Effects of Dietary Phosphate Restriction and Phosphate Binders on FGF23 Levels in CKD

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Summary

Background Elevated levels of fibroblast growth factor 23 (FGF23) are associated with increased risk of adverse outcomes in patients with CKD. Reducing dietary phosphate intake or absorption may decrease FGF23 levels, but data on the combined effects of dietary phosphate restriction and phosphate binders in CKD are limited.

Design, setting, participants, & measurements In this 2×2 factorial, single-blinded, placebo-controlled, 3-month study, conducted between July 2009 and March 2012, 39 patients with CKD stages 3 or 4 and normal serum phosphate levels were randomly assigned to one of four groups: *ad libitum* diet plus lanthanum carbonate (LC) placebo (n=10), 900-mg phosphate diet plus LC placebo (n=10), *ad libitum* diet plus LC (n=11), or 900-mg phosphate diet plus LC (n=8). The dose of LC was 1000 mg three times daily with meals. Dietary restriction was accomplished with outpatient counseling. The primary end point was change in FGF23 levels from baseline.

Results Compared with *ad libitum* diet, the 900-mg phosphate diet did not significantly reduce FGF23 levels (diet × time interaction, P=0.05). Compared with placebo, LC alone also did not significantly reduce FGF23 levels (LC × time interaction, P=0.21). However, the dual intervention significantly decreased FGF23 levels throughout the study period (diet × LC × time interaction, P=0.02), resulting in a 35% (95% confidence interval, 8%–62%) reduction by study end.

Conclusion The combination of LC plus counseling for a phosphate-restricted diet decreased FGF23 levels in patients with CKD stages 3−4 and normal serum phosphate levels.

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Introduction

An elevation of fibroblast growth factor 23 (FGF23) levels is among the earliest and most common manifestations of disordered mineral metabolism in CKD (1). Epidemiologic and experimental data support FGF23 elevation as a novel risk factor for ESRD, cardiovascular disease, and mortality (2–5). These findings, along with evidence that FGF23 levels increase with dietary phosphate loading and decrease with restriction (6–8), have stimulated interest in developing clinical strategies to reduce FGF23 levels in CKD.

Blocking dietary phosphate absorption with phosphate binders may decrease FGF23 levels in patients with CKD (9–11), but the effects of reducing dietary phosphate intake have been less well studied and yielded inconsistent results (12–14). Additional limitations of the existing literature on FGF23 reduction in CKD include lack of information on the longer-term effectiveness of dietary interventions, sparse data on the efficacy of strategies based on outpatient dietary counseling that are feasible in usual clinical practice, and uncertainty about the effect of combining outpatient dietary counseling with phosphate binders. We conducted a 2×2 factorial, single-blinded, placebo-controlled, randomized study to test the hypothesis that a 3-month phosphate binder intervention alone or in combination with dietary phosphate restriction achieved through outpatient dietary counseling would decrease FGF23 levels in patients with CKD stages 3−4.

Materials and Methods

Study Procedures

After a screening visit, participants underwent a 2-week run-in period encompassing three separate visits during which baseline blood and urine were collected. This was followed by a 3-month intervention period with biweekly data collection (Figure 1A). Visit time of day was not standardized. Given the direct hypertrophic effect of FGF23 on the myocardium (5), we also performed a secondary exploratory analysis of the effects of the interventions on cardiac structure and function, as assessed by echocardiography at baseline and end of study (Supplementary Data). The study was approved by the University of Miami Institutional Review Board, was registered at ClinicalTrials.gov on February 12, 2009 (NCT00843349),

