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Changes With Lanthanum Carbonate, Calcium Acetate, and Phosphorus Restriction in CKD: A Randomized Controlled Trial

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Introduction: Abnormal phosphorus homeostasis develops early in chronic kidney disease (CKD). It is unclear if its correction results in improved clinical outcomes in non–dialysis dependent CKD.

Methods: We conducted a randomized controlled, parallel design clinical trial in 120 patients with estimated glomerular filtration rate 15 to 59 ml/min per 1.73 m^2 and abnormal phosphorus homeostasis (serum phosphorus >4.6 mg/dl, parathyroid hormone [PTH] >70 pg/ml or tubular reabsorption of phosphorus [TRP] <80%). Patients were randomized to open-label lanthanum carbonate versus calcium acetate versus dietary intervention over 1 year. The co-primary outcomes were month 12 (vs. baseline) biochemical (serum phosphorus, TRP, PTH, calcium, bone-specific alkaline phosphatase [bALP], and fibroblast growth factor 23 [FGF23]) and vascular parameters (coronary artery calcium score, pulse wave velocity, and endothelial dysfunction) in all patients. Secondary outcomes were between-treatment differences in change for each parameter between month 12 and baseline. All analyses were intention to treat.

Results: Baseline characteristics were similar in the 3 groups. A total of 107 patients (89%) completed 12 months of follow-up. Differences were not significant at month 12 (vs. baseline) for any of the outcomes except bALP (median [25th, 75th] percentile at month 12 versus baseline: 13.8 [10.6, 17.6] vs. 15.8 [12.1, 21.1], $P < .001$) and FGF23 (132 [99, 216] vs. 133 [86, 189], $P = .002$). Changes for all outcomes were similar in the 3 arms except for PTH, which was suppressed more effectively by calcium acetate ($P < .001$).

Conclusion: A 1-year intervention to limit phosphorus absorption using dietary restriction or 2 different phosphorus binders resulted in decreased bALP suggesting improved bone turnover, but no other significant changes in biochemical or vascular parameters in patients with CKD stage 3/4. (ClinicalTrials.gov: NCT01357317)

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Phosphorus plays essential roles as a component of the bony skeleton, adenosine triphosphate, nucleic acids, phospholipid membranes, and blood and urinary buffers.[1] A complex regulatory system ensures the maintenance of phosphorus homeostasis,[2] with the kidney playing a pivotal role as the main organ responsible for phosphorus excretion. Abnormalities affecting phosphorus are one of the centerpieces of chronic kidney disease (CKD) mineral and bone disorder: as glomerular filtration rate decreases and filtration of phosphorus diminishes, compensatory increases in parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF23) result in suppression of tubular reabsorption of phosphorus (TRP) and increased urinary phosphorus excretion, which prevents the development of hyperphosphatemia until late in the course of CKD.[3–9] Elevated serum phosphorus is associated with increased mortality in dialysis patients[10,11] and in patients with non–dialysis dependent (NDD) CKD.[12–14] In addition to elevated serum phosphorus levels, the compensatory mechanisms assuring maintenance of normal serum phosphorus in patients with

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NDD-CKD, such as secondary hyperparathyroidism and increased FGF23 levels, are also associated with poor outcomes.[15]

In spite of compelling observational data and plausible pathophysiologic mechanisms to explain the association of abnormal phosphorus metabolism with adverse outcomes,[16,17] the benefit of phosphorus-lowering therapy remains questionable. The administration of phosphorus binders to dialysis patients[18] and to patients with NDD-CKD[19,20] was associated with lower mortality in observational studies, but clinical trials aimed at phosphorus lowering using various strategies showed inconsistent outcomes on biochemical or vascular end points.[21–25] In a randomized controlled clinical trial (RCT) examining the effects of sevelamer hydrochloride versus calcium carbonate versus dietary phosphate restriction on coronary calcification in 90 patients with NDD-CKD,[21] the highest progression of coronary calcification was seen in the group treated with dietary restriction alone, and the lowest progression in the group administered sevelamer hydrochloride. Contrasting these results, an RCT in 148 patients with NDD-CKD showed no benefit from various phosphorus binders versus placebo on vascular calcification.[22] In another small single-center RCT, the administration of lanthanum carbonate over 12 months had no effect on biochemical or various vascular parameters when compared with placebo.[23] Based on the available data, current guidelines question the effectiveness of phosphate binders in patients with NDD-CKD,[26] but the evidence informing about the long-term effects of phosphorus-lowering strategies in NDD-CKD remains insufficient.

