Int Urol Nephrol
DOI 10.1007/s11255-013-0422-2

NEPHROLOGY-ORIGINAL PAPER

FGF-23, vascular calcification, and cardiovascular diseases in chronic hemodialysis patients

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Received: 25 February 2013 / Accepted: 15 March 2013

Introduction Chronic hemodialysis (HD) patients have bad prognosis and cardiovascular diseases (CVD) represent their main threatening complication. Fibroblast growth factor (FGF-23) has been associated with all kinds of evil consequences, including cardiovascular morbidity, but some studies demonstrated the contrary. Therefore, it is important to know whether FGF-23 is associated with cardiovascular risk or protection. The purpose of this study was to assess the links between FGF-23 and intimal vascular calcification (VC) and with the presence of CVD in chronic HD patients.

Patients and methods This study was carried out on a cohort of randomly selected 88 prevalent HD patients. We recorded demographical, clinical, and biochemical data, including FGF-23. VC was evaluated on carotid ultrasound. CVD were registered.

Results The mean age was 59.68 ± 14.49 years, HD vintage was 59.61 ± 52.39 months, and 20 patients were diabetic (22.72 %). VC was present in 54 patients (61.4 %) and 25 patients (28.4 %) had CVD. FGF-23 correlated positively with HD vintage ($r = 0.37$; $p < 0.001$) and iPTH ($r = 0.21$; $p = 0.048$). FGF-23 did not correlate with VC score. Patients with CVD were older ($p = 0.006$), had lower FGF-23 ($p = 0.008$), higher VC score ($p = 0.009$), lower Hb ($p = 0.008$), albumin ($p = 0.003$), and creatinine ($p = 0.03$). Low FGF-23 was identified as a risk factor for CVD.

Conclusion We report on a novel association between low FGF23 and CVD in chronic HD patients and a lack of correlation of FGF-23 with VC. FGF-23 could play a role in cardiovascular protection that remains to be confirmed in larger studies.

Keywords Fibroblast growth factor 23 · Chronic hemodialysis · Vascular calcification · Cardiovascular diseases

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Introduction

In spite of increasing research and care for end-stage renal disease patients, their mortality is still very high, exceeding 20 % per year [1]. The main cause of mortality is the cardiovascular diseases (CVD) which

Published online: 03 April 2013

was often associated with vascular calcification (VC) [2]. VC is highly prevalent in chronic dialysis patients as we have reported already [3]. Mineral and bone disorders frequently contribute to accelerated VC and CVD, and we have demonstrated that medial VC represents a consequence of increased intact parathyroid hormone levels (iPTH) [3]. Calcification of the media of the arteries and intimal calcification which affects the advanced atherosclerotic plaques can be distinguished and this may be important in view of their different clinical consequences [4]. From a prognostic point of view, the distinction between intima and media calcification appears to be useful as well. London et al. [5] have shown that maintenance hemodialysis (HD) patients with predominant intima calcification have a higher relative risk of mortality than those with predominant media calcification, whose relative risk in turn is much greater than in those with no calcification. Therefore, the study of factors affecting intimal VC is important as well.

Fibroblast growth factor 23 (FGF-23) is a novel discovered biomarker which increases renal phosphate excretion and decreases circulating 1,25-dihydroxyvitamin D concentrations. In recent years, there has been an increasing awareness of the regulatory role of FGF-23 in mineral metabolism [6] and its particular prominence in patients with chronic kidney disease (CKD). FGF-23 is a hormone secreted by osteocytes and osteoblasts and achieves target cell specificity through binding to FGF receptor–Klotho complexes. Some studies support that this bone-derived hormone is linked to early changes in vascular function, arterial stiffness, endothelial dysfunction [7], higher atherosclerosis score [8], predisposing to an increased cardiovascular risk [9] or to peripheral vascular calcification and coronary artery calcification score [10, 11]. Our previous work indicated also close pathogenetic links between bone disease and medial VC in chronic HD patients [12].

Emerging data suggest a potential of FGF-23 to identify CKD patients at high risk for cardiovascular disease and death [13–16] and those who might benefit from early phosphorus-related therapies, such as phosphate binders, active vitamin D, and cinacalcet [17, 18]. On the contrary, animal studies demonstrated that FGF-23 null mice develop VC and FGF-23 is protective against VC [19]. Also, there are clinical studies that have demonstrated the lack of any correlation between FGF-23 and VC [20]. Since alterations in mineral metabolism are associated with increased cardiovascular morbidity and mortality in CKD [10, 15], it is important to know whether FGF-23 is directly associated with cardiovascular risk or protection. In overall actual medical research literature, also, more evidence is required to clarify these issues.