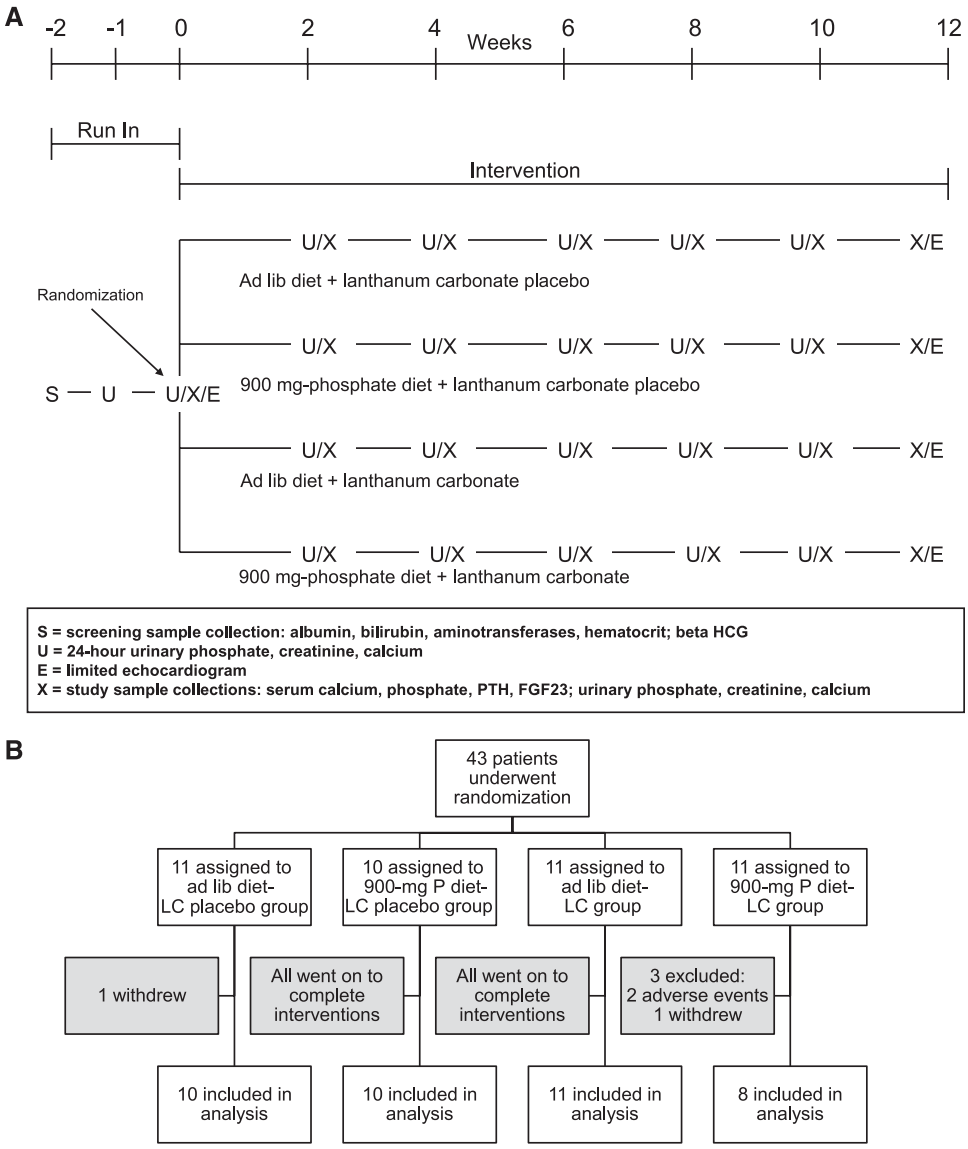

Figure 1. | **Study design and flow of participants.** (A) Study design. (B) Thirty-nine patients completed 3 months of interventions according to random assignment to one of four groups: *ad libitum* diet plus lanthanum carbonate (LC) placebo, 900-mg phosphate (P) diet plus LC placebo, *ad libitum* diet plus LC and 900-mg P diet plus LC.

and was conducted at the Clinical Research Center between July 2009 and March 2012. Written informed consent was obtained from each participant.

Study Participants

Eligible participants were age 18 years or older, had an estimated GFR of 15−59 ml/min per 1.73 m^2 on the basis of the Modification of Diet in Renal Disease equation, and had normal phosphate levels (2.5–4.6 mg/dl). Patients were excluded if they had hyperphosphatemia (phosphate >4.6 mg/dl), rapidly advancing CKD, primary hyper- or hypoparathyroidism or prior parathyroidectomy, malabsorption, malnutrition (serum albumin <3.0 mg/dl), liver disease (alanine aminotransferase or aspartate aminotransferase >100 U/L), cholestasis (direct bilirubin >1.0 mg/dl), or anemia (hematocrit <27%); had received prior counseling by a nutritionist within 6 months; were taking phosphate binders; were hospitalized within the previous 4 weeks; were pregnant or breastfeeding mothers; or were unable to provide written informed consent. Use of active and nutritional vitamin D supplements was permitted, provided that the doses were stable for 3 months before enrollment.

Randomization, Interventions, and Adherence

Eligible participants were randomly assigned to one of four treatment groups: *(1) ad libitum* diet and lanthanum carbonate (LC) placebo, *(2)* 900-mg phosphate diet and LC placebo, *(3) ad libitum* diet and LC, and *(4)* 900-mg phosphate diet and LC. Randomization was stratified by CKD stage using the permuted block algorithm by a research pharmacist. The phosphate binder intervention was double-blinded, but it was necessary for the dietitian and

participants to be unblinded to the assigned dietary counseling group. The investigators remained blinded to the dietary group.

The dose of LC was 1000 mg, three times daily, with meals. This fixed dose was chosen because it reduced urinary phosphate excretion safely and effectively in CKD stages 3–4 (13,15). Matching placebo was prescribed at the same frequency. The doses were halved in participants who reported adverse effects and in those who developed hypophosphatemia (phosphate level < 2.5 mg/dl). Participants who did not eat regular daily meals were instructed to take the full dose with larger meals and half the dose with snacks. To improve adherence to study medications, adherence was monitored by pill counts and reinforced weekly through phone calls and biweekly at in-person visits.

Baseline and follow-up dietary phosphate intake was assessed with 3-day food records that were analyzed using Nutrition Data System for Research software (Nutrition Coordinating Center, University of Minnesota, Minneapolis, MN). The CRC registered dietitian (G.E.) used the food records to counsel participants to follow a diet tailored to their randomization group. Participants assigned to the phosphate-restricted group were counseled not to exceed a daily phosphate intake of 900 mg on the basis of CKD guidelines (16). To achieve this target, the dietitian counseled participants to substitute high-phosphate foods with lower-phosphate alternatives, avoid processed foods rich in phosphate additives, limit consumption of dairy products, and control portion sizes of animal protein. Participants assigned to the unrestricted diet received advice about healthy eating and weight maintenance and were counseled to follow their usual diets. All participants met with the dietitian, who provided personalized dietary recommendations during a 60-minute session at the randomization visit and at 30-minute follow-up visits during weeks 2, 8, and 12, when adherence with the dietary intervention was reassessed with 3-day food records.