We examined the effect of 2 different phosphate binders (lanthanum carbonate and calcium acetate) and of dietary phosphate restriction on various biochemical and vascular end points in 120 patients with NDD-CKD randomized to 1 of these 3 interventions over 1 year. We hypothesized that correction of biochemical markers of phosphorus homeostasis will result in lowering of bone turnover and in improved vascular function and structure.

METHODS

This was an open-label, 2-center, randomized, active controlled study comparing the effects of lanthanum carbonate, calcium acetate, and dietary phosphorus restriction on biochemical and vascular parameters in patients with stage 3 or 4 CKD and biochemical evidence of abnormal phosphorus metabolism, defined as the presence of hyperphosphatemia, secondary hyperparathyroidism, or increased urinary phosphorus. The study was approved by the institutional review boards at the Memphis and Salem Veterans Affairs Medical Centers. All procedures were carried out in accordance with the Declaration of Helsinki.

Study participants were veterans and nonveterans (at the Salem Veterans Affairs Medical Center only) enrolled between June 2011 and January 2016. Main inclusion criteria were estimated glomerular filtration rate of 15 to 60 ml/min per 1.73 m^2 according to the 4-variable isotope dilution mass spectrometry–traceable Modification of Diet in Renal Disease Study equation, and a serum phosphorus >4.6 mg/dl or plasma intact PTH level above 65 pg/ml or TRP <80%. Patients were excluded if they had undergone any invasive intervention on their coronary arteries (e.g., coronary artery bypass grafting or percutaneous coronary intervention), due to the marked effect of these interventions on coronary calcium deposition. Patients could not have received any phosphate binder for at least 4 weeks before screening, and those on vitamin D therapy had to receive stable doses of it for at least 4 weeks before screening and throughout the study period. After prescreening of electronic medical records, potentially eligible patients underwent informed consent followed by 2 screening visits 1 to 2 weeks apart. Detailed inclusion and exclusion criteria and the various study procedures and methods are described in Supplementary Appendix S1. Patients who satisfied all the inclusion and none of the exclusion criteria at the end of the screening period were block-randomized 1:1:1 after stratification by CKD stage to oral lanthanum carbonate, calcium acetate, or dietary intervention, using a computer-generated allocation sequence that was delivered to the study personnel performing the treatment allocation in sequentially numbered sealed envelopes. Patients randomized to one of the phosphate binders underwent as-needed dose titration at monthly visits for the first 3 months of the trial, based on measurements of serum phosphorus, PTH, and TRP, and continued taking the dose achieved at the 3-month visit for the remainder of the study (Supplementary Appendix S1). Patients randomized to the dietary intervention received a pamphlet detailing dietary strategies, which was followed by detailed assessment and counseling by a certified renal dietician if needed (Supplementary Appendix S1). Adherence to the prescribed medication regimens was monitored by performing pill counts at each visit, and considered to be present if >80% of pills were used.

Following randomization, patients were assessed every month for 3 months and then every 3 months for 9 months, with the recording of any adverse events, assessment of medication adherence, and the measurement of biochemical parameters, including serum phosphorus, PTH, calcium, urine phosphorus, and

creatinine and calculation of TRP (see Supplementary Appendix S1 for a complete list of tests and formula for TRP) by the clinical laboratories of the participating institutions. Plasma bone-specific alkaline phosphatase (bALP) and FGF23 were measured at baseline (averaging the values obtained at the 2 screening visits) and at the 12-month visit. FGF23 was measured using an intact FGF23 enzyme-linked immunosorbent assay (Kainos Laboratories, Inc., Tokyo, Japan) in 71 patients enrolled at the Memphis Veterans Affairs Medical Center. Vascular parameters (coronary calcium score [defined as the Agatson score], pulse wave velocity, and reactive hyperemia index for endothelial function[27,28]; see Supplementary Appendix S1) were also measured during baseline and at the 12-month visit in all participants.

