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Oral calcium carbonate affects calcium but not phosphorus balance in stage 3–4 chronic kidney disease

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Abstract

Chronic kidney disease (CKD) patients are given calcium carbonate to bind dietary phosphorus and reduce phosphorus retention, and to prevent negative calcium balance. Data are limited on calcium and phosphorus balance in CKD to support this. The aim of this study was to determine calcium and phosphorus balance and calcium kinetics with and without calcium carbonate in CKD patients. Eight stage 3/4 CKD patients, eGFR 36 mL/min, participated in two 3-week balances in a randomized placebo-controlled cross-over study of calcium carbonate (1500 mg/d calcium). Calcium and phosphorus balance were determined on a controlled diet. Oral and intravenous ^{45}calcium with blood sampling and urine and fecal collections were used for calcium kinetics. Fasting blood and urine were collected at baseline and end of each week of each balance period for biochemical analyses. Results showed that patients were in neutral calcium and phosphorus balance while on placebo. Calcium carbonate produced positive calcium balance, did not affect phosphorus balance, and produced only a modest reduction in urine phosphorus excretion compared with placebo. Calcium kinetics demonstrated positive net bone balance but less than overall calcium balance suggesting tissue deposition. Fasting biochemistries of calcium and phosphate homeostasis were unaffected by calcium carbonate. If they can be extrapolated to effects of chronic therapy, these data caution against the use of calcium carbonate as a phosphate binder.

INTRODUCTION

Patients with chronic kidney disease-mineral bone disorder (CKD-MBD) have altered mineral metabolism due to disruptions in homeostasis of serum phosphate, calcium, and the

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DISCLOSURE

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mineral-regulating hormones, parathyroid hormone (PTH), 1,25-dihydroxyvitamin D (1,25D), and fibroblast growth factor-23 (FGF-23) (1). Progressive hypocalcemia and hyperphosphatemia as kidney function decreased were the original biochemical hallmarks of mineral bone disorder (2). Calcium and phosphorus absorption studies dating back to the 1970s–80s (3–7) showed that intestinal calcium and phosphorus absorption were low in CKD and reversible with calcitriol and vitamin D analogs (7). Hypocalcemia from calcium malabsorption and hyperphosphatemia from phosphorus retention, were considered to be responsible for the progression of secondary hyperparathyroidism, a common feature of CKD (8). More recently it has been established that the reduced 1,25D is more likely due to elevation of the phosphate regulating hormone, FGF-23, which suppresses kidney 1-alpha hydroxylation of 25-hydroxyvitamin D (25D) and that PTH, FGF-23 and 1,25D form a sophisticated hormonal axis that regulate mineral homeostasis and skeletal mineralization (9).

There has been increasing awareness that abnormalities in the mineral regulating hormones occur early in kidney failure (CKD stage 2) before serum calcium and phosphorus move from their fasting reference ranges (10, 11). Increase in serum phosphate and phosphorus retention in CKD-MBD are considered to be the main culprits in exacerbating vascular and other soft tissue complications of CKD, and even within the normal reference range, serum phosphate is independently associated with increased mortality in pre-dialysis CKD patients (12). To prevent phosphate retention and hyperphosphatemia, use of phosphate binders in the management of end stage renal disease began in the mid-1970's (13). Calcium carbonate as a phosphate binder was introduced in the mid-1980's as an alternative to aluminum-based phosphate binders which carried the risk of aluminum toxicity (14). Calcium carbonate is a popular phosphate binder because of both its availability over the counter and its low cost relative to other phosphate binders. Not only does it bind dietary phosphate when given with meals but some believe it has the added advantage of preventing or reversing negative skeletal calcium balance, thought to contribute to the increased fracture risk in CKD (15, 16). However, there is increasing concern over the risk of vascular calcification and cardiovascular events with use of calcium-based phosphate binders (17). There are only limited and inconsistent data regarding the safety of calcium-based versus non-calcium based binders (18). Until recently (19) no data on calcium balance in either early or late stage CKD patients were available and there are no studies utilizing calcium kinetics. One study (19) showed that stage 3 and 4 CKD patients were in neutral calcium balance while consuming an 800 mg/d calcium diet, and in positive calcium balance while consuming a diet of 2000 mg/d calcium. No equivalent data are available on phosphorus balance in CKD patients. The purpose of this study was to determine whether calcium carbonate, used as a phosphate binder, altered calcium and phosphorus balance and calcium kinetics in patients with stage 3/4 CKD while on a controlled diet. Further, the effects of calcium carbonate on fasting serum mineral and mineral-regulating hormone biochemistry were also determined.

RESULTS

Patients

Seventeen volunteers were screened for the study. Five did not qualify based on the inclusion/exclusion criteria. Four enrolled patients were withdrawn from the study in the first week of study used both to assess dietary compliance and to equilibrate patients to the calcium and phosphorus content of the diet: three patients due to difficulties complying with the controlled diet and one patient due to starting kayexalate for high serum potassium. One patient who completed the study inadvertently remained on paricalcitol (2 mcg/d) during the study; despite this, this patient had the lowest calcium absorption out of all the study participants (6–7% on both placebo and calcium carbonate). Therefore, the data from this patient was retained in the analysis. Eight patients completed the entire study and were included in the analysis and results.