The purpose of this study was to test the links between FGF-23 and intimal atherosclerotic plaques calcifications and between FGF-23 and the presence of cardiovascular diseases in chronic hemodialysis patients. We intended also to detect other risk factors for cardiovascular diseases in hemodialysis patients.

Patients and methods

This study was cross-sectional; it was carried out on a cohort of randomly selected HD patients treated in Nefromed Dialysis Center Cluj-Napoca. Among the overall HD population of 190 patients, 88 were recruited. Eligibility criteria: patients prevalent in dialysis, age >18 years, patients from the morning shift, acceptance to the study protocol. Exclusion criteria: life expectancy less than 6 months, parathyroidectomy, previous renal transplant. We recorded data regarding demographical and clinical characteristics (age, gender, HD vintage, presence of diabetes, dialysate calcium (Ca), HD prescription, treatments with phosphates (P) binders and vitamin D derivates; medical history, cardiovascular diseases). A panel of markers was measured: serum calcium (Ca), inorganic phosphorus (P), alkaline phosphatase (ALP), intact parathyroid hormone (iPTH—Roche second-generation assay), urea, albumin, and C-reactive protein (CRP); fibroblast growth factor 23 (Human FGF-23; ELISA; Uscn Life Science Inc., Wuhan, China). Blood samples for the biochemical evaluation were drawn prior to the HD session. Laboratory tests were performed in a central laboratory. All the samples were taken before a midweek session in the same week of the echographical study. Hemodialysis adequacy was assessed using the clearance of urea (spKt/V) and urea reduction ratio (URR). These were calculated using the next formulas: spKt/V $= 2.4*(1-$urea post-HD/urea preHD$)-0.276$ and URR $= (1-$urea post-HD/urea preHD$) * 100$.

Carotid vascular calcifications were evaluated on ultrasound, using the LogicScan 64 digital portable

ultrasound machine (Telemed, Lithuania) with a 5–10 MHz linear transducer. The ultrasound examiner was blinded to the clinical and laboratory data. We examined three segments of the arteries (bilateral): common carotid artery (1 cm proximal to the carotid bifurcation), bifurcation (1–2 cm), and internal carotid artery (1 cm distal to the bifurcation). The blood vessels were studied using real-time and color Doppler sonography through longitudinal and transversal sections. The intra-observer reproducibility of this assessment was assured using 2 consecutive ultrasound exams; in case of discordance, a third examination was performed in order to settle the right result. The VC was considered to be calcified atheroma plaques, represented by hyperechoic images with posterior shadows in the arterial walls. The VC's presence was recorded. Among patients with VC, a VC score was counted ranging from 0 (no calcification) to 6 (calcification of all artery sites examined from both sides).

Cardiovascular diseases (CVD) were defined by ischemic heart disease (acute myocardial infarction, angor pectoris, and positive coronarography), heart failure, stroke, heart failure, arrhythmia, aortic aneurysm, and peripheral artery disease. The CVD diagnosis was established by a specialist (cardiologist, neurologist) and the consultation's document was attached to each patient's chart.

Statistics

For continuous factors, data were expressed as mean ± standard deviation (SD) if variables had normal distribution and as median (interquartile range) if the distribution was not normal. Data were expressed as frequencies for qualitative variables. For continuous variables, the statistical comparison was performed using *t* test or Mann–Whitney Rank Sum Test. Chi square or Fisher exact test evaluated the relation between qualitative variables. The Kolmogorov–Smirnov test was employed for the continuous variables to compare the observed cumulative distribution function with the normal distribution. Parametric (Pearson) and nonparametric (Spearman) correlations were determined. Multivariable regression, stepwise method, and logistic models were performed to examine the relationship between the CVD/VC with FGF-23 and clinical and biochemical parameters. A p value <0.05 was taken as statistically significant. All statistical analyses were performed using SPSS 13.0 statistics packages.

Ethical issues: All patients gave their informed consent. Their privacy was respected. The study protocol was approved by the University Ethics Committee.

