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Lanthanum carbonate reduces FGF23 in chronic kidney disease stage 3 patients

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Abstract

Background. In chronic kidney disease (CKD) patients, the ability to excrete a phosphate load is impaired. Compensatory increase in parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF23) promote phosphaturia. Serum FGF23 concentration is considered an early biomarker of excess phosphate load and high levels of FGF23 have been associated with increased mortality. In the present study, we have evaluated the changes in plasma FGF23 after treatment with the phosphate binder lanthanum carbonate in patients with CKD-3 and a normal serum phosphate concentration.

Methods. Eighteen Caucasian CKD Stage 3a/3b patients with serum phosphate <4.5 mg/dL were recruited in a prospective longitudinal open-label study. Patients received a 4-week period of standardized phosphorus-restricted diet containing 0.8 g/Kg/day protein. Thereafter, the same diet was maintained and patients received lanthanum carbonate (750 mg with the three main meals) for 4 weeks.

Results. No significant changes were observed in serum phosphate, however, lanthanum carbonate significantly decreased urinary excretion of phosphate and fractional excretion of phosphate ($P < 0.004$). This was accompanied by a significant decrease in carboxyterminal FGF23 (median percent change from baseline −21.8% (interquartile range −4.5, −30%), $P = 0.025$). No changes were observed in PTH.

Conclusions. In conclusion, lanthanum carbonate reduced phosphate load, as assessed by urinary phosphate excretion, and also reduced plasma FGF23 in CKD-3 patients. This occurs in the presence of unchanged normal serum phosphate levels.

Keywords: chronic kidney disease; FGF-23; lanthanum; phosphate

Introduction

Cardiovascular mortality is high among chronic kidney disease (CKD) patients [1]. Hyperphosphataemia has emerged as one key factor in the development of vascular calcification [2] and cardiovascular mortality [3]. Hyperphosphataemia has been associated with left ventricular hypertrophy [4] and renal failure progression [5]. In CKD patients, it has been suggested that an elevation in serum phosphate of 1 mg/dL would translate in a 23% increase in mortality [6]. However, daily and postprandial variability of serum phosphorus can be >1 mg/dL, making data interpretation difficult [7]. Additionally, in healthy individuals, serum phosphorus levels in the upper normal range have been associated with higher risk of carotid atherosclerosis, coronary calcification and cardiovascular mortality [8].

In CKD patients, the glomerular filtration of phosphate decreases progressively with the reduction of functioning nephrons. However, the increase in serum levels of both parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF23) reduce the tubular reabsorption of phosphate (TPR) and increase the fractional excretion of phosphate [FE(PO4)]. FGF23 levels increase early in CKD and therefore FGF23 is considered an early biomarker of phosphate overload [9, 10]. Also, the fact that FGF23 increases early in the course of CKD makes it an early biomarker of a decreased glomerular filtration rate (GFR) that may have a direct negative impact on progression of CKD and vascular events [11]. In renal patients receiving an acute load of dietary phosphate, both PTH and FE(PO4) increase, while FGF23 remains stable. Thus, changes in FGF23 appear to be slow and progressive, accompanying the decrease in GFR, independently of transient loads of phosphate [12]. By contrast, serum PTH increases in response to a phosphate load and to hypocalcaemia. These compensatory mechanisms enable the kidney to maintain phosphate excretion, prevent hyperphosphataemia and keep

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serum calcium (Ca) in the normal range until an advanced stage of CKD [13].

High FGF23 levels are associated with increased mortality in haemodialysis patients, independently of serum phosphate levels [14]. Therefore, high FGF23 may behave as a positive phosphate balance marker and may also have potential direct deleterious biological activity. It has been hypothesized that reduction of FGF23 may be a future therapeutic goal in CKD patients. The early use of phosphate binders, even in the presence of normal serum phosphate, significantly reduced mortality in haemodialysis patients [15]. Thus, studies should address whether the early use of phosphate binders, even before serum phosphate is elevated, prevents vascular calcification and reduces mortality in early stages of CKD. In the meantime, it would be interesting to assess whether the early use of phosphate binders decreases FGF23, a biomarker of mortality in CKD [14].

The present study was designed to evaluate prospectively the changes in phosphaturic hormones (FGF23 and PTH) in normophosphataemic patients with Stage 3 CKD in response to the phosphate binder lanthanum carbonate [16, 17].