Patients participated in a randomized cross-over study of calcium carbonate (daily elemental calcium 2457 mg) versus placebo (daily elemental calcium 957 mg) (Figure 1). All eight patients were overweight based on body mass index and had hypertension, and six patients had type 2 diabetes mellitus. At baseline, serum calcium and serum phosphate were within normal ranges (8.8 to 10.2 mg/dL and 2.3 to 4.5 mg/dL for calcium and phosphate, respectively) (20) for all but one patient with serum calcium of 10.3 mg/dL and one patient with serum phosphate of 4.9 mg/dL. Six patients had serum PTH above the upper normal limit of the assay (54 pg/mL) and five patients had serum intact FGF-23 above the upper normal limit of the assay (54.3 pg/mL). Bone mineral density z-scores for total body, lumbar spine (L1–L4), and femoral neck were normal for age, race, and sex (Table 1). Usual dietary intake of calcium by 1-day dietary recall was 533 mg/d (range: 141 to 1211 mg/d) and phosphorus was 981mg/d (range: 351 to 1778 mg/d).

Steady-State and Compliance

As assessed by analysis of food leftovers, patients consumed > 90% of the prescribed dietary calcium and phosphorus. Calcium and phosphorus balance calculations were adjusted for calcium and phosphorus in leftover foods. Fecal calcium-to-polyethylene glycol (PEG) ratios showed that patients were in steady-state by the end of the 1-week equilibration period. Creatinine-corrected urine calcium and phosphate values differed minimally from uncorrected values (by 0.0 to 6.6 mg/d and 0.0 to 27 mg/d, respectively). Compliance for calcium carbonate and placebo was 100% for all participants as assessed by pill count.

Calcium Balance

On placebo (daily elemental calcium content 957 mg), calcium balance was neutral (not significantly different from zero). With calcium carbonate (daily elemental calcium content 2457 mg), calcium balance was positive and significantly higher than placebo (508 vs. 61 mg/d, respectively, $p=0.002$) (Figure 2). Fecal calcium was greater with calcium carbonate (1902 vs. 843 mg/d, $p<0.0001$). Urine calcium was not different between calcium carbonate and placebo (42 vs. 41 mg/d, $p=0.95$) (Figure 2). Net intestinal calcium absorption (Ca Intake – Fecal Ca) was higher with calcium carbonate (550 vs. 102 mg/d, $p=0.002$).

Phosphorus Balance

Phosphorus balance was not significantly different from zero on placebo and did not differ between calcium carbonate and placebo (153 vs. 95 mg/d, p=0.2) (Figure 3). There were no differences between calcium carbonate and placebo for fecal phosphorus (822 vs. 722 mg/d, p=0.11), net intestinal phosphorus absorption (733 vs. 822 mg/d, p=0.13), or percent phosphorus absorption (47 vs. 53%, p=0.11). Urine phosphate excretion was significantly lower with calcium carbonate compared with placebo (580 vs. 728 mg/d, p=0.03) (Figure 3). The decrease in urine phosphate was 1 mg per 10 mg elemental calcium from calcium carbonate.

Calcium Kinetics

A schematic representation of calcium kinetics model is illustrated in Figure 4. Calcium carbonate resulted in greater rates of calcium absorption (V_a, 416 vs. 211 mg/d, p=0.01 and bone balance (V_{Bal}, 259 vs. 62 mg/d, p=0.02). As percent of intake, calcium absorption was 17 vs. 22%, p=0.35. Despite a significant difference in bone balance, the differences in rates of calcium deposition in bone (V_{o+}) and bone resorption (V_{o-}) were not significantly different between calcium carbonate and placebo (438 vs. 371 mg/d, p=0.17, and 179 vs. 309 mg/d, p=0.12, respectively). Rate of endogenous calcium excretion was not different between calcium carbonate and placebo (V_f, 106 vs. 105 mg/d, p=0.95) (Figure 5).

Comparison of Calcium Balance and Kinetics in CKD Patients on Placebo with Healthy Adults

CKD patients not receiving calcium carbonate had lower urine calcium (46 vs. 121 mg/d, p=0.01) and fecal calcium (842 vs. 1092 mg/d, p=0.03) compared with healthy adult women [historical data (21)]. Calcium balance was higher in CKD patients compared with healthy adults (60 vs. −159 mg/d, p=0.03) (Supplemental Figure 1). Calcium kinetics data demonstrated that fractional calcium absorption tended to be lower in CKD patients compared with healthy adults (20 vs. 26%, p=0.09), but this difference was not statistically significant. Total calcium absorption (V_a), endogenous calcium secretion (V_f), bone formation rate (V_{o+}), and bone resorption rate (V_{o-}) were not different between CKD patients and healthy adults. Bone balance (V_{Bal}) was greater in CKD patients compared with healthy adults (57 vs. −108 mg/d, p=0.03) (Figure 6). No equivalent data on phosphorus balance are available on these controls.