Results

The overall HD population in Nefromed Dialysis Center consisted in 190 HD patients. Among them, 19.12 % had diabetes. Eighty-eight patients entered in the study, 45 were males (51.13 %) and 20 patients were diabetic (22.72 %). The mean age was 59.68 ± 14.49 years, ranging from 20 to 87 years. They had been on HD for between 3 and 253 months, with a mean of 59.61 ± 52.39 months (Table 1). They achieved mean spKt/V of 1.53 ± 0.28, being on a standard hemodialysis schedule of 3 × 4 h/week.

Table 1 Demographical, clinical and biochemical parameters of the total study population

Parameter	All 88 patients
Age (years)	61 (53–71.75)
HD vintage (months)	48 (29–65.5)
Male gender (%)	51.13
DM (%)	22.72
FGF-23 (pg/ml)	43.5 (23.1–72.7)
VC score	2 (0–5)
URR (%)	75.96 (69.54–80.16)
spKt/V	1.54 (1.39–1.64)
Bicarbonate (mEq/l)	23.45 ± 3.12
Calcium (mg/dl)	9.06 (8.68–9.46)
Phosphate (mg/dl)	4.44 ± 1.31
iPTH (pg/ml)	267.6 (149.8–552.1)
ALP (UI/l)	75.96 (56.09–100.97)
Hb (g/dl)	11.32 ± 1.4
Ferritin (ng/ml)	564.04 (334.62–807.88)
CRP (mg/dl)	0.66 (0.30–1.36)
Albumin (g/dl)	3.86 (3.62–4.04)
Creatinine (mg/dl)	8.43 ± 2.24

HD hemodialysis, *DM* diabetes mellitus, *FGF-23* fibroblast growth factor 23, *VC score* vascular calcification score, *URR* urea reduction ratio, *spKt/V* urea clearance, *iPTH* parathyroid hormone, *ALP* alkaline phosphatase, *Hb* hemoglobin, *CRP* C-reactive protein

Dialisate Ca had a concentration of 1.25 mmol/l in 31 patients (35.2 %), 1.5 mmol/l in 45 patients (51.1 %), and 1.75 mmol/l in 12 patients (13.6 %). Regarding treatments for mineral metabolism, 47 patients received calcium-based phosphates binders (53.4 %), 20 patients received sevelamer hydrochloride (22.7 %) and 20 patients received vitamin D compounds (22.7 %). Twenty-five patients (28.4 %) had CVD. Hypertension was diagnosed and treated in 63 patients (71.6 %). Carotidal VC was present in 54 patients (61.4 %). Serum FGF-23 levels ranged from 7.6 to 290.8 pg/ml.

FGF-23 correlated positively with HD vintage ($r = 0.37$; $p < 0.001$) and iPTH ($r = 0.21$; $p = 0.048$). FGF-23 did not correlate with the severity of VC score ($r = -0.06$; $p = 0.57$) or serum *P* levels ($r = -0.10$; $p = 0.37$). VC scores correlated positively with age ($r = 0.50$; $p < 0.001$) and negatively with albumin ($r = -0.21$; $p = 0.05$).

A comparison between the patients with and without CVD was performed. Serum FGF-23 levels were significantly lower in the group of HD patients with CVD ($p = 0.008$).

Patients with CVD were older ($p = 0.006$), had significantly more calcified plaques (higher mean VC score) ($p = 0.009$), and were more anemic (lower Hb) ($p = 0.008$). The patients with CVD were more affected by protein malnutrition (had lower albumin ($p = 0.003$) and creatinine levels ($p = 0.03$)). The number of diabetics was significantly higher in the group with CVD (Table 2). The HD efficacy was not different between the two studied groups.

All the studied parameters were introduced in logistic regression stepwise method for CVD: age, FGF-23, and albumin entered in the equation. The enter method introduced in logistic regression only factors significant on univariate analysis and important factors for CVD; it found only FGF-23 as significant predictor for CVD (Table 3).

We also compared the characteristics of patients with VC (VC score > 0) and those without VC (VC score $= 0$). The patients with VC had significantly increased age, HD vintage, and creatinine and lower ALP (Table 4). It was a trend for a higher FGF-23 in VC group versus the group without VC ($p = 0.05$). In the multiple regression models, stepwise method considered VC as dependent variable and all the other studied parameters as independent variables. Age, HD vintage, and serum creatinine were found to be significant predictors for VC's presence. We also used the enter method for logistic regression; only age remained predictive for the development of VC (Table 5).