Patients and methods

Study design

Eighteen consecutive Caucasian CKD patients from two different nephrology outpatient clinics were recruited for this prospective longitudinal open-label study. Inclusion criteria were CKD Stage 3a/3b (estimated GFR by Modification of Diet in Renal Disease-4 formula 30–59 mL/min/1.73m^2) and a serum phosphate concentration <4.5 mg/dL. Patients had to be diagnosed with CKD at least 3 months before the initiation of the study. Exclusion criteria were 25(OH) D levels <20 ng/mL, serum albumin <3.0 mg/dL, diagnosis of systemic disease (bowel disorder, liver disease, inflammatory autoimmune disease, neoplasia) or previous or current treatment with phosphorus binders, vitamin D receptor (VDR) activators or other drugs known to influence Ca and phosphate metabolism, such as anticoagulants and antiepileptic drugs. Local Ethics Committees approved the study protocol. All participants were informed about the study and written informed consent was obtained.

A clinical history with a physical exam was obtained in all patients before the inclusion in the study. Fasting blood sample and a 12-h urine collection were also obtained. Age, gender, anthropometric data and medications were registered. The study was designed to mimic current clinical practice. All patients were prescribed a standardized diet containing 0.8 g/kg/day of protein, with a low content of phosphate-rich foods. The estimated phosphate origin in the recommended diet was <700 mg/day from animal protein. The aim was to provide a homogenous low phosphate intake for all patients as recommended by guidelines. After 28 days in phosphate-restricted diet, fasting blood and 12-h urine samples were collected to provide baseline data. The 12-h urine sample included the nighttime period while patients were fasting. Thereafter, the phosphorus-restricted diet was maintained and patients received lanthanum carbonate (750 mg in each of the three main daily meals), for four additional weeks. Fasting blood and 12-h urine samples were again collected at the end of this period (Figure 1).

Biochemical parameters and analytical methods

Blood samples were centrifuged and serum or plasma was stored at −86°C. Serum creatinine, urea, phosphate, calcium, albumin, aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT) and total alkaline phosphatase (AP) were measured at study entry and at each follow-up visit in an automated analyser (Cobas Modular Roche). Urinary creatinine, calcium and phosphate were determined in urine specimens by the same standard methods. The following parameters were calculated: creatinine clearance (Ccr), fractional excretion of calcium (FECa) and FE(PO4) (urine mineral × serum creatinine/serum mineral × urine creatinine) and TPR [1−(CPi/Ccr) × 100] and calcium excretion index (CaEI) [(urine Ca/urine Cr) × serum creatinine].

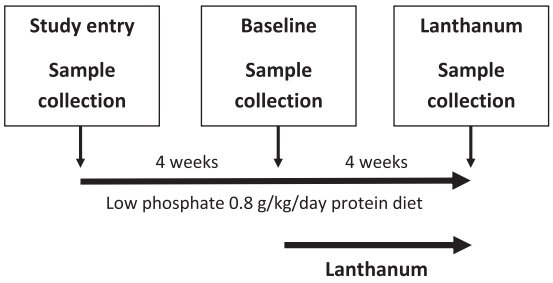

Fig. 1. Design and chronogram of the study.

The different biochemical parameters were measured at the same time in a single batch/run in order to minimize analytical variability. Serum whole PTH (1-84), so-called PTH-Bio, and intact PTH (1-84 plus 7-84, iPTH) were determined simultaneously by respective third- and second-generation immunoradiometric assay (CA-PTH duo; Scantibodies Laboratory Inc.). The ratio 1-84 PTH/non-1-84 PTH was calculated. Serum calcidiol levels were quantified by radioinmmunoassay (DiaSorin) and plasma FGF23 was determined by a C-terminal enzyme immunoassay (cFGF23) (Immutopics Intl).

Statistical analysis

Standard descriptive statistical analysis was performed and distribution of data was tested using the Shapiro–Wilk normality test. Results are expressed as mean or median and 95% confidence interval (CI) and the level of significance was set at $P < 0.05$. Percent changes from baseline measurements were analysed by Wilcoxon signed-rank test. Differences between values at baseline and following lanthanum were compared using Mann–Whitney test. Associations between different variables were evaluated by Spearman's correlation.