Fasting Biochemistries

Fasting serum calcium and phosphate were within normal reference ranges and did not differ between calcium carbonate and placebo (Table 2). Fasting serum 25D was within normal range but was slightly lower with calcium carbonate (25.1 vs. 26.7 ng/mL, p=0.03). Fasting serum PTH and FGF-23 were higher than the normal ranges for the assays, while fasting serum 1,25D was within but in the lower end of the normal range for the assay. Serum osteocalcin (OC) was higher than the normal range, and serum bone alkaline phosphatase (BAP) and urine N-telopeptides of type I collage (NTX) were normal. None of these measures differed between calcium carbonate and placebo.

Kidney Function and Mineral Handling

Kidney function measurements (eGFR, serum creatinine, and creatinine clearance) were not different between calcium carbonate and placebo (data not shown). Urine Ca/Cr, tubular maximal reabsorption of calcium (TmCa), and fractional calcium excretion (C_{Ca}/C_{Cr}) were not different between calcium carbonate and placebo (Table 2). Urine Pi/Cr and fractional phosphate excretion (C_{Pi}/C_{Cr}) tended to be lower and tubular maximal reabsorption of phosphate (TmP) tended to be higher with calcium carbonate compared with placebo, but these differences were not statistically significant.

DISCUSSION

This three-week placebo-controlled balance and kinetic study demonstrated that stage 3/4 CKD patients were in neutral calcium balance while consuming a diet adequate (22) in calcium containing 957 mg per day. Increasing calcium intake with 500 mg calcium from calcium carbonate taken with three daily meals produced positive calcium balance. The ability of CKD patients to maintain neutral calcium balance on an adequate calcium diet was largely due to low urine calcium excretion, and to achieve positive calcium balance with calcium carbonate was largely due to increased calcium absorption and net retention, and failure to increase urine calcium excretion. The study demonstrated that phosphorus balance was also neutral on an average (23) U.S. intake of phosphorus of 1564 mg per day. Further, phosphorus balance was unaffected by calcium carbonate even although there was a reduction in urine phosphate excretion of about 148 mg/d. Thus, the overall effect of a 500 mg calcium supplement with three meals per day in CKD stage 3/4 patients was to produce a large positive calcium balance without affecting neutral phosphorus balance and only a modest effect on reducing urine phosphate. The decrease in urine phosphate was about 1mg for every 10mg elemental calcium supplement which is close to that found by others (24). The reduction in urine phosphate was likely due to a reduction in phosphate absorption although the increase in fecal phosphorus with the calcium supplement was not significant probably reflecting greater imprecision in the fecal phosphorus measurement.

Calcium kinetics demonstrated that calcium carbonate increased bone formation and decreased bone resorption and improved bone balance by about 200 mg/day. Calcium kinetic modeling is currently unable to estimate the rate of calcium deposition into extraskeletal tissues. However, overall calcium balance measured by chemical methods, after subtracting 79 mg calcium /day in sweat (25) showed an increase in calcium balance of over 300 mg/day, suggesting that an appreciable proportion of the retained calcium from calcium carbonate was deposited in extraskeletal tissue and/or in the skeleton independent of bone formation and resorption mechanisms.

It is generally assumed that CKD patients have phosphorus retention due to the need to excrete normal dietary phosphorus by increasing serum phosphate to accommodate for decreased GFR. However, this study demonstrated that despite phosphate retention in serum, CKD patients stage 3/4 remain in overall neutral phosphate balance. Phosphorus balance studies have not been performed previously in CKD patients partly because of concern over the accuracy of measuring fecal phosphorus (26, 27). Analysis of phosphorus-

spiked fecal samples showed that the method used in this study (Supplemental methods) gives 92.2% (82.5–100.5%) mean recovery.

Small sample size may have limited our ability to detect significant differences of calcium and phosphorus balance from zero since the study was only powered to detect mean differences in balance between calcium carbonate and placebo. However, normal bone mineral density of the patients corroborates that they were not in long-term negative calcium balance on their habitual calcium intakes of 533 mg/d. Also the potential bias towards underestimating fecal phosphorus and thus overestimating phosphorus balance lends support to the conclusion that these patients are not retaining phosphorus while consuming a liberal amount of dietary phosphorus.

Fasting serum phosphate was unaffected by calcium carbonate, despite a decrease in urine phosphate. Additionally, the hormones regulating phosphorus homeostasis, PTH, 1,25D, and FGF-23, were not affected by calcium carbonate indicating that the decrease in phosphate excretion with calcium carbonate was insufficient to elicit changes in phosphorus homeostasis. Perhaps longer treatment periods are needed to observe changes in serum phosphate and its regulating hormones since studies with sevelamer showed a reduction in FGF-23 in dialysis patients (28) over four weeks and a reduction in FGF-23 and PTH in normophosphatemic CKD patients over six weeks (29).