Discussion

In the current study, we for the first time report an association between low circulating FGF-23 and the presence of cardiovascular diseases in chronic HD patients. Therefore, increased serum FGF-23 levels could be a protective factor against CVD development. Some authors proposed the FGF-23 measurement in CKD as it could predict faster progression of renal disease in CKD patients [21]. Indeed, a positive relationship between FGF-23 and cardiovascular risk and mortality in HD patients and across the spectrum of CKD has been the result for some studies [22–25]. But this view over the data may not be reliable regarding FGF-23, because it has been discovered as a protection factor against vascular damage. Animal studies demonstrated that FGF-23 null mice display extensive VC and these results support the idea of VC inhibition properties of FGF-23 [19, 26]. Consistent with our study and in contrast with the above-mentioned clinical studies, Ashikaga et al. [27] indicated that FGF-23 was a negative predictor of an increase in carotid intima-media thickness, as marker of atherosclerosis. The FGF-23 level was also an independent negative predictor of peripheral VC, but not aortic medial VC, and FGF-23 behavior was independent of serum phosphate (P) levels, leading to conclusion that FGF-23 had a protective effect on VC [28]. In a cohort of men without CKD, plasma FGF-23, and incident coronary heart disease had not been associated [29] and some authors demonstrated that FGF-23 is not associated with mortality in HD patients, only if they selected a special subgroup [30]. Interestingly, in the study of Gutierrez et al. [7], the association between FGF-23 and cardiovascular pathology (assessed by left ventricular hypertrophy and left ventricular mass index as surrogate markers) lost its significance after multivariable adjustment. Genetically modified animal models have provided valuable insights into the role of FGF-23 in health and disease. Interestingly, FGF-$23^{-/-}$ mice develop a widespread phenotype resembling human premature aging, including muscle wasting, infertility, atrophy of

Table 2 Comparison of clinical and biochemical profiles of hemodialysis patients with and without cardiovascular diseases

Parameter	No CVD (63 pts)	CVD (25 pts)	*p*
Age (years)	58 (49–70)	65 (60–74)	**0.006**
HD vintage (months)	50 (29–80)	39 (27.5–55)	0.13
Male gender (%)	34 pts (53.9 %)	11 pts (44 %)	0.48
DM (%)	11 pts (17.46 %)	9 pts (36 %)	**<0.001**
HTA (%)	48 pts (76.2 %)	15 pts (60 %)	0.10
FGF-23 (pg/ml)	47.2 (26.1–94.9)	30.1 (15.05–45.5)	**0.008**
VC (%)	36 pts (57.1 %)	18 pts (72 %)	0.14
VC score	2 (0–4)	4 (0–6)	**0.009**
URR	76.88 (69.84–81.03)	71.56 (67.04–78.19)	0.36
spKt/V	1.56 (1.40–1.66)	1.44 (1.33–1.60)	0.36
Bicarbonate (mEq/l)	23.1 ± 3.27	24.31 ± 2.55	0.10
Calcium (mg/dl)	9.17 (8.76–9.54)	8.03 (8.52–9.40)	0.21
Phosphate (mg/dl)	4.55 ± 1.32	4.18 ± 1.26	0.23
iPTH (pg/ml)	279.3 (149.8–564.5)	192.1 (109.97–494.57)	0.21
ALP (UI/l)	75.8 (56.07–99.56)	76.13 (56.07–113)	0.54
Hb (g/dl)	11.57 ± 1.39	10.70 ± 1.25	**0.008**
Ferritin (ng/ml)	569.9 (319.24–816.89)	498.51 (359.04–780.77)	0.77
CRP (mg/dl)	0.63 (0.25–1.33)	0.77 (0.35–2.64)	0.39
Albumin (g/dl)	3.89 (3.69–4.07)	3.75 (3.36–3.94)	**0.003**
Creatinine (mg/dl)	8.75 ± 2.36	7.64 ± 1.69	**0.03**
Ca-based P binders use (%)	32 pts (50.8 %)	15 pts (60 %)	0.29
Sevelamer use (%)	16 pts (25.4 %)	4 pts (16 %)	0.25
Vitamin D use (%)	14 pts (22.22 %)	6 pts (24 %)	0.85