Outcomes

Nonfasting blood and urinary markers of mineral metabolism were assessed biweekly (Figure 1A). The primary endpoints were absolute and percentage changes in FGF23 levels from baseline. Other outcomes included changes in serum phosphate, urinary phosphate and calcium, parathyroid hormone (PTH), and 1,25-dihydroxyvitamin D levels. Assay details are provided in the Supplementary Data.

Sample Size

In the absence of preliminary data on the 3-month effects of dietary manipulations on FGF23 levels, we based the sample size calculation on the estimated effects of LC compared with placebo. Assuming a conservative SD of the change in FGF23 from baseline to end of study of 33%, we estimated that 20 participants treated with LC and 20 treated with placebo would provide 80% power at an α of 5% to detect a between-group difference in change in FGF23 of 30%, which is similar to the reduction observed previously (9).

Statistical Analyses

We used standard descriptive statistics to assess baseline clinical and laboratory data. To evaluate the stability of preintervention FGF23, PTH, and serum phosphate levels, we calculated intraclass correlations with 95% confidence intervals (CIs) from three serial measurements of each analyte, which were assessed at three separate visits during the 2-week run-in period.

We evaluated changes over time in FGF23 and other mineral metabolites using mixed-model repeated-measures analyses. To determine the efficacy of 900-mg phosphate diet alone and LC alone, we tested for interaction between time and diet (two diet groups combined) and between time and LC (two LC groups combined) in relation to FGF23 and the other outcome variables. To determine the efficacy of the combined intervention, we tested for interaction between time, diet, and LC in relation to FGF23 and the other outcome variables. Model terms included time, treatment (diet and LC), the interaction between treatment and time (diet × time and LC × time), the interaction between treatments (diet × LC), and the interaction between treatments and time (diet × LC × time). We also tested for significant within-group changes. Natural log transformations were used for analyses of non–normally distributed dependent variables, including FGF23. We calculated Spearman correlation coefficients to analyze the effect of baseline FGF23 on follow-up FGF23. Next, we adjusted the mixed models for baseline FGF23 and calculated a single, baseline FGF23-adjusted summary value of all the postrandomization FGF23 levels within each group using the least square means method. Paired *t* tests were used to examine within-group changes in dietary intake data, echocardiographic measures, and 1,25-dihydroxyvitamin D levels.

Analyses were performed with SAS software, version 9.2 (SAS Institute, Inc., Cary, NC). All statistical tests were two sided, and $P < 0.05$ was considered to represent a statistically significant difference.

Results

Participant Baseline Characteristics

Between July 2009 and November 2011, 73 participants were screened for eligibility, of whom 43 (59%) underwent randomization (Figure 1B). Four participants withdrew before the first follow-up visit, and 39 participants completed the entire study: 10 in the *ad libitum* diet–LC placebo group; 10 in the 900-mg phosphate diet–LC placebo group; 11 in the *ad libitum* diet–LC group; and 8 in the 900-mg phosphate diet–LC group. Apart from differences in FGF23 levels, which were highest in the 900-mg phosphate diet–LC group, baseline characteristics were similar among groups (Table 1). On the basis of three preintervention sets of serial tests, FGF23 had the highest intraclass correlation coefficient (92%; 95% CI, 88%–94%), followed by PTH (82%; 95% CI, 76%–87%) and serum phosphate (53%; 95% CI, 42%–65%). With the lowest within-subject variation, FGF23 was therefore the most reproducible of the three analytes at baseline.

Interventions

Dose reductions of LC or placebo were required in 13 of the 39 participants (33%), but there was no significant difference between LC and placebo (37% versus 30%; P=0.73). Figure 2 shows the biweekly mean delivered LC dose relative to prescribed dose. Seventy-four percent of

Table 1. Baseline characteristics of the participants

Characteristic	All Participants (*n*=39)	*Ad Libitum* Diet–LC Placebo (*n*=10)	900-mg Phosphate Diet–LC Placebo (*n*=10)	*Ad Libitum* Diet–LC (*n*=11)	900-mg Phosphate Diet–LC (*n*=8)	*P* Value
Age (yr)	55.4±10.3	55.1±12.6	56.2±10.1	54.3±9.8	56.1±10.0	0.97
Men, *n* (%)	25 (64.1)	5 (50.0)	7 (70.0)	8 (72.7)	5 (62.5)	0.71
Black, *n* (%)	16 (41.0)	5 (50.0)	4 (40.0)	3 (27.3)	4 (50.0)	0.69
Hispanic, *n* (%)	19 (48.7)	3 (30.0)	4 (40.0)	7 (63.6)	5 (62.5)	0.35
CKD stage 3a/3b/4 (*n*)	12/18/9	5/3/2	2/6/2	2/7/2	3/2/3	0.46
eGFR (ml/min per 1.73 m^2)	37.8±11.0	40.3±12.2	36.9±9.0	38.7±10.0	34.4±14.0	0.71
Creatinine clearance (ml/min)[a]	57.9±22.7	61.2±22.6	60.7±28.7	56.6±19.5	51.5±22.0	0.83
Active vitamin D use, *n* (%)	11 (28.2)	3 (27.3)	4 (36.4)	2 (18.2)	2 (18.2)	0.73
Serum phosphate (mg/dl)	3.6±0.7	3.2±0.6	3.6±0.6	3.9±0.7	3.5±0.8	0.11
Serum calcium (mg/dl)	9.3±0.5	9.4±0.5	9.2±0.4	9.4±0.5	9.3±0.6	0.61
Serum albumin (mg/dl)	4.2±0.4	4.2±0.5	4.0±0.3	4.4±0.5	4.1±0.4	0.27
24-hour urinary phosphate (mg)[a]	612 (525–742)	549 (525–715)	715 (581–1026)	550 (447–659)	671 (592–770)	0.37
24-hour urinary calcium (mg)[a]	50 (21–103)	71 (15–134)	36 (25–73)	70 (29–90)	36 (13–112)	0.82
Fractional excretion of phosphate (%)	0.20±0.07	0.19±0.07	0.20±0.05	0.19±0.06	0.24±0.12	0.52
Fractional excretion of calcium (%)	0.08±0.04	0.06±0.03	0.08±0.03	0.08±0.03	0.09±0.06	0.47
Dietary phosphate (mg/d)	992±326	912±413	926±221	1016±250	1144±395	0.44
Dietary calcium (mg/d)	546±251	469±275	512±116	502±221	741±315	0.23
Caloric intake (kcal/d)	1556±484	1508±515	1493±363	1485±385	1785±679	0.53
FGF23 (RU/ml)	128.5 (89.2–154.6)	90.4 (79.5–118.6)	127.3 (88.2–179.9)	123.2 (94.3–150.7)	228 (152.6–411.5)	0.002
PTH (pg/ml)	54.5 (39.9–73.5)	55.1 (26.4–66.1)	72.8 (39.9–85.2)	51.9 (32.6–64.8)	59.5 (49.0–163.7)	0.19
1,25-dihydroxyvitamin D (pg/ml)	36.9±19.9	44.4±27.2	36.9±19.6	34.1±15.5	31.1±14.4	0.53

