Early Control of PTH and FGF23 in Normophosphatemic CKD Patients: A New Target in CKD-MBD Therapy?

Rodrigo B. Oliveira,* Ana L.E. Cancela,* Fabiana G. Graciolli,* Luciene M. Dos Reis,* Sérgio A. Draibe,† Lilian Cuppari,† Aluizio B. Carvalho,† Vanda Jorgetti,* Maria E. Canziani,† and Rosa M.A. Moysés*

**Nephrology Department, Universidade de São Paulo and †Nephrology Department, Universidade Federal de São Paulo, São Paulo, Brazil*

Background and objectives: Levels of parathyroid hormone (PTH) and the phosphaturic hormone FGF23, a fibroblast growth factor (FGF) family member, increase early in chronic kidney disease (CKD) before the occurrence of hyperphosphatemia. This short-term 6-wk dose titration study evaluated the effect of two phosphate binders on PTH and FGF23 levels in patients with CKD stages 3 to 4.

Design, setting, participants, and measurements: Patients were randomized to receive over a 6-wk period either calcium acetate ($n = 19$) or sevelamer hydrochloride ($n = 21$).

Results: At baseline, patients presented with elevated fractional excretion of phosphate, serum PTH, and FGF23. During treatment with both phosphate binders there was a progressive decline in serum PTH and urinary phosphate, but no change in serum calcium or serum phosphate. Significant changes were observed for FGF23 only in sevelamer-treated patients.

Conclusions: This study confirms the positive effects of early prescription of phosphate binders on PTH control. Prospective and long-term studies are necessary to confirm the effects of sevelamer on serum FGF23 and the benefits of this decrease on outcomes.

Clin J Am Soc Nephrol 5: 286–291, 2010. doi: 10.2215/CJN.05420709

Mineral metabolism and bone disorders (CKD-MBD) are associated with poor outcomes in dialysis patients, but few studies have evaluated their effects in chronic kidney disease (CKD) patients who are not yet on dialysis. Moreover, studies have shown that complications such as vascular calcification, CKD progression, and mortality are associated with serum phosphate levels within the upper limits of the normal range (1,2). In addition, increased parathyroid hormone (PTH) levels occur early in CKD patients, accompanied by normal serum calcium and phosphate (3).

Recent studies indicate that the phosphaturic hormone FGF23, a fibroblast growth factor (FGF) family member, may play a role in early CKD (4). FGF23 is primarily produced by osteocytes and directly acts on the kidney to downregulate the production of 1,25-vitamin D_3 and the expression of the 2a and 2c sodium-phosphate cotransporters (5) in response to phosphate overload in healthy individuals (6) and in patients with CKD (7). Growing evidence indicates that rising FGF23 levels in early stages of CKD are partially responsible for maintaining phosphatemia within the normal range. Early management of serum FGF23 levels may prevent the premature decrease in serum 1,25-vitamin D_3 and the subsequent increase in serum PTH. Beneficial effects of lowering FGF23 levels are suggested by the correlation between FGF23, vascular calcification, CKD progression, and mortality (8–10).

These current concepts indicate that early treatment of CKD-MBD may result in improved management of CKD progression and associated complications such as vascular calcification. However, no studies have evaluated the effects of phosphate binder administration on serum phosphate and PTH in normophosphatemic CKD patients. The objective of this pilot study was to evaluate whether the administration of two different phosphate binders (calcium acetate or sevelamer hydrochloride) would alter biomarkers of mineral disorders, including serum PTH and FGF23 in CKD patients not yet on dialysis.

Patients and Methods

Study Design

The study included adult, clinically stable patients with phase 3 or 4 CKD from the Uremia Outpatient Clinic of the EPM-UNIFESP Nephrology Department. Excluded were patients who had a body mass index <17 or >37 kg/m^2, proteinuria >3.5 g/24 h, diabetes mellitus, intact PTH >500 pg/ml, or were receiving any drug that could interfere with mineral metabolism. Informed consent was obtained from all patients. This study was approved by the local ethics committee (CAPPesq) and was registered on the Brazilian official trial registry (SISNEP) under the number CAAE-0714.0.015.000-07.

The study was conducted over an 8-wk period, which involved 6 wk of titration of the two phosphate binders, calcium acetate and sevelamer hydrochloride, and 2 wk of washout. Forty patients were selected and randomized in a 1:1 ratio to receive open-label sevelamer (Renagel, 800-mg tablets; Genzyme Co., Cambridge, MA) or calcium acetate (PhosLo, 667-mg tablets; Fresenius Medical Care, Waltham, MA). Randomization was computer generated, in blocks of four, and the inves-

Received July 31, 2009. Accepted October 8, 2009.