HD hemodialysis, *DM* diabetes mellitus, *HTA* hypertension, *FGF-23* fibroblast growth factor 23, *VC* vascular calcification, *URR* urea reduction ratio, *spKt/V* urea clearance, *iPTH* parathyroid hormone, *ALP* alkaline phosphatase, *Hb* hemoglobin, *CRP* C-reactive protein, *Ca* calcium, *P* phosphate

Table 3 Multiple regression analysis of factors associated with the presence of cardiovascular diseases in chronic hemodialysis patients

Independent variable	*p*	OR	95.0 % CI for OR	
			Lower	Upper
Age	0.10	1.05	0.99	1.11
Gender	0.48	1.63	0.42	6.25
HD vintage	0.34	1.01	0.99	1.03
DM	0.05	0.25	0.06	0.99
FGF-23	0.02	0.97	0.94	1.00
VC score	0.20	1.20	0.90	1.60
Hb	0.06	0.51	0.26	1.02
Albumin	0.35	0.35	0.04	3.26
Creatinine	0.64	0.92	0.64	1.32

HD hemodialysis, *DM* diabetes mellitus, *FGF-23* fibroblast growth factor 23, *VC* vascular calcification, *Hb* hemoglobin

multiple organ systems, pulmonary emphysema, osteoporosis, atherosclerosis, extensive soft tissue calcifications, and a severely shortened lifespan [19]. Genetic restoration of the systemic actions of human FGF-23 in FGF-23-knockout mice reverses hyperphosphatemia to hypophosphatemia and prevents aging associated complications, including cardiovascular diseases [31].

Hyperphosphatemia increases death risk in HD patients [1], and usually, FGF-23 and serum P display a positive relationship in CKD [21]. FGF-23 decreases serum P, and lower P levels are inevitably linked to a reduction in cardiovascular risk in HD patients. Therefore, higher FGF-23 should decline the cardiovascular risk. In spite of the fact that, in our study, FGF-23 did not correlate with serum P levels, high FGF-23 was associated with lower rate of CVD. It is

Table 4 Comparison of clinical and biochemical profiles of chronic hemodialysis patients with and without carotid vascular calcifications

Parameter	No VC (34 pts)	VC (54 pts)	*p*
Age (years)	54 (38.75–60)	65 (58.75–73)	**0.01**
HD vintage (months)	36.5 (13.75–60.05)	50 (36–78.75)	**0.04**
Male gender (%)	18 pts (52.94 %)	27 pts (50 %)	0.48
DM (%)	7 pts (20.58 %)	13 pts (24.07 %)	0.70
HTA (%)	22 pts (64.70 %)	41 pts (75.92 %)	0.25
FGF-23 (pg/ml)	41.1 (18.5–64.52)	43.8 (22.97–80.42)	**0.05**
URR	76.33 (70.31–81.86)	74.19 (68.38–79.71)	0.57
spKt/V	1.55 (1.41–1.68)	1.50 (1.36–1.63)	0.57
Bicarbonate (mEq/l)	23.41 ± 3.68	23.46 ± 2.74	0.93
Calcium (mg/dl)	9.08 (8.59–9.48)	9.06 (8.75–9.47)	0.83
Phosphate (mg/dl)	4.42 ± 1.38	4.44 ± 1.27	0.94
iPTH (pg/ml)	215.2 (140.57–608.82)	286.8 (154.1–541.45)	0.65
ALP (UI/l)	69.51 (45.29–97.12)	77.98 (63.69–110.47)	**0.003**
Hb (g/dl)	10.98 ± 1.51	11.53 ± 1.29	0.27
Ferritin (ng/ml)	542.56 (307.74–824.97)	564 (371.1–794.48)	0.88
CRP (mg/dl)	1.57 (0.18–1.29)	0.68 (0.30–1.40)	0.17
Albumin (g/dl)	3.95 (3.73–4.07)	3.79 (3.61–3.97)	0.24
Creatinine (mg/dl)	8.29 ± 2.72	8.45 ± 1.90	**0.01**
Ca-based P binders use (%)	16 pts (47 %)	31 pts (54 %)	0.34
Sevelamer use (%)	8 pts (23.50 %)	12 pts (22.22 %)	0.88
Vitamin D use (%)	6 pts (17.64 %)	14 pts (25.92 %)	0.36