Values are *n* (%), means ± SDs, or medians (interquartile ranges). LC, lanthanum carbonate; eGFR, estimated GFR; PTH, parathyroid hormone; FGF23, fibroblast growth factor 23; RU, reference units.

[a]Mean values of two 24-hour urine collections before randomization.

participants were adherent with study drugs, defined as >80% pill consumption throughout the study as estimated from pill counts. Adherence was greatest in the *ad libitum* diet–LC placebo group (90% of participants taking >80% of prescribed pills), followed by the 900-mg phosphate diet–LC group (88%), the *ad libitum* diet–LC group (64%), and the 900-mg phosphate diet–LC placebo group (60%) ($P = 0.29$ for between-group differences).

The mean ± SD estimated dietary phosphate intake at baseline was 992±326 mg/d. Among participants who received active dietary counseling, the mean estimated dietary phosphate intake decreased significantly from 926±221 to 719±161 mg/d in the 900-mg phosphate diet–LC placebo group (P=0.04) and from 1144±395 to 814±190 mg/d in the 900-mg phosphate diet LC group (P=0.004). In contrast, estimated dietary phosphate intake did not change significantly among participants assigned to the *ad libitum* diet (Table 2). Weight did not significantly change in any group (Table 2).

By week 2 after randomization, there were modest trends for decline in 24-hour urinary phosphate excretion in the 900-mg phosphate diet–LC placebo group (change, −13% ±23%) and 900-mg phosphate diet–LC group (change, −19%±34%), but these within-group changes did not reach significance (Figure 3, A and E, and Tables 3 and 4). There were no significant changes in fractional excretion of phosphate in any group (Supplementary Table 1).

FGF23 and Other Mineral Metabolites

Tables 3 and 4 and Figure 3 show the effects of the interventions on levels of blood and urinary analytes during the study across randomization groups. Although there

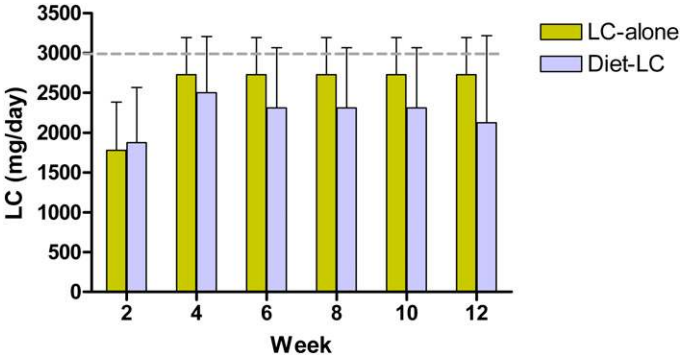

Figure 2. | **Average daily doses of lanthanum carbonate (LC) during the study.** Mean ± SD dose of lanthanum carbonate throughout the study is shown for each treated group in relation to the protocol specified dose, indicated by the dashed horizontal gray line.

Table 2. Effects of study interventions on estimated dietary intake and weight

Variable	Baseline	Week 2	Week 8	Week 12	*P* Value
Caloric intake (kcal/d)					
Ad libitum diet–LC placebo	1508±515	1599±383	1655±541	1770±521	0.1
900-mg phosphate diet–LC placebo	1493±363	1449±450	1620±148	1388±387	0.3
Ad libitum diet–LC	1485±385	1645±624	1496±586	1548±522	0.3
900-mg phosphate diet–LC	1785±679	1150±199	1284±300	1298±239	0.007
Dietary phosphate (mg/d)					
Ad libitum diet–LC placebo	912±413	922±229	1002±325	970±245	0.5
900-mg phosphate diet–LC placebo	926±221	727±258	784±128	719±161	0.04
Ad libitum diet–LC	1016±250	1136±400	938±359	1021±322	0.1
900-mg phosphate diet–LC	1144±395	698±151	795±219	814±190	0.004
Dietary calcium (mg/d)					
Ad libitum diet–LC placebo	469±275	464±180	493±165	437±152	0.7
900-mg phosphate diet–LC placebo	512±116	398±125	421±118	357±113	0.01
Ad libitum diet–LC	502±221	639±206	515±238	498±202	0.06
900-mg phosphate diet–LC	741±315	335±133	356±183	419±137	<0.001
Weight (lb)					
Ad libitum diet–LC placebo	172.2±49.5	172.7±50.7	171.9±49.3	171.9±49.5	0.72
900-mg phosphate diet–LC placebo	197.4±37.6	195.4±38.0	197.0±39.0	192.8±39.2	0.67
Ad libitum diet–LC	198.4±42.4	203.9±46.4	199.6±40.1	201.9±47.3	0.13
900-mg phosphate diet–LC	188.2±34.1	185.1±33.4	185.9±34.8	186.4±34.8	0.52