Results

All patients (8 women and 10 men) completed the study. Mean age was 69.9 years (95% CI: 65.8–73.9 years) and mean body mass index (BMI) 26.3 (95% CI: 24.2–28.5). Etiology of renal disease was diabetes in three, vascular nephropathy in nine and unknown in six. Main baseline laboratory data are registered in Table 1. Low estimated glomerular filtration rate (eGFR) was confirmed by creatinine clearance. All patients had ALAT, ASAT, albumin, Ca and phosphate serum levels within the reference range. Two (11.1%) patients had a mildly increased serum AP. One patient (5.5%) had iPTH <35 pg/mL and in six (33.3%), the PTH was >70 pg/mL, the upper reference limit. All patients had high cFGF23 levels (cutoff value is 50 RU/mL). No side effects were recorded and compliance was estimated to be 100%.

At baseline, cFGF23 was inversely correlated with: eGFR (−0.621; P 0.0001), TPR (−0.491; P 0.000) and directly correlated with PTH-bio (0.355; P 0.011) and iPTH (0.379; P 0.009). Baseline mean serum 25(OH) D levels were 24.0 ng/mL (95% CI 18.7–28.7).

Biochemical data after 4 weeks in a 0.8 g/kg/day protein diet is shown in Table 1. The addition of lanthanum to the low phosphate diet did not change serum phosphate concentration but it significantly decreased the 12-h urinary phosphorus excretion ($P < 0.006$) and the FE(PO4)

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Table 1. Main laboratory data obtained in the eighteen CKD Stage 3 studied patients at study entry, after dietary homogenization (baseline) and after lanthanum treatment

	Study entry mean (CI 95%)	Baseline mean (CI 95%)	Lanthanum mean (CI 95%)
Serum creatinine (mg/dL)	2.09 (1.78–2.39)	1.97 (1.68–2.25)	2.00 (1.69–2.31)
Creatinine clearance (mL/min)	42.08 (35.6–48.5)	44.48 (38.3–50.2)	44.35 (38.8–49.9)
Serum calcium (mg/dL)	9.44 (9.2–9.7)	9.22 (9.0–9.5)	9.41 (9.1–9.7)
FeCa (%)	0.83 (0.4–1.2)	1.44 (1.0–1.8)	0.92* (0.5–1.3)
Serum phosphate (mg/dL)	3.47 (3.4–3.7)	3.41 (3.2–3.6)	3.64 (3.4–3.9)
Urinary phosphate (mg/12 h)	396.20 (323.1–469.0)	364.13 (292.6–435.8)	265.15* (217.5–312.8)
$Fe(PO_4)$ (%)	33.08 (27.8–38.3)	34.85 (27.9–41.7)	23.28* (18.8–27.7)
TPR (%)	69.23 (65.9–74.2)	67.81 (61.4–74.1)	77.24* (73.3–81.7)
Urea (mg/dL)	81.88 (66.2–97.5)	71.43 (59.5–83.3)	76.56 (63.5–89.6)
AP (U/L)	87.35 (71.4–103.3)	89.0 (74.3–103.7)	99.25 (83.0–115.6)
Intact PTH (pg/mL)	77.65 (55.9–99.4)	77.47 (58.3–100.6)	85.37 (63.7–111.6)
Bio PTH (pg/mL)	50.92 (36.1–65.7)	49.39 (36.2–65.5)	54.53 (39.6–72.4)
1-84 PTH/non-1-84 PTH	1.87 (1.7–2.1)	1.74 (1.5–2.0)	1.75 (1.6–1.9)
cFGF23 (RU/mL)	211.77 (153.7–269.8)	222.54 (140.0–312.3)	174.64* (121.3–235.2)

*$P < 0.05$ with respect baseline values.

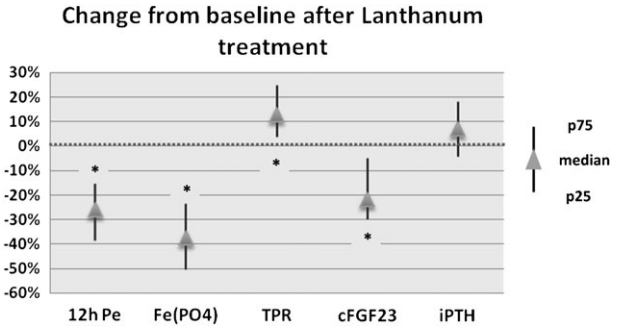

Fig. 2. Median percentage of change in 12-h urinary phosphate excretion (12 hPe), fractional excretion of phosphorous [$Fe(PO_4)$], TPR, cFGF23 and iPTH from baseline after lanthanum administration. *$P < 0.05$ versus baseline.