Published online ahead of print. Publication date available at www.cjasn.org.

Correspondence: Dr. Rosa Maria Affonso Moysés, Rua Iperoig, 690 ap 121, São Paulo, Brazil, 05016-000. Phone: +5511-30689428; Fax: +5511-30831693; E-mail: rosa.moyses@uol.com.br

ISSN: 1555-9041/502–0286

tigator assigned the treatment using concealed envelopes. After randomization, patients received calcium acetate, initially at a 1.32-g/d dose then doubled every 2 wk (2.64 and 5.28 g/d), or sevelamer hydrochloride, initially at a 1.6-g/d dose then doubled every 2 wk (3.2 and 6.4 g/d). The washout period was included as a control of the treatment because this study did not have a control (placebo) group.

Clinical and Laboratory Evaluation

At the study outset and then every 2 wk, blood samples were analyzed for total calcium; phosphorus; venous blood gas analysis; alkaline phosphatase; intact PTH [chemiluminescent substrate, DPC; Medlab; reference range (RR) 10 to 65 pg/ml]; intact FGF23 (Elisa assay, Kainos, Japan; RR 8.2 to 54.3 pg/ml); albumin; 1,25-dihydroxy vitamin D (RIA, Dia-Sorin; RR 15.9 to 55.6 pg/dl); urea; and creatinine. Samples were also analyzed at study outset and at week 6 for 25-hydroxy vitamin D (chemoluminescent assay, Dia-Sorin); bone alkaline phosphatase (enzyme immunoassay, Metra Biosystem, Inc.; RR 11.6 to 42.7 U/L); and deoxypyridinoline (enzyme immunoassay, Quidel Corporation,; RR 3.25 ± 0.66 nmol/L). Urine samples were analyzed at study outset and every 2 wk for calcium and phosphorus.

Nutritional Evaluation

The seven-point subjective global assessment method was used to determine the nutrition status (11). The overall subjective evaluation method, adapted to patients with CKD, was used for the nutritional diagnosis. The dietary phosphate prescription was performed according to the amount of protein in the diet and maintained 615 ± 63 mg/d. Patients were instructed not to modify the intake of food sources of phosphorus during the 8 wk of the study.

Statistical Analyses

Demographic characteristics and biochemical parameters were described as mean ± SD [except for PTH and FGF23, which were expressed as median (25th to 75th percentile)]. Change from baseline was compared between treatment groups using Wilcoxon rank sum tests. Changes from baseline within groups were compared with the Wilcoxon signed rank. Statistical analyses were performed using the Graph Pad Prism version 4.0 and SPSS 10.0. A P value <0.05 was considered significant.

Results

Patients (23 men and 19 women) were randomized to each phosphate binder group. Two patients in the calcium acetate group withdrew from the study during the first week because of irregular heart rhythm and gastrointestinal symptoms, respectively, and were excluded from the analysis. Table 1 shows the clinical and biochemical characteristics of the patients at

Table 1. Baseline demographical, clinical, and biochemical parameters of the total study population and the two subgroups: Calcium acetate-treated patients and sevelamer hydrochloride-treated patients[a]