Values are means ± SDs. *P* values are for within-group changes. LC, lanthanum carbonate.

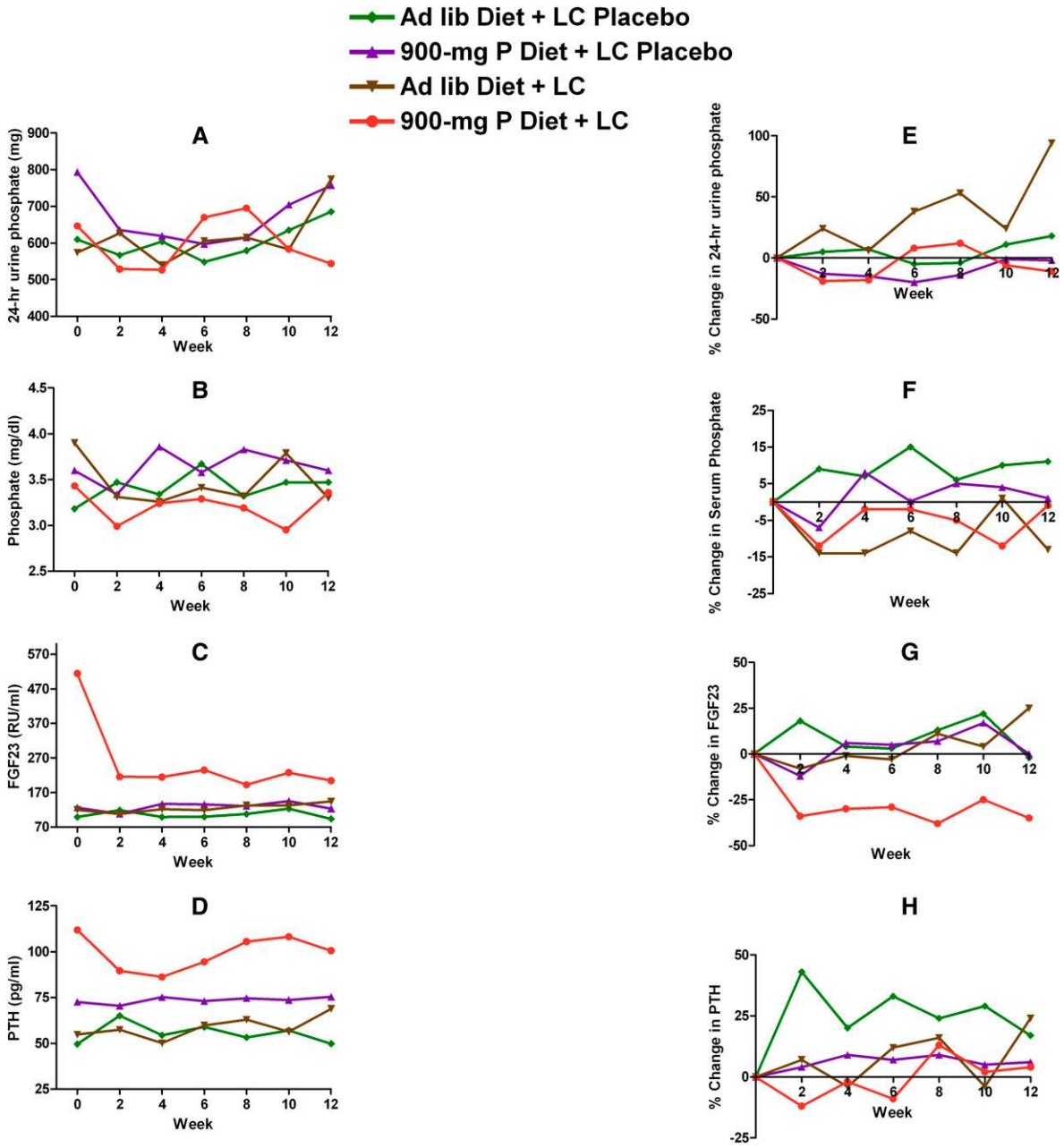

Figure 3. | Combined effects of lanthanum carbonate (LC) and dietary intervention on fibroblast growth factor 23 (FGF23) and other markers of mineral metabolism according to four treatment groups. (A–D) Mean values for 24-hour urinary phosphate, serum phosphate, FGF23, and parathyroid hormone (PTH) throughout the study period. (E–H) Percentage changes in these measures from baseline.

were no significant changes in FGF23 in the LC and 900-mg phosphate diet groups (Figure 3C) (*P* for diet × time interaction = 0.05; *P* for LC × time interaction = 0.21), FGF23 decreased significantly in the 900-mg phosphate diet–LC group (Figure 3C) (*P* for diet × LC × time interaction = 0.02). The corresponding percentage change in FGF23 levels from baseline to end of study was 35% ±32% in the dual intervention group (Figure 3G and Table 4). Adjustment for active vitamin D use did not change the findings.