($P < 0.004$) with the corresponding increase in TPR ($P < 0.001$) (Table 1, Figure 2). The percentage of patients with TPR >82% (limit of normal for the laboratory) increased from 5% (1/18) before lanthanum to 22% (4/18) after lanthanum. The median per cent decrease in Fe(PO4) after lanthanum carbonate was –37.6 % (95% CI: −48.6 to −3.89%) (Figure 2). Basically, all patients showed a decrease in FE(PO4) after receiving lanthanum carbonate. The use of phosphate binder decreased the mean total 12-h urine phosphate excretion from 364 to 265 mg (Table 1). The decrease in FE(PO4) was accompanied by a reduction in the plasma concentration of cFGF23 ($P = 0.025$) (Table 1, Figures 2 and 3). However, serum PTH levels did not change significantly after the administration of the phosphate binder. After lanthanum carbonate, there was a moderate decrease in the FECa (Table 1).

Discussion

The main finding of the study is that in CKD-3 patients with normal serum phosphate and elevated plasma cFGF23 levels, the administration of lanthanum carbonate caused a significant reduction of plasma cFGF23. In addition, it reduced urinary excretion of phosphate suggesting a decrease in the intestinal absorption of phosphate. This is observed even when patients are on a phosphate-restricted diet and despite no change in serum phosphate levels.

In our CKD patients, the low phosphate diet did not produce a significant decrease in urinary excretion of phosphate, which suggests that participants were on a fairly low phosphate diet at study entry. In CKD patients with advanced age on a Mediterranean diet, phosphate ingestion is relatively low and similar to that observed in our patients [18]. The lack of significant changes in dietary phosphorus may underlie the absence of significant changes in FGF23 following the dietary intervention.

Lanthanum decreased FGF23 in CKD patients with normal serum phosphate and a low phosphate intake. Other authors using sevelamer obtained similar results [19]. These results suggest that the change in FGF23 is independent of the type of phosphate binder, it reflects the phosphate load and as such, it may be a valuable parameter to assess phosphate ‘status’. In these patients, PTH was only moderately increased and it did not decrease after treatment with the phosphate binder. From these results, one may deduct that at this stage of renal disease, plasma FGF23 is more sensitive than PTH to assess the degree of phosphate load. However, a previous pilot study of normophosphataemic CKD Stages 3–4 patients on lanthanum carbonate for 2 weeks did not observe changes in FGF23, despite significant reduction in 24-h urinary phosphate excretion compared with baseline [20]. The authors hypothesized that lanthanum or lowering dietary phosphorus restriction may require interventions with a longer duration than in healthy volunteers to induce a reduction in FGF23 levels in CKD patients. Our current data support this hypothesis. Indeed, sevelamer use for 6 weeks decreased FGF23 [19]. In this regard, although our study was relatively short (4 weeks), it does suggest that beneficial effects

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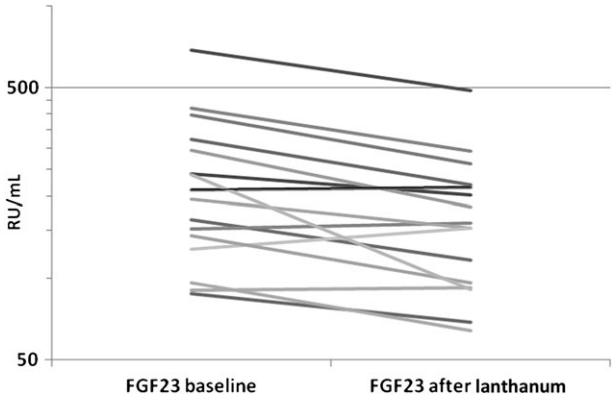

Fig. 3. Change from baseline in cFGF23 levels for each patient. Note the logarithmic scale of the vertical axis.

of phosphorus binders on FGF23 may already be observed at 4 weeks.