HD hemodialysis, *DM* diabetes mellitus, *HTA* hypertension, *FGF-23* fibroblast growth factor 23, *VC* vascular calcification, *URR* urea reduction ratio, *spKt/V* urea clearance, *iPTH* parathyroid hormone, *ALP* alkaline phosphatase, *Hb* hemoglobin, *CRP* C-reactive protein, *Ca* calcium, *P* phosphate

Table 5 Multiple regression analysis of factors associated with the presence of carotid vascular calcifications in chronic hemodialysis patients

Independent variable	*p*	OR	95.0 % CI for OR	
			Lower	Upper
Age	<0.0001	1.21	1.11	1.32
HD vintage	0.07	1.02	1.00	1.04
DM	0.65	0.67	0.12	3.86
FGF-23	0.31	1.01	0.99	1.02
Creatinine	0.13	1.32	0.92	1.90
ALP	1.00	1.00	0.99	1.01
URR	0.16	0.96	0.90	1.02
Calcium	0.83	0.88	0.28	2.75
Phosphate	0.50	1.21	0.69	2.14
iPTH	0.46	1.00	1.00	1.00

HD hemodialysis, *DM* diabetes mellitus, *FGF-23* fibroblast growth factor 23, *ALP* alkaline phosphatase, *URR* urea reduction ratio, *iPTH* parathyroid hormone

noteworthy a very recent paper by Shalhoub et al. [32]. In order to reduce PTH, monoclonal antibodies against FGF-23 were administered to a rat model. The authors reported that mortality increased with decreasing FGF-23. This study illustrates the danger in leaping from epidemiologic studies that associate elevated FGF-23 with adverse consequences to thinking that if we reduce these levels, we will improve possible consequences [33].

In our study, the patients with CVD were older, with more extended VC. They were significantly more affected by protein malnutrition and anemia. Advanced age and low albumin were recognized as additional risk factors for CVD.

FGF-23 correlated positively with iPTH; similar evidence has derived from Nakanishi et al. [34, 35] who reported that FGF-23 is a predictor of secondary hyperparathyroidism.

Current evidence on the association of FGF-23 with VC is mixed; some studies demonstrated a positive and independent association with aortic [11], peripheral [10] or coronary calcification in HD patients [36]. Other studies reported negative correlations. Tamei et al. [37] had studied the relation of FGF-23 with the progression of VC; they demonstrated that FGF-23 level in repressors was significantly higher than in non-progressors and progressors. Inaba et al. [28] showed that FGF-23 is linked to peripheral VC in prevalent HD patients. But, in our study, FGF-23 was significantly higher with increasing HD vintage; VC score increased with age. Our study failed to demonstrate any correlation between FGF-23 and the severity of VC (VC score). Similar results had Roos et al. [20], reporting that FGF-23 did not correlate with coronary artery calcification in patients with normal renal function. Testing the relationship between FGF-23 and aortic calcification, Kojima et al. [38] also demonstrated a lack of significance.

FGF-23 was higher in the group of patients with VC than those without VC, but this association became non-significant after multivariable adjustment. Increasing age was found as risk factor for VC in the present study, in conformity with others [10].

At the present time, the exact mechanisms of FGF-23 influence on VC and CVD development remains uncertain. Additional studies are warranted to evaluate whether low FGF-23 can predict bad cardiovascular outcomes, and whether it is a modifiable risk factor. There were a few limitations of our study, such as its observational and its cross-sectional nature. Our analysis was limited by the study population and the subjective manner of ultrasound examination.

In conclusion, we report on a novel association between low FGF-23 and CVD in chronic HD patients. To our knowledge, only few investigations have explored the relationship between FGF-23 and the presence of CVD in the HD patients. The use of FGF-23 as a clinical marker or for predicting cardiovascular outcomes has to be established subsequently. It remains to be determined whether FGF-23 plays a direct role in cardiovascular protection, or whether FGF-23 intervenes in atherosclerotic complications indirectly through regulation of mineral metabolism.

Acknowledgments We thank the medical staff of Nefromed Dialysis Center for the help in collecting medical records, Rodica Rahaian for determining plasma FGF-23 levels and Cosmina Bondor for assistance in the statistical analysis. This work was supported by a research grant from "Iuliu Hatieganu" University of Medicine and Pharmacy Cluj-Napoca.