The co-primary efficacy end points of the study were month 12 (vs. baseline) biochemical (serum phosphorus, calcium, PTH, FGF-23, TRP, and bALP) and vascular parameters (coronary calcium score, pulse wave velocity, and reactive hyperemia index) in all patients. Secondary efficacy end points included between-treatment differences in change for each (biochemical and vascular) parameter between month 12 and baseline. The primary safety end points were hypercalcemia and hyperphosphatemia, defined as a serum albumin–corrected calcium of >10.7 mg/dl, and a serum phosphorus >4.6 mg/dl. If corrected calcium exceeded 10.7 mg/dl, calcium acetate was to be stopped with corrected calcium levels followed weekly until normalization, and calcium acetate restarted at a lowered dose once serum calcium was <10.7 mg/dl. If serum phosphorus level exceeded 4.6 mg/dl, interventions including dietary advice or alternative phosphorus binders (as needed) could be implemented at the discretion of the investigators and titrated to normalization of serum phosphorus.

Statistical Considerations

Sample size calculations were performed for the effects of the interventions on coronary calcium score and biochemical parameters for both within-patient change and for between-group differences. As the sample size estimates for between-group differences were higher for all end points, these were used to determine the final study sample size. For between-group differences in changes in coronary calcium score, we estimated that 29 patients per group are needed to detect a significant difference with a power of 80% and a significance level of .05, assuming a difference in means between 2 groups of approximately 150 and an SD of 200 (translating to an effect size of Cohen's $d = 0.75$)[29] based on data from Russo *et al.*[21] This sample size of 29 in all 3 groups results in comparable power for the analysis of variance test as also applied in this analysis; for example, if the third group's mean is assumed to differ approximately 130 from the same comparison group and with same SD 200 (Cohen's $f = 0.33$), the resulting power for the analysis of variance test is 78%. For the effect of various interventions on different biochemical parameters, we made assumptions based on results from studies by Sprague *et al.*[30] and Russo *et al.*,[21] resulting in a lowest estimate of 9 patients (3 patients/group) and a highest estimate of 90 patients (30 patients/group) needed to detect a difference with a power of 80% and a significance level of .05. Using the highest estimated number from these calculations and to account for potential attrition, we established a final sample size of 120 patients (40 patients/intervention). Patients who discontinued treatment were encouraged to continue attending study visits and remained in the group to which they were originally randomized if their data were available for final analysis, but were deemed noncompliant when assessing treatment adherence.

Continuous data are presented as means ± SDs or medians (25th, 75th percentiles) and categorical data are presented as numbers (percentages). Skewed variables were log-transformed. Within-group differences were compared by paired t tests, and between-group differences were compared by analysis of variance. All analyses were intention to treat. All tests were 2-tailed and $P < .05$ was considered significant. All analyses were prespecified and there was no adjustment for multiple comparisons. All analyses were performed using Stata version 11 (StataCorp, College Station, TX; www.stata.com).

RESULTS

The study participant flow is presented in Figure 1. A total of 166 patients were deemed eligible based on electronic chart review and underwent screening. Of the 120 patients who were randomized to one of the treatment arms, 107 completed 12 months of intervention (37 in the lanthanum carbonate arm, 35 in the calcium acetate arm, and 35 in the dietary intervention arm) and provided data for final analyses. Two patients died (both in the dietary intervention arm), with both events deemed unrelated to the study intervention or procedures. None of the additional 11 early terminations were caused by treatment-related adverse events. No patient crossed over to the other treatment group, no patient required rescue therapy, and no patient required treatment interruption due to hypercalcemia or hyperphosphatemia.