There were no significant between-group changes in serum phosphate (*P* for diet × LC × time interaction = 0.13) or PTH levels (P for diet × LC × time interaction = 0.72) (Figure 3, B and D). However, PTH levels increased in the *ad libitum* diet–LC placebo group (17%±62%; *P*=0.03 for the within-group difference at end of study (Figure 3, D and H, and Table 4). In addition, no significant between-group changes occurred in 1,25-dihydroxyvitamin D levels, serum calcium, fractional excretion of calcium, or 24-hour urinary calcium throughout the study (data not shown).

Whereas individual participants' longitudinal FGF23 responses varied widely in each group, nearly all participants randomly assigned to the 900-mg phosphate diet–LC

Table 3. Effects of study interventions on absolute levels of mineral metabolites

Variable	*Ad Libitum* Diet–LC Placebo (*n*=10)	900-mg Phosphate Diet–LC Placebo (*n*=10)	*Ad Libitum* Diet–LC (*n*=11)	900-mg Phosphate Diet–LC (*n*=8)
24-hour urinary phosphate (mg)				
Baseline	610±159	794±324	574±162	647±140
Week 2	567±278	636±259	627±390	529±280
Week 4	604±277	619±186	540±201	527±247
Week 6	548±247	597±227	606±189	670±224
Week 8	579±214	615±305	615±240	695±280
Week 10	635±264	705±349	583±222	583±213
Week 12	686±294	757±371	774±438	544±294
Serum phosphate (mg/dl)				
Baseline	3.2±0.6	3.6±0.6	3.9±0.7	3.4±0.7
Week 2	3.5±0.6	3.3±0.4	3.3±0.7	3.0±0.7
Week 4	3.3±0.3	3.9±0.7	3.3±0.6	3.2±0.6
Week 6	3.7±1.2	3.6±0.7	3.4±0.6	3.3±0.7
Week 8	3.3±0.6	3.8±0.8	3.3±0.4	3.2±0.7
Week 10	3.5±0.8	3.7±0.5	3.8±0.7	3.0±0.6
Week 12	3.5±0.8	3.6±0.5	3.3±0.4	3.4±0.6
FGF23 (RU/ml)				
Baseline	99.1±26.7	126.5±48.8	119.7±35.0	513.9±770.7
Week 2	118.8±59.0	108.4±60.1	107.8±43.6	215.4±168.8
Week 4	98.7±31.7	137.1±78.3	121.5±60.1	214.4±158.1
Week 6	99.7±28.3	135.6±88.3	118.8±46.5	235.1±202.2
Week 8	107.7±21.7	130.6±69.1	133.1±48.0	192.2±143.5
Week 10	123.1±81.4	145.1±66.9	132.8±64.3	227.7±145.6
Week 12	93.5±31.4	123.2±46.5	144.0±65.4	204.4±149.7
PTH (pg/ml)				
Baseline	49.6±21.9	72.6±28.6	54.8±31.2	111.9±104.9
Week 2	65.1±34.8	70.5±23.4	57.4±29.2	89.5±71.1
Week 4	54.4±25.4	75.2±24.1	50.2±23.7	86.2±50.1
Week 6	58.9±38.0	73.0±22.7	59.8±37.9	94.5±89.7
Week 8	53.2±25.2	74.7±46.3	62.9±37.7	105.5±72.7
Week 10	57.0±22.9	73.7±27.8	56.3±47.5	108.2±106.3
Week 12	49.8±18.0	75.4±27.7	68.9±43.0	100.5±80.7

Values are means ± SDs. LC, lanthanum carbonate; FGF23, fibroblast growth factor 23; RU, reference units; PTH, parathyroid hormone.

group experienced a decline in FGF23 levels by end of study (Figure 4). In the 900-mg phosphate diet–LC group, percentage change in FGF23 from baseline to study end correlated significantly with baseline levels (r=0.71; P=0.05); the largest reductions were observed in participants with baseline FGF23 levels >200 RU/ml (n=5).

The significant effect of the dual intervention to reduce FGF23 was unchanged when baseline FGF23 levels were included in the mixed model. The mean postintervention, baseline-adjusted FGF23 level in the 900-mg phosphate diet–LC group of 110.0 RU/ml was significantly lower than in the *ad libitum* diet–LC placebo group (133.0 RU/ml; P=0.036), the 900-mg phosphate diet group (147.7 RU/ml; P<0.001), and the *ad libitum* diet–LC group (135.6 RU/ml; P=0.002).

Echocardiographic Measurements

After the 3-month intervention, neither changes in ejection fraction nor changes in measures of wall thickness differed significantly between the groups (Supplementary Table 2).

Safety

Hypophosphatemia necessitating dose reduction developed in three participants. Five participants (three who received LC and two who received LC placebo) reported gastrointestinal adverse effects that subsided with dose reduction. Two participants randomly assigned to the 900-mg phosphate diet–LC group had nausea and vomiting necessitating withdrawal from the study. Three participants (two who received LC and one who received LC placebo) were briefly hospitalized for reasons unrelated to the study.