To assess the abnormalities that occur in CKD patients, calcium balance and kinetics were compared with historical data (21) from healthy postmenopausal women on a similar calcium-controlled diet. CKD patients had lower urine calcium and lower fractional calcium absorption than postmenopausal women. Importantly, calcium balance was higher in CKD patients, providing further support that stage 3/4 CKD patients are not in negative calcium balance. The strength of these comparisons is that the historical data were generated by the same research group using the same methodologies in healthy postmenopausal women of similar age to the CKD patients.

Calcium balance studies combined with calcium kinetics in subjects in mineral equilibrium are the gold standard for measuring rates of calcium transport at gut, bone and kidney. Using the standard one week of dietary and environmental equilibration followed by two weeks of balance (32) our patients were well equilibrated as corroborated by constant outputs of fecal and urinary markers. As in most balance studies, the dietary calcium and phosphorus intake was fixed by protocol to be close to the average intake in the USA, and not on each patient's usual intake. Balance utilizing a randomized cross-over intervention represents a strong study design to test the effects of a treatment on mineral balance. On the other hand, balance studies are very exacting both for patient and investigator and they inevitably suffer from small sample size. Further, in this study as is typical of stage 3/4 CKD, the patients were not a homogenous sample and included men and women, American blacks and whites and a high incidence of obesity and type 2 diabetes, all factors known to affect mineral metabolism and bone mass. Thus the results may not be directly generalizable to all stage 3/4 CKD patients or to all dietary levels of calcium and phosphorus intake. Further, the results may not reflect the effects of chronic therapy on mineral balance.

This study is the first balance study in CKD to include both calcium and phosphorus balance and calcium kinetics, and to evaluate the effects of calcium carbonate on these measures. These results challenge the rationale for using calcium-based phosphate binders in stage 3/4 CKD patients to prevent negative calcium balance, reduce PTH, reduce serum phosphate, and prevent phosphorus retention because: 1) patients were not in negative calcium balance or positive phosphorus balance on placebo, and 2) calcium carbonate did not affect serum PTH, serum phosphate, or phosphorus balance. Although it is unknown whether the calcium retained from calcium carbonate is deposited into bone or soft tissue in these patients, it is unlikely that bone could serve as the sole reservoir considering the magnitude of the positive calcium balance and the patients' age. Therefore, the positive calcium balance produced by calcium carbonate cautions against its use as a phosphate binder in stage 3/4 CKD patients.

METHODS

Patients and Study Design

Men and women ≥35 years old with GFR < 45 mL/min and serum PTH ≥ mid normal range mean were recruited (Table 1 and Supplemental Methods) and studied on the Indiana Clinical Research Center under an Institutionally Review Committee approved protocol using a randomized cross-over design (Figure 1).

Controlled Diet, Calcium Intervention, and Compliance

The controlled diet, given as a 4-day cycle menu (Supplemental Methods) , contained 957 ± 23 mg/d calcium (22) and 1564 ± 52 mg/d phosphorus (23). Energy requirements (30) matched the patients' needs; distilled water was provided as desired; and 400 IU/d of oral vitamin D_3 (Finest Natural® softgels) was given for two weeks before and throughout the balance. Calcium carbonate (Calci-Mix®, Rugby Laboratories, Duluth, GA) was given as a capsule contained 500 mg elemental calcium three times a day with meals and placebo was given as identical capsules. During the equilibrium week1, study food was packed and labeled for each meal and patients kept diet and pill checklists and returned any unconsumed food and pills. During week 2 and 3, patients were inpatients and meals were served and pills administered and by research staff. Dietary compliance was assessed by meal checklists and leftover food was recorded, weighed, and saved for analysis. Pill compliance was assessed by pill count. Polyethylene glycol (PEG, 3 g/d), a non-absorbable marker, was given with meals to assess steady state and was measured in feces using a turbidimetric assay (31). Urine creatinine from 24 h collections was used to assess urine collection compliance.

Calcium and Phosphorus Balance

The balance technique is described in further detail in Supplemental Methods. Previous data in healthy adults (32) show six days are needed to achieve steady state on a new dietary calcium intake level. Therefore, the first week of the 3-week study period was as an outpatient and was used both as an equilibration period to the diet to achieve steady state and as an assessment for compliance with the diet. All urine and feces were collected during week 2 and 3. Urine was pooled into 24 h collections and calcium and phosphorus measured by inductively coupled plasma optical emission spectrometry (ICP-OES). Feces were pooled

and homogenized by day of collection and aliquots ashed at 600°C (for calcium) and 550°C (for phosphorus), and analyzed by ICP-OES. A modified version of the dry-combustion method described by Yokato et al. (27) was used for fecal phosphorus analysis (Supplemental Methods). Urine creatinine was measured by colorimetric assay using a COBAS MIRA clinical analyzer (Roche Diagnostic, Indianapolis, IN). Balance and net absorption were calculated as the average (mg/d) over week 2 and 3: mineral balance (mg/d) = dietary intake minus urine and fecal excretion; net absorption (mg/d) = dietary intake (mg/d) minus fecal excretion (mg/d). Absorption as percent of intake (%) was calculated as net absorption (mg/d)/dietary intake of mineral (mg/d)*100.