Baseline characteristics overall and in patients randomized to the different interventions are shown in

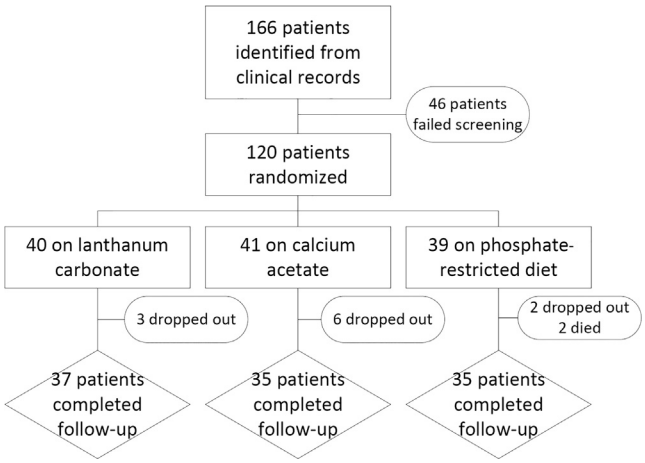

Figure 1. Flowchart of patient selection.

Table 1. Patients were 66.1 ± 11.4 years old, 87% were men, 52% were African American, 55% were diabetic, and the mean estimated glomerular filtration rate was 32 ± 10 ml/min per 1.73 m^2. None of the baseline patient characteristics were significantly different among the 3 intervention arms, except for reactive hyperemia index, which was lower in patients assigned to calcium acetate. The median prescribed dose of lanthanum carbonate was 500 mg (25th, 75th percentile: 500–1000 mg, range 500–1500 mg), and the median prescribed dose of calcium acetate was 1334 mg (25th, 75th percentile: 1334–1334 mg, range 667–2001 mg) after 3 months of titration. Compliance with the prescribed intervention (defined as consumption of >80% of prescribed pills at each visit) was present in 81% of patients on lanthanum carbonate and 69% of patients on calcium acetate who completed the study.

Table 2 shows biochemical and vascular parameters at month 12 compared with baseline. Serum levels of bALP were significantly lower, and those of FGF23 were significantly higher at month 12 compared with baseline. None of the other biochemical or vascular characteristics were significantly different between month 12 and baseline in the overall study sample. Table 3 shows differences between the various biochemical and vascular parameters between month 12 and baseline in groups of patients assigned to the 3 different interventions, with detailed information on all measurements at each study visit shown in Table 4. Differences of biochemical and vascular parameters between month 12 and baseline were similar for all interventions, except for PTH, which was suppressed in patients receiving calcium acetate but increased in patients receiving lanthanum carbonate and dietary restriction (Table 3). Clinical adverse and severe adverse events occurred with similar frequency in the 3 treatment groups (data not shown).

Table 1. Baseline characteristics overall and of patients randomized to dietary intervention, calcium acetate, and lanthanum carbonate

Characteristics	All (n = 120)	Lanthanum (n = 40)	Ca acetate (n = 41)	Diet (n = 39)	P
Age (yr)	66.1 ± 11.4	64.6 ± 11.2	67.1 ± 11.8	66.5 ± 11.4	.6
Gender (men)	105 (87)	34 (85)	35 (85)	36 (92)	.5
Race (African American)	63 (52)	21 (52)	24 (58)	18 (46)	.8
Body mass index (kg/m^2)	33.6 ± 8.3	32.5 ± 8.0	34.1 ± 9.0	34.2 ± 8.1	.6
Systolic blood pressure (mm Hg)	139 ± 17	138 ± 19	140 ± 15	140 ± 16	.8
Diastolic blood pressure (mm Hg)	80 ± 12	79 ± 12	82 ± 11	79 ± 13	.5
Coronary artery disease	13 (11)	4 (10)	4 (10)	5 (13)	.9
Diabetes mellitus	66 (55)	24 (60)	21 (51)	21 (54)	.7
Hypertension	112 (93)	39 (97)	37 (90)	36 (92)	.4
Vitamin D therapy	76 (63)	20 (50)	27 (66)	29 (74)	.07
eGFR (ml/min per 1.73 m^2)	32 ± 10	32 ± 11	32 ± 9	31 ± 10	.8
Serum phosphorus (mg/dl)	3.8 ± 0.6	3.9 ± 0.6	3.8 ± 0.5	3.8 ± 0.5	.4
iPTH (pg/ml)	142 (106, 204)	141 (111, 202)	150 (100, 203)	132 (106, 220)	.9
FGF23 (pg/ml)	139 (86, 213)	169 (115, 199)	105 (76, 175)	125 (95, 238)	.4
Tubular reabsorption of phosphorus (%)	65 (53, 71)	65 (55, 71)	67 (52, 77)	62 (52, 67)	.21
25OHD (ng/ml)	28 ± 12	27 ± 11	28 ± 12	30 ± 14	.4
Bone-specific alkaline phosphatase (μg/l)	15.9 (12.3, 21.1)	14.5 (12.1, 20.7)	17.9 (13.8, 23.9)	15.3 (11.7, 20.3)	.09
Serum calcium (mg/dl)	9.1 ± 0.5	9.1 ± 0.5	9.1 ± 0.5	9.2 ± 0.5	.6
Serum albumin (g/dl)	4.0 ± 0.3	4.1 ± 0.3	4.0 ± 0.4	4.0 ± 0.3	.4
Pulse wave velocity (m/s)	11.1 (8.7, 13.5)	10.9 (8.5, 13.7)	10.7 (9.1, 12.5)	11.4 (8.3, 13.1)	.9
Reactive hyperemia index	2.05 ± 0.58	2.21 ± 0.62	1.87 ± 0.53	2.09 ± 0.55	.03
Coronary calcium score	317 (36, 1009)	431 (52, 1107)	203 (32, 1001)	214 (16, 963)	.8