Parameter	All	Calcium Acetate	Sevelamer Hydrochloride	Reference Values
n	40	19	21	
Age (yr)	50.38 ± 11.40	51.21 ± 9.98	49.62 ± 12.75	–
Body mass index (kg/m^2)	26.28 ± 4.58	26.95 ± 4.16	25.67 ± 4.95	18 to 25
Gender (male/female)	21/19	9/10	12/9	–
Cr (mg/dl; male/female)	2.55 ± 0.78	2.52 ± 0.76	2.59 ± 0.82	0.8 to 1.2/ 0.6 to 1.0
CrCl (ml/min/1.73 m^2; male/female)	34.55 ± 15.89	32.07 ± 9.92	36.9 ± 20	85 to 125/ 75 to 115
Bic (mmol/L)	21.63 ± 3.79	20.82 ± 2.97	22.37 ± 4.34	23 to 30
Alb (g/dl)	4.35 ± 0.30	4.35 ± 0.21	4.36 ± 0.37	3.5 to 5
Ca (mg/dl)	9.29 ± 0.50	9.34 ± 0.56	9.24 ± 0.45	8.6 to 10.2
P (mg/dl)	3.53 ± 0.60	3.61 ± 0.54	3.45 ± 0.65	2.7 to 4.5
TAP (U/L)	81.20 ± 21.72	84.42 ± 25.32	78.29 ± 18.01	35 to 104
BAP (U/L)	35.10 ± 11.46	36.91 ± 12.62	33.46 ± 10.35	11.6 to 42.7
DPD (nmol/L)	10.32 ± 3.38	9.81 ± 3.25	10.80 ± 3.52	3.25 ± 0.66
25vitD (ng/ml)	34.75 ± 20.65	35.71 ± 18.66	33.88 ± 22.73	> 30
1,25vitD (pg/ml)	31.27 ± 21.18	32.82 ± 16.67	29.79 ± 25.08	15.9 to 55.6
PTH (pg/ml)	101 (70 to 130)	89 (52 to 141)	107 (76 to 130)	10 to 65
FGF23 (pg/ml)	97 (64 to 142)	97 (62 to 148)	103 (62 to 142)	8.2 to 54.3
uCa (mg/24 h)	24.27 ± 25.61	23.39 ± 24.49	25.11 ± 27.27	100 to 320
uP (mg/24 h)	490.5 ± 150.9	444.5 ± 154.6	534.1 ± 137.3	400 to 1300
FeP (%)	59.7 ± 32.4	58.2 ± 37.2	61.0 ± 28.4	5 to 18
uProt (g/24 h)	0.45 ± 0.75	0.35 ± 0.67	0.55 ± 0.82	<0.1

[a]Mean ± SD values are shown [except for PTH and FGF23, which are expressed as median (25th to 75th percentile interval)]. Cr, creatinine; CrCl, creatinine clearance; Ca, serum calcium; P, serum phosphate; Bic, serum bicarbonate; Alb, serum albumin; TAP, total alkaline phosphatase; BAP, bone alkaline phosphatase; DPD, deoxypyridinoline; 25vitD, 25-vitamin D; 1,25vitD, 1,25-vitamin D; uCa, urinary calcium; uP, urinary phosphate; FeP, fractional excretion of phosphate; uprot, urinary protein.

baseline. Patients were randomized to each phosphate binder group such that there were no significant differences between the two groups at baseline. The main cause of CKD was hypertension ($n = 25$; 62.5%), followed by chronic GN ($n = 3$; 7.5%), chronic pielonephritis ($n = 4$; 10%), and adult polycystic kidney disease ($n = 3$; 7.5%). In five patients (12.5%) the etiology for CKD was unknown. According to the Cockroft–Gault formula, 22 patients were classified as having CKD stage 3 (12 in calcium group and 10 in sevelamer group), whereas 18 were classified as having CKD stage 4 (7 in calcium group and 11 in sevelamer group). All patients were considered well nourished as evaluated by the subjective global assessment.

Despite low phosphate ingestion (739 ± 253 mg/d), normal serum phosphate levels, and a relatively low phosphaturia, patients presented with an elevated fractional excretion of phosphate and serum PTH levels higher than normal. Mean 25-hydroxy-vitamin D was 34.8 ± 20.6 ng/ml, and all but five patients presented elevated serum FGF23 levels.

The mean values of biochemical parameters observed at baseline, biweekly, and after washout are shown in Table 2. After treatment with both phosphate binders, there was a progressive decline in serum PTH, urinary phosphate, and fractional excretion of phosphate, but no significant change in serum calcium or serum phosphate in either group (Figure 1). Sevelamer-treated patients presented a greater increase in bone alkaline phosphatase and a greater decrease in deoxypyridinoline than did calcium-treated patients. Patients treated with sevelamer also presented a significant decrease in 25-vitamin D levels. No significant changes were observed in urinary calcium or in 1,25-vitamin D_3 levels in both groups. However, 60% ($n = 13$) of the sevelamer-treated patients presented an increase in 1,25-vitamin D_3 levels, whereas this increase was seen in only 31.6% ($n = 6$) of calcium-treated patients ($P = 0.07$).