Conflict of interest Dr D Moldovan, Dr Kacso and Prof Dr Gherman have served as speakers for Amgen. Dr Ioan Moldovan has served as a speaker for GlaxoSmithKline and Boehringer Ingelheim. Dr Rusu and Dr Patiu have served as speakers for Abbott.

References

1. Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM (2004) Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. J Am Soc Nephrol 15(8):2208–2218
2. Adragao T, Pires A, Lucas C et al (2004) A simple vascular calcification score predicts cardiovascular risk in haemodialysis patients. Nephrol Dial Transpl 19(6):1480–1488
3. Moldovan D, Rusu C, Patiu IM et al (2010) Could the serum parathormone be a predictive marker for peripheral vascular calcification in chronic dialysis patients? Acta Endo (Buc) 1:43–55
4. Druke T (2008) Arterial intima and media calcification: distinct entities with different pathogenesis or all the same? Clin J Am Soc Nephrol 3:1583–1584
5. London GM, Guérin AP, Marchais SJ, Métivier F, Pannier B, Adda H (2003) Arterial media calcification in end-stage renal disease: impact on all-cause and cardiovascular mortality. Nephrol Dial Transpl 18(9):1731–1740
6. Razzaque MS (2009) The FGF23–klotho axis: endocrine regulation of phosphate homeostasis. Nat Rev Endocrinol 5:611–619
7. Mirza MA, Larsson A, Melhus H et al (2009) Serum intact FGF23 associate with left ventricular mass, hypertrophy and geometry in an elderly population. Atherosclerosis 207: 546–551
8. Mirza MA, Hansen T, Johansson L et al (2009) Relationship between circulating FGF23 and total body atherosclerosis in the community. Nephrol Dial Transpl 24:3125–3131
9. Bernheim J, Benchetrit S (2011) The potential roles of FGF23 and Klotho in the prognosis of renal and cardiovascular diseases. Nephrol Dial Transpl 26(8):2433–2438
10. Jean G, Bresson E, Terrat JC et al (2009) Peripheral vascular calcification in long-haemodialysis patients: associated factors and survival consequences. Nephrol Dial Transpl 24:948–955
11. Nasrallah MM, El-Shehaby AR, Salem MM et al (2010) Fibroblast growth factor-23 (FGF-23) is independently correlated to aortic calcification in haemodialysis patients. Nephrol Dial Transpl 25(8):2679–2685
12. Moldovan D, Moldovan I, Rusu C et al (2011) Vascular calcifications and renal osteodystrophy in chronic hemodialysis patients: what is the relationship between them? Int Urol Nephrol 43:1179–1186
13. Seiler S, Reichart B, Roth D, Seibert E et al (2010) FGF-23 and future cardiovascular events in patients with chronic kidney disease before initiation of dialysis treatment. Nephrol Dial Transpl 25(12):3983–3989