eGFR, estimated glomerular filtration rate; FGF23, fibroblast growth factor 23; iPTH, intact parathyroid hormone; 25OHD, 25 hydroxyl vitamin D.
Data are presented as means ± SDs, median (25th, 75th percentile), or number (%). Baseline values for biochemical parameters were defined as the average of the 2 values measured at 7–14 days' interval during screening evaluations. Comparisons among the 3 groups were made by analysis of variance or χ^2 tests.
To convert GFR in ml/min per 1.73 m^2 to ml/s per 1.73 m^2, multiply by 0.01667; serum iPTH in pg/ml to pmol/l multiply by 0.1061; serum 25OH vitamin D from ng/ml to nmol/l, multiply by 2.496; serum calcium in mg/dl to mmol/l, multiply by 0.2495; serum phosphorus in mg/dl to mmol/l, multiply by 0.3229.

Table 2. Month 12 versus baseline values of biochemical and vascular parameters in 107 patients who completed 1 year of intervention

Characteristics	Baseline	Month 12	P
Serum phosphorus (mg/dl)	3.8 ± 0.6	3.7 ± 0.8	.15
iPTH (pg/ml)	141 (105, 203)	146 (92, 204)	.5
Tubular reabsorption of phosphorus (%)	63 ± 14	64 ± 16	.5
Serum calcium (mg/dl)	9.2 ± 0.5	9.1 ± 0.6	.15
Bone-specific alkaline phosphatase (μg/l)	15.8 (12.1, 21.1)	13.8 (10.6, 17.6)	<.001
FGF23 (pg/ml)	133 (86, 189)	132 (99, 216)	.002
Coronary artery calcium score	356 (40, 1016)	309 (51, 1048)	.5
Pulse wave velocity (m/s)	11.5 (8.7, 13.1)	10.7 (8.5, 13.7)	.4
Reactive hyperemia index	2.03 ± 0.59	2.05 ± 0.61	.8

FGF23, fibroblast growth factor 23; iPTH, intact parathyroid hormone.
Data are presented as means ± SDs or median (25th, 75th percentile). Comparisons were made by paired *t* tests.
To convert serum iPTH in pg/ml to pmol/l, multiply by 0.1061; serum calcium in mg/dl to mmol/l, multiply by 0.2495; serum phosphorus in mg/dl to mmol/l, multiply by 0.3229.

DISCUSSION

In this 1-year prospective, randomized, active comparator controlled, open-label, 2-center clinical trial of interventions aimed at correcting abnormal phosphorus homeostasis in patients with CKD stages 3/4, we did not find a significant effect on biochemical abnormalities except for a decrease in bALP, or on vascular parameters in the overall study population. Changes in all study end points were similar in patients assigned to the 3 interventions, except for PTH levels, which were statistically significantly (but only to a modest degree) suppressed in patients assigned to calcium acetate.