Figure 1 shows the absolute changes and Figure 2 shows the percentage changes in serum FGF23 and PTH in sevelamer- and calcium-treated patients. Sevelamer patients presented a tendency to have a greater reduction in FGF23 at the 4th week than did calcium acetate patients ($P = 0.06$). At the 6th week, sevelamer-treated patients presented a significant reduction in FGF23 (107 pg/ml at baseline *versus* 54 pg/ml at the 6th week; $P < 0.05$), whereas this was not observed in calcium-treated patients (97 pg/ml at baseline *versus* 77 pg/ml at the 6th week; NS). A comparison between the treatment groups also shows a significant difference between the changes observed (−53.6 ± 64.7 pg/ml in sevelamer group *versus* −16 ± 49.1 pg/ml in calcium group; $P < 0.05$). When patients were divided according to the stage of CKD, we also observed that in stage 3 group sevelamer patients presented a significant decrease in serum FGF23 (78 pg/ml at baseline *versus* 51 pg/ml at the 6th week; $P < 0.05$), whereas this was not observed in calcium-treated patients (93 pg/ml at baseline *versus* 70 pg/ml at the 6th week; NS). The same findings were seen in CKD stage 4 patients [109 pg/ml at baseline *versus* 63 pg/ml at the 6th week ($P < 0.05$) for sevelamer-treated patients; 130 pg/ml at baseline *versus* 87 pg/ml at the 6th week (NS) for calcium-treated patients].

After the washout period, all parameters values were similar to those found at the baseline in both groups.

Table 2. Biochemical parameters at baseline, 2nd, 4th and 6th weeks and at the washout in patients treated with calcium acetate ($n = 19$) or sevelamer hydrochloride ($n = 21$)

Laboratory Parameter	Calcium Acetate Group					Sevelamer Hydrochloride Group				
	Baseline	Week 2	Week 4	Week 6	Washout	Baseline	Week 2	Week 4	Week 6	Washout
P (mg/dl)	3.61 ± 0.54	3.52 ± 0.52	3.54 ± 0.72	3.50 ± 0.64	3.68 ± 0.62	3.45 ± 0.65	3.49 ± 0.73	3.37 ± 0.65	3.31 ± 0.63	3.53 ± 0.61
Ca (mg/dl)	9.34 ± 0.56	9.29 ± 0.55	9.45 ± 0.50	9.38 ± 0.52	9.33 ± 0.56	9.24 ± 0.45	9.36 ± 0.44	9.30 ± 0.43	9.27 ± 0.53	9.26 ± 0.42
Cr (mg/dl)	2.52 ± 0.76	2.39 ± 0.71	2.44 ± 0.70	2.56 ± 0.69	2.47 ± 0.69	2.59 ± 0.82	2.43 ± 0.68	2.48 ± 0.72	2.42 ± 0.72	2.37 ± 0.75
TAP (U/L)	84.42 ± 25.32	81.95 ± 22.61	88.11 ± 26.33	89.05 ± 32.87	80.58 ± 24.73	78.29 ± 18.01	80.71 ± 19.76	92.57 ± 56.64	102.6 ± 76.22[a]	83.95 ± 25.41
BAP (U/L)	36.91 ± 12.62	–	–	37.94 ± 13.79[b]	–	33.46 ± 10.35	–	–	38.56 ± 16.41[a,b]	–
DPD (nmol/L)	9.81 ± 3.25	–	–	9.62 ± 3.69[b]	–	10.8 ± 3.52	–	–	10.25 ± 3.06[2]	–
25vitD (ng/ml)	35.71 ± 18.66	–	–	33.27 ± 13.60[b]	–	33.88 ± 22.73	–	–	28.64 ± 19.76[a,b]	–
1,25vitD (pg/ml)	32.82 ± 16.67	34.59 ± 18.56	31.26 ± 11.04	28.55 ± 13.50	43.72 ± 34.20	29.79 ± 25.08	29.70 ± 17.26	32.26 ± 21.88	30.42 ± 14.97	32.92 ± 16.16
PTH (pg/ml)	89 (52 to 141)	95 (64 to 110)	76 (43 to 105)	75 (40 to 110)[a]	108 (63 to 146)	107 (76 to 130)	102 (60 to 147)	77 (51 to 126)	69 (47 to 94)[a]	105 (63 to 146)
FGF23 (pg/ml)	97 (62 to 148)	60 (39 to 91)	90 (46 to 135)	77 (56 to 120)[b]	87 (65 to 144)	103 (62 to 142)	90 (52 to 124)	60 (41 to 145)	54 (38 to 94)[a,b]	93 (46 to 125)
uCa (mg/24 h)	23.39 ± 24.49	23.47 ± 17.58	30.11 ± 21.68	35.93 ± 14.73	24.28 ± 14.79	25.11 ± 27.27	31.8 ± 27.61	29.71 ± 30.56	36.71 ± 30.58	35.24 ± 42.19
uP (mg/24 h)	445 ± 155	400 ± 182	380 ± 144[a]	244 ± 121[a]	478 ± 152	534 ± 137	401 ± 139	346 ± 160[a]	313 ± 135[a]	464 ± 197
FeP (%)	58.2 ± 37.2	42.3 ± 30.8	35.5 ± 22.1[a]	27.1 ± 13.3[a]	47.5 ± 25.0	61.0 ± 28.4	69.3 ± 52.9	52.6 ± 38.7[a]	35.8 ± 25.9[a]	62.7 ± 42.7

Data are expressed as mean ± SD [except for PTH and FGF23, which are expressed as median (25th to 75th percentile interval)].
[a]Within-group change from baseline; $P < 0.05$.
[b]Between-group change; $P < 0.05$.