The decrease in plasma FGF23 levels may be a clinical target by itself. It is unknown whether FGF23 has systemic effects in addition to the regulation of phosphate balance. Increased FGF23 is linked to the development of atherosclerosis and vascular calcifications, which have been reported in CKD Stage 2/3 patients even before serum phosphate increases. In addition, high FGF23 levels are associated with the progression of renal disease [11] and with events previously related to high serum phosphate, such as left ventricular hypertrophy [21] and coronary calcification [22]. Furthermore, high FGF23 levels are associated with higher mortality in haemodialysis patients, independently of serum phosphate [14]. Higher FGF23 was associated with the occurrence of cardiovascular events in CKD patients prior to dialysis [23]. Among outpatients with stable coronary artery disease, those with FGF23 in the highest tertile had a 2-fold greater risk for mortality and cardiovascular events after adjustment for traditional cardiovascular risk factors, C-reactive protein levels and kidney function compared with those in the lowest tertile [24]. In the healthy population, an association has been described between serum phosphate and mortality but a potential association between FGF23 and mortality has not been studied. Nevertheless, phosphate binders reduce both serum phosphate and FGF23, and thus, it is unclear which of the two effects contributes more to the potential beneficial effects of phosphate binders on survival [19].

Since FGF23 assays are not available in daily clinical practice, assessment of urinary phosphate excretion or TPR can be used as indicators of phosphate burden. The phosphate binder lanthanum carbonate decreased intestinal absorption of phosphate resulting in a decrease in urinary excretion of phosphate and an increase in TPR and cFGF23. While TPR may provide insights into the renal effects of phosphaturic hormones, 24-h urine phosphate excretion depends dramatically on daily phosphate intake/absorption [13].

Weaknesses of the study include the lack of dietary recall ascertainment of adherence to the prescribed diet. This may also be considered a strength since this is the usual clinical condition and the results can be directly extrapolated to the everyday clinical practice since dietitian follow-up of dietary compliance is not always available. Nevertheless, a period of dietary prescription was introduced before lanthanum prescription in order to separate potential variability in dietary compliance from the drug effect. Additional limitations were the lack of a control arm and the low number of patients, which does not allow any firm conclusions to be drawn on the observed nonsignificant trends for higher serum phosphate and PTH values.

The moderate increase in serum calcium levels after administration of lanthanum carbonate may be a consequence of a reduced phosphate load. In animals and humans, a decreased dietary phosphate improves the calcaemic response to PTH [25–27]. Thus, with the same PTH, more calcium is coming from bone. This should result in an increased FeCa. However, in CKD, FeCa is low due to a poor gastrointestinal absorption of calcium. In the present study, patients did not receive vitamin D or calcium supplements. Nevertheless, the change in FeCa is very small and within the low values that are usually seen in CKD patients. Phosphate binders allow a greater intestinal absorption of calcium [28]. However, lanthanum carbonate may have a different effect than other phosphate binders. In human volunteers, lanthanum carbonate prevented the expected increase in calcium absorption associated with the use of phosphate binders [28]. The high lanthanum concentration in the gut blocks calcium channels involved in calcium absorption [29]. Therefore, the use of lanthanum carbonate may not be associated with an increase in calcium load.

Recent publications have shown that FGF23 acts on parathyroid glands causing a decrease in PTH production [30, 31]. This effect is not observed in hyperplastic glands since FGFR and Klotho expression are reduced [31–34]. It is likely that in early stages of secondary hyperparathyroidism, FGF23 can decrease PTH production. PTH levels did not decrease after reducing the phosphate load, the decrease in FGF23 may have contributed to the lack of reduction in PTH.

Our study should be interpreted in the context of the growing evidence that higher FGF23 levels are associated with adverse outcomes in CKD patients [14]. In this regard, phosphate binders, such as lanthanum, should be studied as agents with the potential to decrease the adverse outcomes associated with high FGF23 levels.

In conclusion, the administration of lanthanum carbonate reduced phosphate absorption, as assessed by the decrease in urinary phosphate excretion, and reduced plasma FGF23 levels. This is observed in the absence of changes in serum phosphate levels. In CKD-3, serum phosphate cannot be considered a good marker of phosphate load.

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Conflict of interest statement. None declared.

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(See related article by Ketteler *et al.* Phosphate and FGF23 in early CKD: on how to tackle an invisible foe; *Nephrol Dial Transplant* 2011; 26: 2430–2432.)

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