The hypothesis that elevations in serum phosphorus level are deleterious is rooted in observations showing associations between higher serum phosphorus levels and adverse clinical outcomes in patients with all levels of kidney function.[10–14] A causal role of phosphorus in these associations has been implied based on experimental data suggesting that phosphorus can be instrumental in inducing pathologic changes in the vasculature,[16,17] and based on observational studies showing associations between the administration of phosphate binders and better clinical outcomes in patients with NDD-CKD[19,20] and end-stage renal disease.[18] However, no clinical trials were ever designed to prove that lowering serum phosphorus (vs. not lowering it) can improve mortality or cardiovascular event rates, and a network meta-analysis of available clinical trial data from studies assessing other end points also suggested no effects on mortality compared with placebo.[31] An RCT examining the effects of sevelamer hydrochloride versus calcium carbonate versus dietary phosphate restriction on coronary calcification over 2 years in 90 patients with NDD-CKD in Italy showed suppression of urine phosphorus by both binders but an increase in urine phosphorus in the group receiving diet restriction; no changes were detected in PTH or in serum phosphorus in any of the groups, and FGF23 levels were not measured.[21] Coronary calcification was stable in patients receiving sevelamer, but increased in patients receiving calcium carbonate and increased even more in those assigned to the diet intervention.[21] Contrasting these findings, a pilot RCT in 148 patients with NDD-CKD assigned to 3 different phosphate binders versus placebo showed that the phosphate binders resulted in modest decreases in serum and urine phosphorus, but no effect on PTH and FGF23, and an increase in coronary calcification compared with placebo.[22] Another RCT examining lanthanum carbonate versus placebo for 12 months in 38 normophosphatemic patients with CKD stage 3 reported no effects on biochemical markers (including serum phosphorus, PTH, TRP, and FGF23) and on vascular parameters (vascular calcification, pulse wave velocity, and carotid intima media thickness). Opposite findings were reported in an RCT of 100 patients with CKD stage

Table 3. Differences in biochemical and vascular parameters in patients allocated to 3 different phosphate-lowering treatments, at month 12 versus baseline

Characteristics		Difference between month 12 and baseline (mean ± SD)	P
Phosphorus (mg/dl)	Lanthanum	−0.17 ± 0.78	.25
	Ca acetate	−0.21 ± 0.72	
	Diet	0.07 ± 0.74	
iPTH (pg/ml)	Lanthanum	21 ± 80	<.001
	Ca acetate	−33 ± 46	
	Diet	35 ± 82	
TRP (%)	Lanthanum	1.0 ± 12.6	.4
	Ca acetate	3.7 ± 22.4	
	Diet	−2.1 ± 13.5	
Calcium (mg/dl)	Lanthanum	−0.13 ± 0.50	.28
	Ca acetate	0.04 ± 0.43	
	Diet	−0.10 ± 0.45	
Bone-specific ALP (μg/l)	Lanthanum	−2.24 ± 6.31	.18
	Ca acetate	−4.43 ± 5.45	
	Diet	−1.98 ± 6.28	
FGF23 (pg/ml)	Lanthanum	81 ± 306	.07
	Ca acetate	44 ± 145	
	Diet	104 ± 199	
CAC (Agatson score)	Lanthanum	137 ± 351	.19
	Ca acetate	84 ± 243	
	Diet	−198 ± 1762	
PWV (m/s)	Lanthanum	−0.05 ± 3.30	.6
	Ca acetate	0.11 ± 2.98	
	Diet	0.61 ± 3.04	
RHI	Lanthanum	0.07 ± 0.66	.5
	Ca acetate	0.07 ± 0.69	
	Diet	−0.10 ± 0.69	

ALP, alkaline phosphatase; Ca acetate, calcium acetate; CAC, coronary artery calcium; FGF23, fibroblast growth factor 23; PTH, parathyroid hormone; PWV, pulse wave velocity; RHI, reactive hyperemia index; TRP, tubular reabsorption of phosphorus.
Data are presented as means ± SDs. Comparisons were made by analysis of variance.
To convert serum iPTH in pg/ml to pmol/l multiply by 0.1061; serum calcium in mg/dl to mmol/l, multiply by 0.2495; serum phosphorus in mg/dl to mmol/l, multiply by 0.3229.