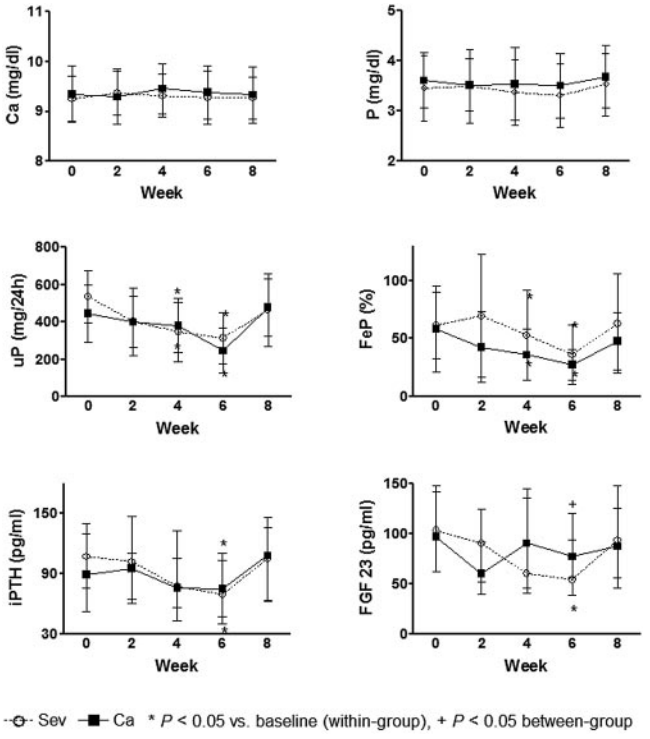

Figure 1. Absolutes changes in the levels of serum calcium (Ca), serum phosphate (P), urinary phosphate (uP), fractional excretion of phosphate (FeP), serum PTH, and serum FGF23 in patients treated with sevelamer hydrochloride (○) or calcium acetate (■) over a 6-wk period followed by a 2-wk washout period. Statistical comparisons within and between treatment groups are shown. Data are expressed as mean ± SD, except for FGF23 and PTH, which are expressed as median (25th to 75th percentile interval).

Discussion

Previous studies have shown that increased serum PTH concentrations occur in patients with CKD stage 3 who typically have normal calcium and phosphate levels (3,7). The Study to Evaluate Early Kidney Disease (SEEK) (12), a cross-sectional analysis of 1814 patients with CKD stage 3 to 5, demonstrated that calcium and phosphate values did not become abnormal until GFR fell below 40 ml/min. However, nearly 60% of patients with GFR <60 ml/min had elevated PTH levels. Despite these findings, the current guidelines only recommend a dietary phosphate restriction for these patients. In this 6-wk, dose-titration study, we demonstrate for the first time that the use of phosphate binders in early CKD patients with normal serum phosphate is effective at lowering total urinary phosphate excretion, fractional phosphate excretion, and serum PTH without significant changes in serum calcium or phosphate levels. Thus, these data demonstrate that early phosphate binder use provides additional PTH control beyond that of a phosphate-restricted diet.

In study presented here, sevelamer hydrochloride treatment appeared more effective at lowering serum FGF23 levels. These findings cannot be attributed to differential control of serum phosphorus or 1,25-vitamin D_3, two known regulators of FGF23. It is possible that sevelamer's increased ability to reduce FGF23 occurs through an unknown effect. In addition, these findings also raise the possibility that increased calcium load may contribute to FGF23 elevation. Serum FGF23 levels have been found to correlate with serum calcium independent of serum phosphate in individuals with primary hyperparathyroidism who underwent parathyroidectomies (13). In addition, in vitamin-D-receptor null mice, dietary calcium supplementation significantly increased FGF23 mRNA abundance (14), indicating that calcium could be another determinant of FGF23 production. On the basis of these studies, further analyses of factors controlling FGF23 production are warranted.

