underlines the need for further research to elucidate the factors influencing FGF-23 removal by distinct dialysis strategies.

In our study, while overall heart calcification assessed by echocardiography (ECHO score) and plaque burden in the carotid arteries (carotid duplex score) were not significantly different among HD and HDF groups, the carotid intima-media thickness, (IMT) was significantly greater in the HD category in comparison to the HDF category. This suggests that although HD and HDF patients may have similar levels of overall arterial calcification and plaque, HD patients might have an elevated risk of specific cardiovascular complications because of thicker carotid artery walls.

The discrepancy between the significant increase in carotid IMT and the non-significant echocardiographic and duplex calcification scores may be attributed to differences in sensitivity, anatomical focus, and the nature of vascular changes assessed by each modality. IMT primarily reflects early atherosclerotic changes and structural arterial remodeling, making it a sensitive marker of subclinical vascular damage. In contrast, echocardiographic and duplex scoring systems often detect more advanced or localized calcific lesions, which may not yet be prominent in all patients. Additionally, IMT measurements are quantitative and less operator-dependent, whereas calcification scores from echocardiography are semi-quantitative and influenced by image quality and interpretation. These differences highlight the need for multimodal vascular assessment in patients with ESRD to capture the full spectrum of vascular pathology [19].

Supporting our results, Hao et al. [3] observed a statistically significant difference in AAC score increase in the first year favouring hemodiafiltration (0.79 vs. 0.44 in HDF and HD groups, respectively). This suggests that while hemodiafiltration might offer initial advantages in limiting AAC, long-term outcomes might be similar for both modalities.

Mirroring our findings, Pradeep et al. [20] revealed a statistically significant positive correlation among FGF-23 levels and CIMT, indicating that higher FGF-23 levels were associated with thicker arterial walls.

Offering a contrasting perspective to our findings, Lee et al. [21] observed no significant differences in echocardiographic measures like left ventricular function over a year, their results diverged from ours in terms of CAC. Notably, CAC scores remained stable in the HDF group, whereas HD patients exhibited a trend towards increasing CAC scores.

Our study revealed that both HDF and regular HD exhibited positive correlations between post-treatment FGF-23 levels and various blood markers, including calcium, phosphorus, PTH, and CRP. These findings suggest potential links between FGF-23 and various biological processes relevant to cardiovascular health in dialysis patients.

Supporting our findings, Tashiro et al. [2] observed significant correlations among FGF-23 levels and serum calcium, phosphorus, PTH, and magnesium. Notably, the results did not show any significant correlations among FGF-23 and markers of cardiovascular health, including arteriosclerosis score, heart function by echocardiography, blood pressure, carotid artery health by ultrasound, and survival prognosis.

Zeng et al. [22] revealed that serum FGF23 showed a positive correlation among blood calcium levels, blood phosphorus levels, and PTH levels in hemodialysis patients, and FGF23 levels in HD patients.

Our study revealed a statistically significant difference in CRP levels between the hemodiafiltration and hemodialysis groups. Notably, CRP levels were significantly decrease in the category that underwent hemodiafiltration in contrast to the category that underwent hemodialysis.

Supporting our findings, Mady et al. [23] observed a statistically significant difference in CRP levels among the 2 categories. Notably, diseased people receiving HDF had lower mean CRP levels (63.5 ± 40.9 mg/dL) compared to those on HD (73.4 ± 33.2 mg/dL).

Although our findings revealed a positive correlation between FGF-23 levels and both CRP and PTH, these results should be interpreted with caution. The association between FGF-23 and CRP may reflect the role of chronic inflammation in promoting FGF-23 expression, as inflammation has been shown to upregulate FGF-23 production in osteocytes. Similarly, the correlation between FGF-23 and PTH may be attributed to their interlinked roles in mineral metabolism, where disturbances in phosphate and vitamin D homeostasis—common in ESRD—can lead to parallel elevations in both hormones. However, due to the cross-sectional nature of the study, we cannot determine the directionality or causality of these relationships. Longitudinal and mechanistic studies are warranted to explore whether FGF-23 actively contributes to inflammatory processes or is merely a consequence of the altered mineral and inflammatory milieu in dialysis patients.

LIMITATIONS

This study has several limitations that should be acknowledged. First, its cross-sectional design prevents the establishment of causal relationships between FGF-23 levels and vascular calcification outcomes. Second, the relatively small sample size may limit the statistical power and generalizability of the findings. Third, there was no inclusion of a healthy or non-dialysis control group for comparison. Fourth, long-term follow-up data were not available, preventing assessment of progression over time. Additionally, we did not analyze correlations between FGF-23 and key biomarkers such as PTH, calcium, phosphorus, and CRP, which could have provided further insights into the interplay between mineral metabolism and inflammation. Moreover, potential confounders such as the use of phosphate binders, vitamin D analogs, dialysate calcium concentration, dialysis adequacy, and other treatment-related variables were not fully accounted for.

We recommend that future studies adopt longitudinal designs with larger, randomized cohorts, include appropriate control groups, and comprehensively evaluate both dialysis-related parameters and broader biomarker profiles to clarify the mechanistic links between FGF-23, inflammation, and cardiovascular.

CONCLUSIONS

The implementation of online HDF led to a statistically significant decrease in FGF-23 levels and an improvement in the calcification score of the carotid intima-media thickness, which is indicative of prospective cardiovascular benefits.

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