Calcium Kinetics

Calcium kinetics provides a direct measure of bone formation and resorption and balance, absorption and endogenous secretion and is described in further detail in the Supplemental Methods. On the first inpatient day, patients were orally administered 10μCi ^{45}Ca as $CaCl_2$ in sterile saline mixed in 2% milk with breakfast that contained a third of the daily total calcium intake (approximately 300 mg (diet alone) on placebo and 800 mg (diet plus supplement) on calcium carbonate). Blood was collected prior to dosing, and at 1, 2, 3, 6, and 24 hours thereafter. On the second inpatient day 1 hour after breakfast, patients were intravenously administered 10μCi ^{45}Ca as $CaCl_2$ in sterile saline. Blood samples were collected prior to dosing and at 5, 10, 20, 40 minutes and 1.5, 2, 2.5, 3, 4, 5, 7, 10, 24, 36 hours, and 2, 3, 5, 7, 9, 11, and 18 days thereafter. ^{45}Ca activity of urine, serum, and feces was measured by beta liquid scintillation counting (LS6500, Beckman Coulter) and used in a multi-compartment model (33–35) (Figure 4).

Fasting Biochemical Measures and Derived Variables

Fasting serum and urine were collected at baseline and the end of week 1,2 and 3 and stored at −80°C until analyzed. Serum osteocalcin and bone alkaline phosphatase were measured by EIA (MicroVue^{TM}, Quidel, San Diego, CA), PTH by IRMA (N-tact®, DiaSorin, Stillwater, MN, 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D by RIA (Diasorin, Stillwater, MN), and intact fibroblast growth factor-23 by ELISA (Kainos Laboratories, Inc., Tokyo, Japan,); urine cross-linked N-telopeptides of type 1 collagen (NTX) was measured by EIA (Osteomark®, Wampole Laboratories, Princeton, NJ). Serum and urine calcium, phosphate, and creatinine were measured by colorimetric assay using a COBAS MIRA clinical analyzer (Roche Diagnostic, Indianapolis, IN).

Estimate glomerular filtration rate was calculated by the MDRD Study equation (36, 37), creatinine clearance was calculated by V (mL/min)* urine Cr (mg/dL)/serum (mg/dL) from average 24 h urine volume and creatinine and serum creatinine during week 2 and 3.Tubular maximum reabsorption of phosphate (TmP), calcium (TmCa), fractional excretion of calcium (C_{ca}/C_{cr}), and fractional excretion of phosphate (C_{pi}/C_{cr} ; FE_{phos})were calculated from fasting serum and 2 h urine (see Supplemental Methods).

Anthropometrics, Body Composition, Bone Densitometry, and Usual Dietary Intake

Height (cm) and weight (kg) were measured at week 2 and 3. Body mass index was calculated as kg/m^2. Bone mineral density (BMD, mg/cm^2, z-score) and body composition

were determined at baseline by dual-energy x-ray absorptiometry (Lunar Prodigy Advance, GE Healthcare). A 24-hour dietary recall was obtained using online software (ASA24^{TM} beta version, National Cancer Institute) to assess usual dietary intake.

Calcium Balance and Kinetics Comparison of CKD Patients on Placebo with Healthy Adults

Calcium balance and kinetics were compared with historical data from 13 healthy postmenopausal women (mean age 57 ± 6 years) studied by our group (21) using exactly the same calcium balance and kinetic methodologies as used in the present study. Data from CKD patients during the placebo arm (calcium intake = 957 mg/d) were compared with data from the healthy postmenopausal women who were consuming a controlled diet of 1083 mg/d calcium. Means, standard deviations, and sample sizes were used to calculate two-tailed independent t-tests to determine differences between CKD patients and healthy postmenopausal women. These data are presented as means ± pooled SEM.

Statistical Analysis

One-sample t-tests were used to test if calcium and phosphorus balances on placebo and calcium carbonate were different from zero (38). These data are presented as mean ± standard error of the mean (SEM). The differences in outcome measures between calcium carbonate and placebo were analyzed using repeated measures ANOVA for cross-over designs (39, 40). These data are presented as least squares mean (lsmeans) ± pooled SEM. Statistical analysis was performed using SAS® 9.2 (SAS Institute, Cary, NC). The significance level was set at $\alpha = 0.05$.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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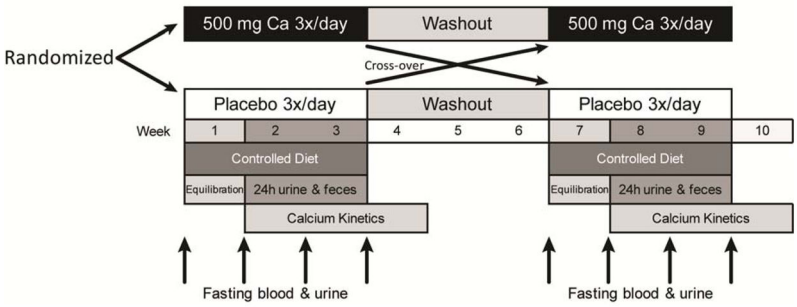

Figure 1.
Randomized cross-over study design.