The current understanding of the role of FGF23 is still emerging. Similar to the "trade-off hypothesis" (15) proposed for PTH, small elevations of FGF23 may have a beneficial effect by preventing hyperphosphatemia in early CKD. Over the long term, high FGF23 levels can favor the development of hyperparathyroidism because FGF23 inhibits the activity of 1α-hydroxylase, the rate-limiting enzyme responsible for 1,25-vita-

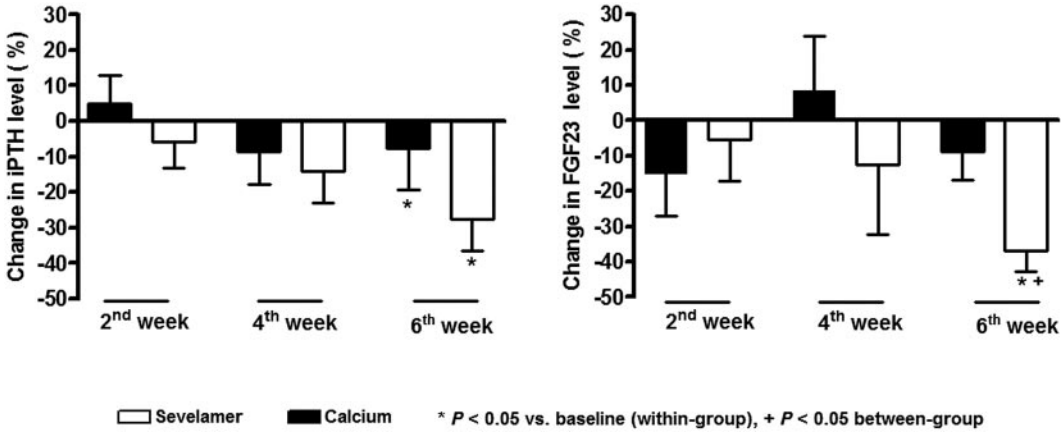

Figure 2. Percentage change in serum FGF23 and PTH levels in patients treated with sevelamer hydrochloride (□) or calcium acetate (■) over a 6-wk period. Statistical comparisons within and between treatment groups are shown. Data are expressed as mean ± SD.

min D synthesis (9). In a prospective study performed in dialysis patients with mild secondary hyperparathyroidism, serum FGF23 levels were significantly associated with the development of severe hyperparathyroidism (16). In an observational study, Fliser *et al.* (9) found FGF23 to be an independent predictor of disease progression in patients with nondiabetic CKD. Furthermore, FGF23 levels were a more accurate predictor of progression than serum phosphate, calcium, or PTH concentrations. Finally, a recent study has shown that FGF23 levels are independently associated with mortality among patients initiating hemodialysis treatment (10). The mortality risk associated with elevated FGF23 was substantially larger than that reported for serum phosphate. Together, these results suggest that the management of FGF23 may become an important goal in the treatment of CKD-MBD.

The significant increase in bone alkaline phosphatase and decrease in deoxypyridinoline that was found exclusively in the sevelamer group could be considered as an improvement in bone remodeling of these patients. However, bone biopsies were not performed, preventing definitive diagnosis of renal osteodystrophy and only a long-term study with bone biopsy analysis could confirm these findings. In a similar way, the significant decrease of 25-vitamin D should be seen cautiously, because no other study found a sevelamer-related effect on serum levels of this hormone.

To the best of our knowledge, this is the first clinical study that has evaluated the effects of phosphate binders on FGF23 in CKD stages 3 to 4. An experimental study involving uremic rats showed that the administration of sevelamer decreased FGF23 levels (17). Another study involving six dialysis patients demonstrated that the suspension of phosphate binders increased FGF23 levels, albeit not significantly (18). A Japanese study performed in 46 hemodialysis patients who were randomized to receive calcium carbonate alone or calcium carbonate and sevelamer hydrochloride showed that only the second group presented a significant decrease in serum FGF23 (19). The study presented here extends these data by demonstrating that a reduction in FGF23 can occur in patients without any changes in serum phosphate levels, suggesting that they do not adequately reflect phosphate balance. Similar observations have already been be made with serum calcium (20)

The current study presents several limitations. We excluded diabetic patients, and diabetic nephropathy is a main cause of CKD. However, in our study we preferred to exclude patients with a significant proteinuria, which would certainly be associated with vitamin D deficiency, and diabetic patients would certainly present a significant degree of proteinuria. A similar decision was taken by Fliser (9), who evaluated only young, nondiabetic CKD patients in the Mild to Moderate Kidney Disease (MMKD) study and found that FGF23 was a good predictor of CKD progression. Indeed, our group also recently found that FGF23 is a good predictor of CKD progression in diabetic patients (21). Nevertheless, in a long-term, prospective study diabetic patients will necessarily be included and the benefits of phosphate binders on serum PTH and FGF23 control must be confirmed in this population.