Discussion

Over the course of 3 months, the combination of LC and counseling for a 900-mg phosphate-restricted diet decreased FGF23 levels in patients with CKD stages 3–4 with normal serum phosphate levels. In contrast, neither phosphate binders alone nor dietary counseling alone reduced FGF23 significantly. Assuming a fixed ceiling of the amount of phosphate that binders can capture, excess consumption of dietary phosphate could limit phosphate binder efficacy, especially when the dose of phosphate

Table 4. Percentage change from baseline in mineral metabolites according to study group

Variable	*Ad Libitum* Diet– LC Placebo (n=10)	900-mg Phosphate Diet–LC Placebo (n=10)	*Ad Libitum* Diet–LC (n=11)	900-mg Phosphate Diet–LC (n=8)
24-hour urinary phosphate (mg)				
Baseline	0	0	0	0
Week 2	0.05±0.38	−0.13±0.23	0.24±0.84	−0.19±0.34
Week 4	0.07±0.44	−0.15±0.28	0.06±0.57	−0.18±0.28
Week 6	−0.05±0.33	−0.20±0.27	0.38±1.49	0.08±0.40
Week 8	−0.04±0.29	−0.14±0.32	0.53±1.77	0.12±0.62
Week 10	0.11±0.33	−0.01±0.51	0.24±1.36	−0.06±0.39
Week 12	0.18±0.34	−0.02±0.37	0.94±2.84	−0.11±0.51
Serum phosphate (mg/dl)				
Baseline	0	0	0	0
Week 2	0.09±0.15	−0.07±0.07	−0.14±0.18	−0.12±0.18
Week 4	0.07±0.12	0.08±0.19	−0.14±0.18	−0.02±0.28
Week 6	0.15±0.27	0.002±0.16	−0.08±0.21	−0.02±0.23
Week 8	0.06±0.19	0.05±0.20	−0.14±0.16	−0.05±0.23
Week 10	0.10±0.24	0.04±0.10	0.01±0.25	−0.12±0.19
Week 12	0.11±0.27	0.01±0.09	−0.13±0.16	−0.01±0.14
FGF23 (RU/ml)				
Baseline	0	0	0	0
Week 2	0.18±0.33	−0.12±0.29	−0.08±0.24	−0.34±0.23
Week 4	0.04±0.34	0.06±0.36	−0.01±0.29	−0.30±0.39
Week 6	0.03±0.25	0.05±0.40	−0.03±0.22	−0.29±0.36
Week 8	0.13±0.29	0.07±0.54	0.11±0.28	−0.38±0.28
Week 10	0.22±0.50	0.17±0.42	0.04±0.29	−0.25±0.37
Week 12	−0.02±0.29	0.00±0.24	0.25±0.53	−0.35±0.32
PTH (pg/ml)				
Baseline	0	0	0	0
Week 2	0.43±0.78	0.04±0.29	0.07±0.32	−0.12±0.14
Week 4	0.20±0.47	0.09±0.24	−0.04±0.22	−0.02±0.37
Week 6	0.33±0.78	0.07±0.27	0.12±0.46	−0.09±0.23
Week 8	0.24±0.71	0.09±0.61	0.16±0.30	0.13±0.40
Week 10	0.29±0.56	0.05±0.27	−0.04±0.24	0.02±0.29
Week 12	0.17±0.62	0.06±0.22	0.24±0.42	0.04±0.45

Values are mean percentages ± SDs. LC, lanthanum carbonate; FGF23, fibroblast growth factor 23; PTH, parathyroid hormone.

binders is suboptimal because of poor adherence or dose reductions in response to adverse effects. Thus, our data emphasize the importance of dietary interventions and the need to further develop innovative approaches to dietary counseling and maintaining adherence with prescribed diets to accompany phosphate binder use in CKD.

An important finding from our study is that FGF23 decreased the most in patients with the highest levels at baseline. Although it is tempting to invoke regression to the mean to explain this finding, the stability of the pre-intervention FGF23 levels, as indicated by the extremely low within-subject variability over three separate measurements, points to biologic factors. Our data suggest that interventions to reduce net phosphate absorption are most likely to successfully reduce FGF23 in participants who have high FGF23 levels at baseline. We propose that FGF23 elevation in CKD might be composed of a fixed, non-modifiable component attributable to poorly understood mechanisms intrinsic to kidney disease and a modifiable component that is driven by phosphate intake and therefore amenable to reduction with clinical interventions. Further work is needed to delineate clinical characteristics and laboratory results that identify patients most likely to respond to FGF23-lowering interventions, which can then be used as entry criteria in future interventional studies.

An unexpected finding was the lack of reduction in the 24-hour urinary phosphate or the fractional excretion of phosphate despite the significant change in FGF23 levels in the double intervention group. This contrasts with findings from prior studies of dietary phosphate restriction or phosphate binder use in CKD, which reported significant reductions in urinary phosphate excretion commensurate with the intensity of the interventions (9,13,15). Possible explanations for this lack of an effect are insufficient dietary phosphate restriction, lower doses of LC than in prior reports (15,17), within-person variability in 24-hour urinary collections, and waning adherence with the interventions in later weeks of the study. Regardless of the mechanism, this null finding suggests that urinary phosphate may not be an ideal measure for monitoring adherence or titrating interventions aimed at reducing FGF23 levels in future interventional studies.