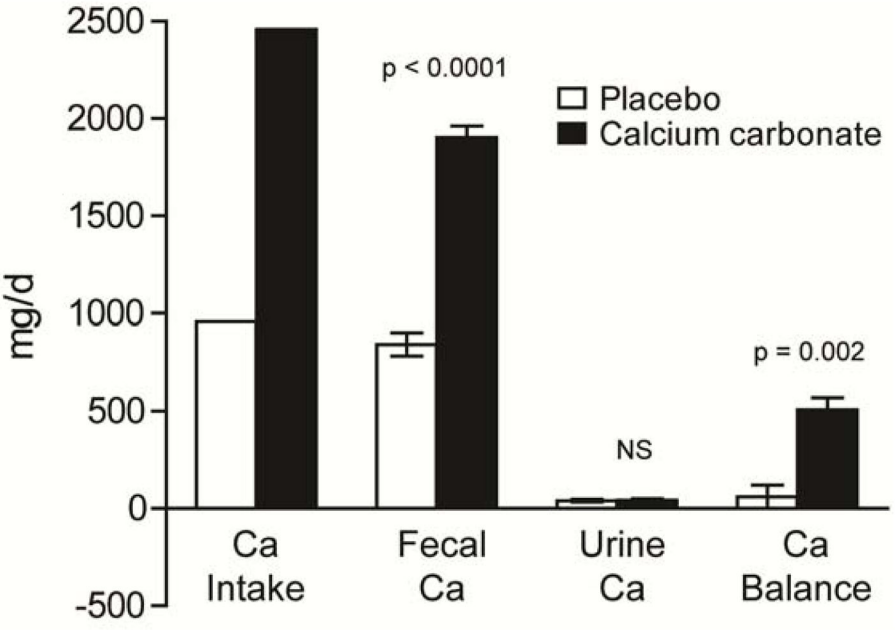

Figure 2.

Calcium balance in stage 3/4 CKD patients with and without calcium carbonate. Calcium balance was greater with calcium carbonate compared with placebo. Ca intake was experimentally controlled and statistical analysis does not apply. White bars = placebo; Black bars = calcium carbonate. Ca = calcium; NS = not significant ($p > 0.05$). Data are presented as least squares mean ± pooled SEM.

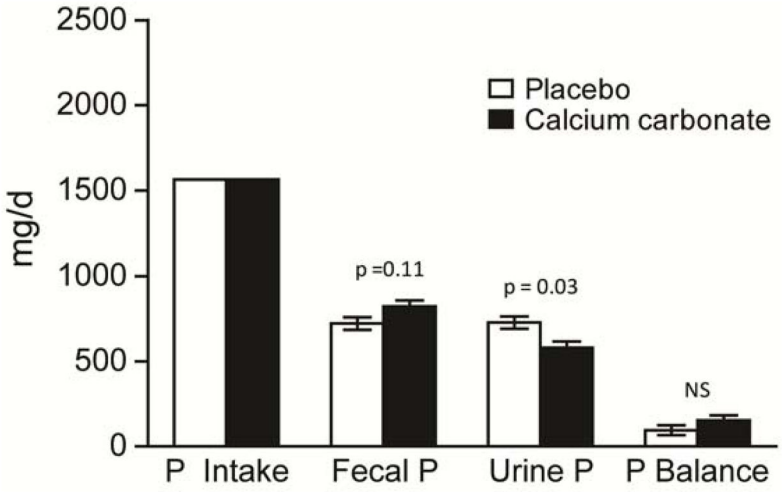

Figure 3.

Phosphorus balance in stage 3/4 CKD patients with and without calcium carbonate. Phosphorus balance was not different between calcium carbonate and placebo but urine phosphate was lower on calcium carbonate. P intake was experimentally controlled and statistical analysis does not apply. White bars = placebo; Black bars = calcium carbonate. P = phosphorus; NS = not significant ($p > 0.05$). Data are presented as least squares mean ± pooled SEM.