Our study is also limited by a small population size and the short duration. However, the current understanding of phosphate management in CKD leads us to propose a change in the paradigm: To move from the recommendation of the current guidelines [Kidney Disease Outcomes Quality Initiative (K/DOQI) and Kidney Disease: Improving Global Outcomes (KDIGO), which recognize the use of phosphate binders for CKD 2 to 4 patients only when serum phosphate is greater than 4.6 mg/dl] to a more aggressive control of phosphate load using phosphate binders even in the presence of normal serum phosphate values. A recent review published by Isakova (22) calls our attention to the need of a better understanding of the role played by phosphate and FGF23 in CKD, proposing to the nephrologic community a long-term study in this population. Certainly a long-term, randomized and probably multicentric study will be necessary to confirm this theory. In such a study, the long-term benefits of early binder treatment on vascular calcification, bone health, and disease progression would also be assessed. However, our preliminary findings showed that the use of phosphate binders in this population is not associated with serious adverse events in the short term. They also provided some preliminary data regarding PTH control and surprisingly showed that the FGF23 response could be distinct dependent on the phosphate binder that was used.

In conclusion, the use of phosphate binders in CKD patients with normal serum phosphate levels was associated with improved control of secondary hyperparathyroidism without corresponding changes in serum phosphate levels. Sevelamer was also able to decrease serum FGF23. The benefits of these findings should be confirmed in long-term studies.

Acknowledgments

This study was presented, in part, at the 2007 Annual Meeting of the American Society of Nephrology in San Francisco, California. The authors acknowledge the assistance given by Claudia Veludo and Marianna D. Unger in the nutritional evaluation, Scott Chasan-Taber (Genzyme Co.) in the statistical analyses, Christine McKillop for assistance in preparation of this manuscript, and by Susan Schiavi and Robert Guiberteau (Genzyme Co.) for critical reading of this manuscript.

Disclosures

Genzyme Corporation provided the funding for this trial. The investigators were solely responsible for the design, conduct, analysis, and publication of the trial. There were no restrictions on publications, and all data were maintained and analyzed solely by the authors. Drs. Canziani, Carvalho, Jorgetti, and Moysés report have received consulting fees and research grants from Genzyme.

References

1. Tomiyama C, Higa A, Dalboni MA, Cendoroglo M, Draibe SA, Cuppari L, Carvalho AB, Neto EM, Canziani ME: The impact of traditional and non-traditional risk factors on coronary calcification in pre-dialysis patients. *Nephrol Dial Transplant* 21: 2464–2471., 2006
2. Kestenbaum B, Sampson JN, Rudser KD, Patterson DJ, Seliger SL, Young B, Sherrard DJ, Andress DL: Serum phosphate levels and mortality risk among people with chronic kidney disease. *J Am Soc Nephrol* 16: 520–528, 2005