Table 4. Biochemical and vascular parameters at baseline and at various study time points in 108 patients receiving various interventions and completing 12 months of follow-up

Characteristics	Assignment	Baseline	Month 1	Month 2	Month 3	Month 6	Month 9	Month 12	P^a	P^b
Phosphorus (mg/dl)	Diet	3.9 ± 0.5	3.7 ± 0.8	3.6 ± 0.7	3.8 ± 0.6	3.9 ± 0.9	4.1 ± 1.1	3.9 ± 0.8	.6	.25
	Ca acetate	3.7 ± 0.5	3.5 ± 0.6	3.6 ± 0.6	3.8 ± 0.7	3.7 ± 0.6	3.5 ± 0.6	3.5 ± 0.8	.1	
	Lanthanum	3.9 ± 0.6	3.6 ± 0.8	3.5 ± 0.6	3.6 ± 0.7	3.7 ± 0.7	3.8 ± 0.9	3.7 ± 0.9	.18	
PTH (pg/ml)	Diet	130 (106, 228)	149 (91, 228)	136 (99, 236)	122 (81, 183)	163 (114,246)	180 (112,307)	158 (107,248)	.07	<.001
	Ca acetate	147 (97,195)	118 (85,173)	97 (76,154)	139 (980,169)	99 (60,167)	109 (68,161)	108 (79,177)	<.001	
	Lanthanum	141 (110,201)	136 (102,177)	127 (92,169)	131 (94,162)	143 (113,190)	176 (90,208)	161 (102,215)	.6	
TRP (%)	Diet	0.58 ± 0.13	0.60 ± 0.14	0.58 ± 0.14	0.64 ± 0.12	0.58 ± 0.13	0.55 ± 0.19	0.55 ± 0.15	.4	.4
	Ca acetate	0.66 ± 0.15	0.68 ± 0.13	0.71 ± 0.13	0.71 ± 0.14	0.70 ± 0.11	0.69 ± 0.14	0.69 ± 0.17	.3	
	Lanthanum	0.65 ± 0.14	0.66 ± 0.14	0.68 ± 0.14	0.67 ± 0.15	0.66 ± 0.14	0.69 ± 0.13	0.66 ± 0.13	.5	
Calcium (mg/dl)	Diet	9.2 ± 0.5	9.1 ± 0.5	9.1 ± 0.5	9.2 ± 0.5	9.1 ± 0.6	9.0 ± 0.7	9.1 ± 0.6	.2	.28
	Ca acetate	9.2 ± 0.6	9.1 ± 0.5	9.2 ± 0.5	9.3 ± 0.5	9.3 ± 0.6	9.2 ± 0.8	9.2 ± 0.6	.6	
	Lanthanum	9.1 ± 0.5	9.0 ± 0.7	9.1 ± 0.6	9.1 ± 0.6	9.1 ± 0.6	9.0 ± 0.7	9.0 ± 0.5	.11	
Bone-specific ALP (μg/l)	Diet	15.3 (11.6, 20.6)						13.9 (10.0, 19.7)	.05	.18
	Ca acetate	17.5 (13.2, 22.7)						13.4 (10.9, 15.4)	<.001	
	Lanthanum	14.5 (12.1, 20.9)						13.7 (10.4, 17.6)	.01	
FGF23 (pg/ml)	Diet	125 (95, 238)						179 (111, 294)	.006	.07
	Ca acetate	105 (76, 175)						109 (71, 180)	.4	
	Lanthanum	169 (115, 199)						132 (101, 216)	.15	
PWV (m/s)	Diet	11.4 (8.7, 12.8)						10.5 (7.9, 14.0)	.3	.6
	Ca acetate	10.6 (8.9, 12.3)						10.7 (9.0, 13.2)	.7	
	Lanthanum	10.7 (8.6, 13.7)						11.1 (8.5, 13.8)	.9	
CAC (Agatson score)	Diet	214 (16,1739)						263 (40,1800)	.6	.19
	Ca acetate	248 (36,922)						161 (44,905)	.8	
	Lanthanum	457 (113,1108)						487 (172,1188)	.05	
RHI	Diet	2.10 ± 0.57						2.01 ± 0.50	.4	.5
	Ca acetate	1.81 ± 0.52						1.85 ± 0.64	.6	
	Lanthanum	2.18 ± 0.60						2.26 ± 0.63	.6	