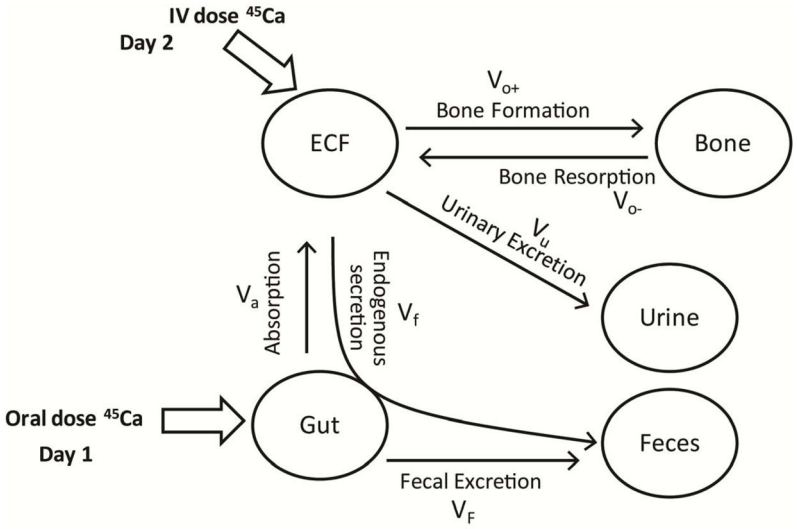

Figure 4.

Illustration of calcium kinetics (33). ECF = extracellular compartment. ^{45}Ca = ^{45}Calcium radiotracer; V_a = rate of calcium absorption; V_f = rate of endogenous calcium excretion; V_F = rate of fecal calcium excretion; V_u = rate of urine calcium excretion; V_{o+} = rate of bone formation; V_{o-} = rate of bone resorption. Bone balance is V_{o+} minus V_{o-}, and overall calcium retention is dietary calcium minus urine and fecal calcium.

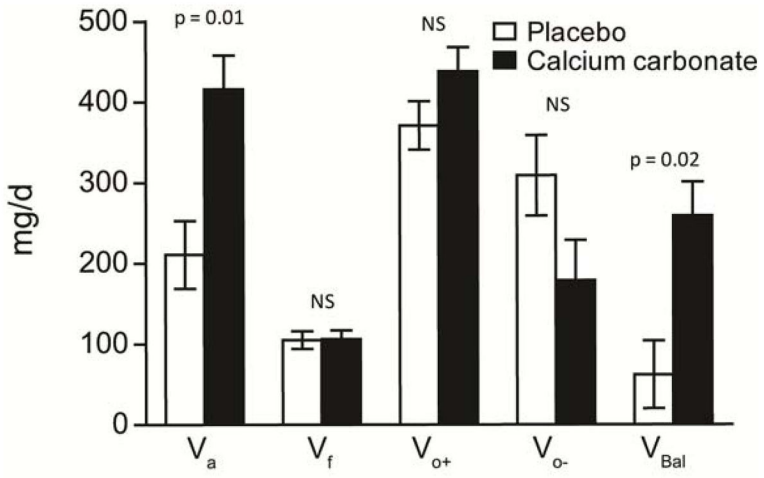

Figure 5.

Calcium kinetics in stage 3/4 CKD patients with and without calcium carbonate. Calcium absorption (V_a, mg/d) and bone balance (V_{Bal}=V_{o+} minus V_{o-}) were higher, and endogenous secretion (V_f) was unchanged with calcium carbonate compared with placebo. White bars = placebo; Black bars = calcium carbonate. Ca = calcium; NS = not significant ($p > 0.05$). Data are presented as least squares mean ± pooled SEM.

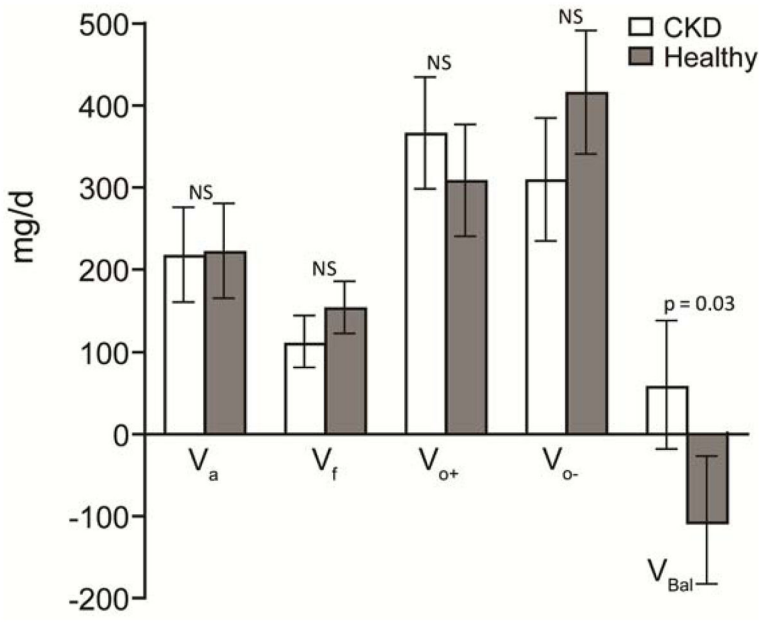

Figure 6.