3. Vassalotti JA, Uribarri J, Chen SC, Li S, Wang C, Collins AJ, Calvo MS, Whaley-Connell AT, McCullough PA, Norris KC: Kidney Early Evaluation Program Investigators: Trends in mineral metabolism: Kidney Early Evaluation Program (KEEP) and the National Health and Nutrition Examination Survey (NHANES) 1999–2004. *Am J Kidney Dis* 51[Suppl 2]: S56–S68, 2008
4. Schiavi SC: Fibroblast growth factor 23: The making of a hormone. *Kidney Int* 69: 425–427, 2006
5. Fukumoto S, Yamashita T: FGF23 is a hormone-regulating phosphate metabolism—Unique biological characteristics of FGF23. *Bone* 40: 1190–1195, 2007
6. Burnett SA, Gunawardene SC, Bringhurst FR, Juppner H, Lee H, Finkelstein JS: Regulation of C-terminal and intact FGF-23 by dietary phosphate in men and women. *J Bone Miner Res* 21: 1187–1196, 2006
7. Gutierrez O, Isakova T, Rhee E, Shah A, Holmes J, Collerone G, Juppner H, Wolf M: Fibroblast growth factor-23 mitigates hyperphosphatemia but accentuates calcitriol deficiency in chronic kidney disease. *J Am Soc Nephrol* 16: 2205–2215, 2005
8. Jean G, Bresson E, Terrat JC, Vanel T, Hurot JM, Lorriaux C, Mayor B, Chazot C: Peripheral vascular calcification in long-haemodialysis patients: Associated factors and survival consequences. *Nephrol Dial Transplant* 24: 948–955, 2008
9. Fliser D, Kollerits B, Neyer U, Ankerst DP, Lhotta K, Lingenhel A, Ritz E, Kronenberg F; MMKD Study Group, Kuen E, König P, Kraatz G, Mann JF, Müller GA, Köhler H, Riegler P: Fibroblast growth factor 23 (FGF23) predicts progression of chronic kidney disease: the Mild to Moderate Kidney Disease (MMKD) Study. *J Am Soc Nephrol* 18: 2600–2608, 2007
10. Gutiérrez OM, Mannstadt M, Isakova T, Rauh-Hain JA, Tamez H, Shah A, Smith K, Lee H, Thadhani R, Jüppner H, Wolf M: Fibroblast growth factor 23 and mortality among patients undergoing hemodialysis. *N Engl J Med* 359: 584–592, 2008
11. Canada - USA (CANUSA) Peritoneal Dialysis Study Group: Adequacy of dialysis and nutrition in continuous peritoneal dialysis: Association with clinical outcomes. *J Am Soc Nephrol* 7: 198–207, 1996
12. Levin A, Bakris GL, Molitch M, Smulders M, Tian J, Williams LA, Andress DL: Prevalence of abnormal serum vitamin D, PTH, calcium, and phosphorus in patients with chronic kidney disease: Results of the Study to Evaluate Early Kidney Disease. *Kidney Int* 71: 31–38, 2007
13. Kobayashi K, Imanishi Y, Miyauchi A, Onoda N, Kawata T, Tahara H, Goto H, Miki T, Ishimura E, Sugimoto T, Ishikawa T, Inaba M, Nishizawa Y: Regulation of plasma fibroblast growth factor 23 by calcium in primary hyperparathyroidism. *Eur J Endocrinol* 154: 93–99, 2006
14. Shimada T, Yamazaki Y, Takahashi M, Hasegawa H, Urakawa I, Oshima T, Ono K, Kakitani M, Tomizuka K, Fujita T, Fukumoto S, Yamashita T: Vitamin D receptor-independent FGF23 actions in regulating phosphate and vitamin D metabolism. *Am J Physiol Renal Physiol* 289: F1088–F1095, 2005
15. Slatopolsky E, Caglar S, Pennell JP, Taggart DD, Canterbury JM, Reiss E, Bricker NS: On the pathogenesis of hyperparathyroidism in chronic experimental renal insufficiency in the dog. *J Clin Invest* 50: 492–499, 1971
16. Nakanishi S, Kazama JJ, Nii-Kono T, Omori K, Yamashita T, Fukumoto S, Gejyo F, Shigematsu T, Fukagawa M: Serum fibroblast growth factor-23 levels predict the future refractory hyperparathyroidism in dialysis patients. *Kidney Int* 67: 1171–1178, 2005
17. Nagano N, Miyata S, Abe M, Kobayashi N, Wakita S, Yamashita T, Wada M: Effect of manipulating serum phosphorus with phosphate binder on circulating PTH and FGF23 in renal failure rats. *Kidney Int* 69: 531–537, 2006
18. Pande S, Ritter CS, Rothstein M, Wiesen K, Vassiliadis J, Kumar R, Schiavi SC, Slatapolsky E, Brown AJ: FGF-23 and sFRP-4 in chronic kidney disease and post-renal transplantation. *Nephron Physiol* 104: 23–32, 2006
19. Koiwa F, Kazama JJ, Tokumoto A, Onoda N, Kato H, Okada T, Nii-Kono T, Fukagawa M, Shigematsu T; ROD21 Clinical Research Group: Sevelamer hydrochloride and calcium bicarbonate reduce serum fibroblast growth factor 23 levels in dialysis patients. *Ther Apher Dial* 9: 336–339, 2005
20. Houillier P, Froissart M, Maruani G, Blanchard A: What serum calcium can tell us and what it can't. *Nephrol Dial Transplant* 21: 29–32, 2006
21. Titan SM, Zatz R, Jorgetti V, Moysés RMA: FGF23 as predictor of renal outcome in diabetic nephropathy. Presented at the American Society for Nephrology 2009 Meeting, Poster F-PO1872
22. Isakova T, Gutiérrez OM, Wolf M: A blueprint for randomized trials targeting phosphorus metabolism in chronic kidney disease. *Kidney Int* 76L 705–716, 2009