Previous studies of dietary phosphate restriction or phosphate binders in CKD reported salutary effects on PTH (9,18). In contrast, the interventions did not decrease

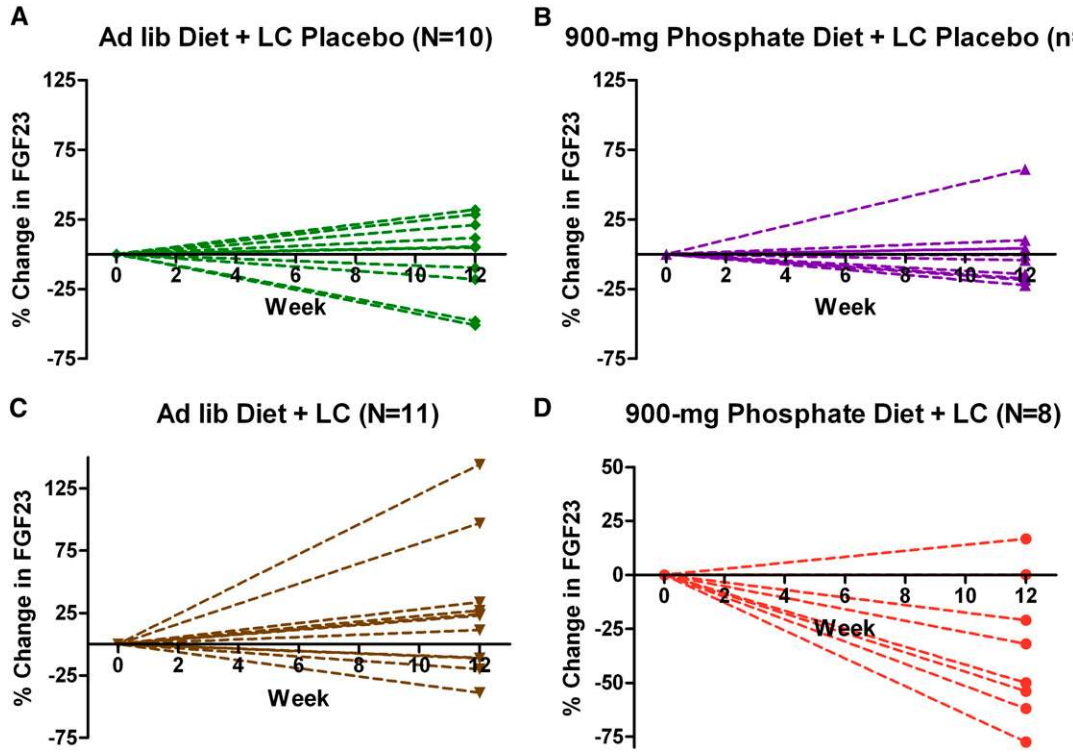

Figure 4. | Effects of lanthanum carbonate (LC) and dietary intervention on fibroblast growth factor 23 (FGF23) in individual participants according to four treatment groups. Percentage changes in FGF23 from baseline to end of study for individual patients.

PTH in this study. This discrepancy may be related to differences in baseline PTH levels across the studies. In our study, baseline PTH levels were within the normal range, whereas the preintervention PTH levels in earlier studies were often elevated. We did, however, detect an increase in PTH levels over time in the placebo group, which is consistent with the findings of a recent study of phosphate binders in CKD (17). Taken together, the existing data suggest that dietary phosphate interventions may delay the onset of secondary hyperparathyroidism in those with normal PTH levels at baseline and reduce PTH levels in those with elevated preintervention levels.

Limitations of this study deserve mention. First, the participants randomly assigned to the dual intervention group had significantly higher baseline FGF23 levels than the other groups, and more participants withdrew from the dual intervention group. Nevertheless, we were able to detect significant differences in the primary outcome, and this effect persisted after adjustment for baseline FGF23. Second, we used the C-terminal FGF23 assay, which detects both the full molecule and its C-terminal fragments. A recent longer-term study of phosphate binders in CKD reported no significant change in C-terminal FGF23 and modest reductions with the intact assay (17). Additional studies are needed to define optimal FGF23 testing strategies in CKD. Third, because diurnal variability in mineral metabolites is preserved in CKD, lack of standardization of the time of day of blood and random urine sampling may have affected the results for phosphate, PTH, and fractional excretion of phosphate. Lack of fasting random urine samples also prevented us from calculating the renal threshold for phosphate. However, diurnal variability was less likely to affect the FGF23 results because C-terminal FGF23 levels exhibit relative stability throughout the day (19). Fourth, dietary intake was estimated with use of instruments that do not capture intake of phosphate additives or consider the bioavailability of different sources of dietary phosphate. This may have led us to underestimate baseline phosphate intake and thus deliver dietary restriction of insufficient magnitude. Finally, we were not able to evaluate effects of other classes of phosphate binders that have been reported to have varying effects on FGF23 levels in CKD (9,11).

FGF23 excess has consistently been associated with increased risks of adverse clinical outcomes in CKD. By supplying "real-world" data on the effectiveness of the available interventions, this study adds to the existing data on the feasibility of FGF23 reduction in CKD. These findings suggest that dietary phosphate restriction in combination with phosphate binder therapy may have a role in reducing FGF23 levels in patients with CKD stages 3–4 and normal serum phosphate levels.

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Disclosures

T.I. has served as a consultant to or received honoraria from Genzyme and Shire. M.W. has served as a consultant to or received honoraria from Abbott, Amgen, Diasorin, Genzyme, Kai, Luitpold, Mitsubishi, and Shire. O.M.G. has served as a consultant to Vifor Pharma. Shire Pharmaceuticals gave full rights of publication to the investigators. Shire did review the manuscript but did not participate in the conceptual design, data analysis, interpretation of the results, or writing of the manuscript.

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