Comparison of calcium kinetics on placebo of stage 3/4 CKD patients with healthy postmenopausal women. Stage 3/4 CKD patients (white bars, n = 8, current study, on controlled diet + placebo) had similar rate of calcium absorption (V_a), endogenous calcium excretion (V_f), bone formation (V_{o+}), bone resorption (V_{o-}), and "bone" balance (V_{Bal}) compared with healthy postmenopausal women [grey bars, n = 13, historical data (21)]. Data are presented as mean ± pooled SEM.

Table 1

Patient Demographics and Baseline Characteristics[a]

Male/Female, n	2/6	
Black/White, n	5/3	
Diabetes present, n	6	
Hypertension present, n	8	
Age, years	58.5 ± 6.9	(47.2, 68.7)
BMI, kg/m^2	38.7 ± 8.7	(27.9, 52.2)
eGFR, mL/min/1.73m^2	36 ± 8.8	(26, 53)
serum Ca, mg/dL	9.6 ± 0.3	(9.3, 10.3)
serum Pi, mg/dL	3.8 ± 0.6	(3.2, 4.9)
serum PTH, pg/mL	84.5 ± 58.7	(36.6, 214.0)
serum Intact FGF-23, pg/mL	79.4 ± 39.7	(33.7, 149.6)
Total Body BMD, g/cm^2	1.26 ± 0.10	(1.11, 1.38)
Z-score	0.4 ± 1.0	(−0.8, 1.9)
Lumbar Spine BMD, g/cm^2	1.29 ± 0.21	(0.98, 1.51)
Z-score	0.5 ± 1.5	(−1.3, 2.6)
Femoral Neck BMD, g/cm^2	0.98 ± 0.12	(0.80, 1.11)
Z-score	−0.5 ± 0.5	(−1.3, 0.3)

[a]Values are means ± SD (min, max) unless otherwise noted. N = 8. BMD z-scores are matched for age, race, and sex.

Table 2

Fasting serum and urine biochemistries on placebo and calcium carbonate [a]

	p-value				
	Placebo	**Calcium**	**Placebo v. Calcium**	**Reference Range**	**(source)**
sCa, mg/dL	**9.5** *0.1* (9.0, 9.9)	**9.7** *0.1* (8.8,10.2)	0.15	8.8–10.2	KDOQI
sPi, mg/dL	**3.8** *0.1* (3.3, 4.2)	**4.0** *0.1* (3.7, 5.2)	0.29	2.3 – 4.5	KDOQI
s25OHD, ng/mL	**26.7** *0.4* (20.1, 39.7)	**25.1** *0.4* (18.5, 37.6)	0.03	15 – 80	Merck Manual
s1,25OH2D, pg/mL	**33.1** *2.3* (15.7, 57.9)	**30.6** *2.3* (15.6, 62.9)	0.49	25 – 65	Merck Manual
sPTH, pg/mL	**63.1** *3.0* (38.2, 111.5)	**58.9** *3.0* (26.7, 113.1)	0.37	13 – 54	(Diasorin Assay)
sFGF23, pg/mL	**75.6** *14.5* (52.4, 142.5)	**89.9** *14.5* (38.7, 286.1)	0.51	8.2 – 54.3	(Kianos Assay)
sOC, ng/mL	**20.8** *1.2* (14.0, 41.3)	**20.1** *1.2* (14.7, 34.5)	0.71	3.7 – 10.0	(MicroVue Assay)
sBAP, U/L	**31.9** *1.0* (21.2, 47.4)	**32.4** *1.0* (19.7, 51.7)	0.73	Men: 15.0 – 41.3 Women: 14.2 – 42.7	(MicroVue Assay) (post-menopausal)
uNTX/Cr, nM/mM	**38.8** *4.1* (19.8, 66.1)	**34.9** *4.1* (12.1, 96.4)	0.53	Men: 3 – 63 Women: 5 – 65	(Osteomark Assay) (pre-menopausal)
uCa/Cr	**0.03** *0.01* (0.003, 0.12)	**0.03** *0.01* (0.002, 0.14)	0.82		
uPi/Cr	**0.4** *0.04* (0.2, 0.7)	**0.4** *0.04* (0.05, 0.52)	0.24		
TmP, mg/100mL GF	**2.8** *0.1* (2.5, 3.3)	**3.1** *0.1* (2.7, 3.8)	0.11		
C_{Pi}/C_{Cr}	**0.23** *0.01* (0.11, 0.30)	**0.19** *0.01* (0.02, 0.24)	0.10		
TmCa, mg/100mL GF	**5.2** *0.04* (4.7, 5.5)	**5.3** *0.04* (4.5, 5.7)	0.22		
C_{Ca}/C_{Cr}	**0.01** *0.003* (0.001, 0.05)	**0.01** *0.003* (0.001, 0.06)	0.94		

[a] Values are least squares means and *pooled SEM* (Min, Max), n = 8. For each patient, the values during placebo and calcium carbonate are the average of three fasting measurements.