14. Kirkpantur A, Balci M, Gurbuz OA et al (2011) Serum fibroblast growth factor-23 (FGF-23) levels are independently associated with left ventricular mass and myocardial performance index in maintenance haemodialysis patients. Nephrol Dial Transpl 26(4):1346–1354
15. Gutierrez OM, Januzzi JL, Isakova T et al (2009) Fibroblast growth factor 23 and left ventricular hypertrophy in chronic kidney disease. Circulation 119:2545–2552
16. Hsu HJ, Wu MS (2009) Fibroblast growth factor 23: a possible cause of left ventricular hypertrophy in hemodialysis patients. Am J Med Sci 337:116–122
17. Oliveira RB, Cancela ALE, Graciolli FG et al (2010) Early Control of PTH and FGF23 in Normophosphatemic CKD Patients: a New Target in CKD-MBD Therapy? Clin J Am Soc Nephrol 5:286–291
18. Ford ML, Smith ER, Tomlinson LA et al (2012) FGF-23 and osteoprotegerin are independently associated with myocardial damage in chronic kidney disease stages 3 and 4. Another link between chronic kidney disease–mineral bone disorder and the heart. Nephrol Dial Transpl 27(2):727–733
19. Shimada T, Kakitani M, Yamazaki Y et al (2004) Targeted ablation of FGF23 demonstrates an essential physiological role of FGF23 in phosphate and vitamin D metabolism. J Clin Invest 113:561–568
20. Roos M, Lutz J, Salmhofer H et al (2008) Relation between plasma fibroblast growth factor-23, serum fetuin-A levels and coronary artery calcification evaluated by multislice computed tomography in patients with normal kidney function. Clin Endocrinol 68(4):660–665
21. Fliser D, Kollerits B, Neyer U et al (2007) Fibroblast growth factor 23 (FGF23) predicts progression of chronic kidney disease: the Mild to Moderate Kidney Disease (MMKD) Study. J Am Soc Nephrol 18(9):2600–2608
22. Gutierrez OM, Mannstadt M, Isakova T et al (2008) Fibroblast growth factor 23 and mortality among patients undergoing hemodialysis. N Engl J Med 359:584–592
23. Seiler S, Cremers B, Rebling NM et al (2011) The phosphatonin fibroblast growth factor 23 links calcium-phosphate metabolism with left-ventricular dysfunction and atrial fibrillation. Eur Heart J 32(21):2688–2696
24. Jean G, Terrat JC, Vanel T et al (2009) High levels of serum fibroblast growth factor (FGF)-23 are associated with increased mortality in long haemodialysis patients. Nephrol Dial Transpl 24:2792–2796
25. Isakova T, Xie Huiliang, Yang Wei et al (2011) Fibroblast growth factor 23 and risks of mortality and end-stage renal disease in patients with chronic kidney disease. JAMA 305(23):2432–2439
26. Stubbs JR, Liu S, Tang W et al (2007) Role of hyperphosphatemia and 1,25-dihydroxyvitamin D in vascular calcification and mortality in fibroblastic growth factor 23 null mice. J Am Soc Nephrol 18:2116–2124
27. Ashikaga E, Honda H, Suzuki H et al (2010) Impact of fibroblast growth factor 23 on lipids and atherosclerosis in hemodialysis patients. Ther Apher Dial 14(3):315–322
28. Inaba M, Okuno S, Imanishi Y et al (2006) Role of fibroblast growth factor-23 in peripheral vascular calcification in non-diabetic and diabetic hemodialysis patients. OsteoporosInt 17(10):1506–1513
29. Taylor EN, Rimm EB, Stampfer MJ, Curhan GC (2011) Plasma fibroblast growth factor 23, parathyroid hormone, phosphorus, and risk of coronary heart disease. Am Heart J 161(5):956–962
30. Olauson H, Qureshi AR, Miyamoto T et al (2010) Relation between serum fibroblast growth factor-23 level and mortality in incident dialysis patients: are gender and cardiovascular disease confounding the relationship? Nephrol Dial Transpl 25(9):3033–3038
31. DeLuca S, Sitara D, Kang K et al (2008) Amelioration of the premature aging-like features of FGF-23 knockout mice by genetically restoring the systemic actions of FGF-23. J Pathol 216:345–355
32. Shalhoub V, Shatzen EM, Ward SC et al (2012) FGF23 neutralization improves chronic kidney disease-associated hyperparathyroidism yet increases mortality. J Clin Invest 122:2543–2553
33. Moe OW (2012) Fibroblast growth factor 23: friend or foe in uremia? J Clin Invest 122:2354–2356
34. Nakanishi S, Kazama J, Nii-Kono T et al (2005) Serum fibroblast growth factor-23 levels predict the future refractory hyperparathyroidism in dialysis patients. Kidney Int 67:1171–1178
35. Schoppet M, Hofbauer LC, Brinskelle-Schmal N et al (2012) Serum level of the phosphaturic factor FGF23 is associated with abdominal aortic calcification in men: the STRAMBO study. J Clin Endocrinol Metab 97(4):E575–E583
36. Coen G, De Paolis P, Ballanti P et al (2011) Peripheral artery calcifications evaluated by histology correlate to those detected by CT: relationships with fetuin-A and FGF-23. J Nephrol 24(3):313–321
37. Tamei N, Ogawa T, Ishida H et al (2011) Serum fibroblast growth factor-23 levels and progression of aortic arch calcification in non-diabetic patients on chronic hemodialysis. J Atheroscler Thromb 18:217–223
38. Kojima F, Uchida K, Ogawa T et al (2008) Plasma levels of fibroblast growth factor-23 and mineral metabolism in diabetic and non-diabetic patients on chronic hemodialysis. Int Urol Nephrol 40:1067–1074