ALP, alkaline phosphatase; Ca acetate, calcium acetate; CAC, coronary artery calcium; FGF23, fibroblast growth factor 23; PTH, parathyroid hormone; PWV, pulse wave velocity; RHI, reactive hyperemia index; TRP, tubular reabsorption of phosphorus.
Values presented as means ± SD or medians (25th, 75th percentiles).
[a] *P* value for intraindividual difference between month 12 and baseline.
[b] *P* value for between-treatment arm difference in change from baseline to month 12.

4 assigned to receive sevelamer versus calcium acetate for 8 weeks, which showed significant decreases in serum phosphorus in both treatment arms, and decreases in FGF23 and improved flow-mediated vasodilatation in patients receiving sevelamer.[25] Based on the results of these (admittedly suboptimal) clinical trials, the most recent Kidney Disease Global Outcomes clinical practice guidelines have questioned the efficacy and safety of phosphate binder therapy in NDD-CKD,[26] and made only suggestions (as opposed to recommendations) based on low-level evidence about the treatment of hyperphosphatemia in this population. The lack of a benefit seen in our study is in general concordant with these recommendations, although the small size of all the available clinical trials makes a conclusive assessment of the benefits of phosphate binders in NDD-CKD difficult.

The reason for the discrepant results of the various RCTs (including ours) on both biochemical and vascular end points may be related to the small size of the trials and the heterogeneity of patient populations and the applied treatment regimens, but also the differences in treatment duration. The latter factor may be of particular importance given the longer time it might take for vascular effects, such as calcification and changes in vascular stiffness, to materialize, the difficulty adhering to binder regimens over extended periods of time, and also because of the potential for adaptive upregulation of intestinal phosphate transporters in the face of phosphorus-lowering therapies,[32,33] which could offset the effects of binders and mitigate their long-term clinical effectiveness. The latter phenomenon has resulted in attempts to design interventions that combine phosphate binders with those that inhibit phosphate transporters,[34] the results of which are pending.

The results of our study need to be interpreted with due consideration of its limitations. We examined predominantly men at 2 institutions, which limits the generalizability of our results. The interventions were not blinded, which could have introduced bias. This is less likely in a study with objective end points like ours, but we cannot rule out the possibility that knowledge of the intervention may have affected patients' adherence to the intervention. Only 71 patients had measurements of FGF23 level performed, which

limits our ability to compare the effects of the various interventions on its plasma concentration, but is sufficient to assess overall intraindividual changes. Like with any RCT, the external validity of our study is also limited by our trial design. Our study was powered to primarily detect changes in biochemical parameters, but it may have been underpowered to detect meaningful changes in some of the examined vascular parameters, which also may require a longer time to be affected by interventions. Larger trials of longer duration may be needed to determine with certainty the effect of phosphate binders on vascular health.

In conclusion, in this small clinical trial, limiting phosphorus absorption by the administration of lanthanum carbonate, calcium acetate, or a dietary intervention over 1 year resulted in a lowering of bALP, but no other biochemical or vascular changes in patients with CKD stages 3 and 4. Larger clinical trials of longer duration may be needed to examine the effect of phosphate binders on vascular parameters and on hard clinical end points.

DISCLOSURE

CPK received research support from Shire to conduct this trial, and honoraria from Amgen, Keryx, and Sanofi-Aventis. All the other authors declared no competing interests.

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Results of this study were presented at the American Society of Nephrology Kidney Week 2017.

SUPPLEMENTARY MATERIAL

Appendix S1. Detailed inclusion and exclusion criteria, study procedures, and time and events schedule.

Supplementary information is linked to the online version of the paper at http://www.kireports.org/.

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