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Associations of Dietary Phosphorus Intake, Urinary Phosphate Excretion and Fibroblast Growth Factor 23 with Vascular Stiffness in Chronic Kidney Disease

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Abstract

Objective—Elevated serum phosphate concentrations are established risk factors for cardiovascular disease and mortality in chronic kidney disease (CKD). Independent associations of other indices of phosphorus metabolism, such as phosphorus intake, urinary phosphate excretion, or hormones that regulate these systems such as fibroblast growth factor 23 (FGF23), with markers of cardiovascular disease in CKD have been studied in less detail.

Design—Cross-sectional study

Participants—74 adult CKD patients with mean creatinine clearance of 51±19 ml/min.

Outcome—Augmentation index (AI)—a surrogate marker of arterial stiffness.

Results—Whereas serum phosphate varied little across quartiles of creatinine clearance, average daily phosphorus intake and 24-hour urinary phosphate excretion decreased from highest to lowest quartile (by 31 and 60%, respectively, P for trend<0.05). FGF23 was associated with serum phosphate (r = 0.24, P = 0.03) and creatinine clearance (r= −0.4, P = 0.001), but not with dietary phosphorus or 24-hour urinary phosphate excretion (P > 0.05 for both). Older age, higher systolic blood pressure, female gender and black race were independently associated with increased AI. In contrast, there were no associations of serum phosphate, dietary phosphorus intake, urinary phosphate excretion, or FGF23 with AI in multivariable-adjusted models.

Conclusions—In this sample of patients with CKD, established risk factors for arterial stiffness but not mediators of phosphorus metabolism were associated with increased augmentation index. In addition, there were no significant associations between FGF23 and dietary phosphorus or urinary phosphate excretion. Future studies are needed to determine the main factors associated with elevations in FGF23 in CKD and to further assess the association of disordered phosphorus metabolism with subclinical markers of vascular disease.

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Keywords

Phosphorus; vascular stiffness; FGF23; augmentation index; urinary phosphate excretion

Introduction

Elevated serum phosphate concentrations are associated with increased risks of cardiovascular disease events and death among hemodialysis patients,[1, 2] patients with pre-dialysis chronic kidney disease (CKD),[3, 4] and the general population.[5, 6] Even relatively mild increases in serum phosphate within the normal range have been associated with cardiovascular morbidity and mortality in both CKD and non-CKD populations.[3–5] When coupled with *in vitro*[7] and animal data[8, 9] showing that excess phosphate promotes arterial calcification, endothelial dysfunction, and myocardial hypertrophy, these data suggest that abnormalities of phosphorus metabolism may be detrimental to cardiovascular health at all levels of kidney function.

Serum phosphate concentrations reflect a highly dynamic balance between dietary absorption, renal excretion, and exchanges with bone, soft tissue, and intracellular phosphorus stores.[10] As such, serum phosphate measurements alone provide only a limited assessment of the independent risks associated with disturbances in phosphorus homeostasis related to alterations in dietary phosphorus intake, renal phosphorus clearance or bone turnover. For example, animal and human studies have shown that excess dietary phosphorus intake is associated with accelerated kidney disease progression and mortality, independent of contemporaneous serum phosphate concentrations.[8, 11] In addition, our group and others have shown that higher fibroblast growth factor 23 (FGF23)—a phosphorus-regulating hormone and early marker of disordered phosphorus metabolism—was independently associated with kidney disease progression, left ventricular hypertrophy and mortality across the spectrum of CKD, particularly when serum phosphate concentrations were within the normal range.[12–15] These data suggest that indices of phosphorus metabolism other than serum phosphate concentrations may provide important prognostic information with respect to cardiovascular disease risk in patients with CKD.

Increased central arterial stiffness is an established risk factor for cardiovascular disease and mortality.[16, 17] Augmentation index is a validated surrogate measure of central arterial stiffness that can be non-invasively estimated from peripheral arterial waveforms using digital plethysmography.[17, 18] Although previous studies have examined relationships between serum phosphate concentrations and markers of arterial stiffness,[19, 20] few examined the associations of arterial stiffness with other key components of phosphorus metabolism, such as dietary phosphorus intake, urinary phosphorus excretion, and FGF23, in patients with CKD. Accordingly, we performed a cross-sectional analysis of 74 patients with CKD not yet requiring hemodialysis in order to examine whether indices of disordered phosphorus metabolism other than serum phosphate were associated with increased arterial stiffness in kidney disease.

Methods

Study Population

Study participants were recruited from the outpatient nephrology clinics of the Massachusetts General Hospital (MGH). Patients were eligible if they were at least 18 years of age or older and had stage 3 or 4 CKD, defined as an estimated glomerular filtration rate (eGFR) of 15–59 ml/min/1.73m^2 for ≥ 3 months. eGFR was calculated from the simplified Modification of Diet in Renal Disease equation using the screening visit serum creatinine

concentration. Exclusion criteria included current treatment with activated vitamin D analogs, oral phosphorus binders or phosphorus supplements; history or laboratory evidence of liver disease, cholestasis, or gut malabsorption; and severe anemia (hemoglobin < 8 g/dl for men and < 6 g/dl for women).

Study Protocol

Potential subjects were invited to a screening visit during which medical history and medication use were recorded, and baseline blood samples were collected. Subjects determined to be eligible for further participation after review of screening labs were asked to provide two 24-hour urine collections on non-consecutive days over the ensuing two weeks for measurement of creatinine clearance, urinary phosphate excretion, and urinary calcium excretion (averaged between the two collections). In addition, a certified research nutritionist instructed subjects on how to record all meals, beverages and snacks consumed over the course of three nonconsecutive weekdays and one weekend day during the same two week period of time. Dietary intake results were not available for 9 subjects owing to insufficient or implausible data in the four-day food records submitted for analysis. After completion of the urine collections and four-day food records, subjects underwent the final study visit during which estimation of augmentation index by digital plethysmography was performed as detailed below. The study was approved by the MGH institutional review board, and all subjects provided written, informed consent.

Measurements

Blood and urine samples for measurement of standard laboratory tests were immediately processed in the MGH central laboratory using standard commercial assays. All other blood samples were centrifuged, separated into aliquots, and stored at −80°C for future batched assays. 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) concentrations were measured using extraction/liquid chromatography-tandem mass spectrometry (Mayo Medical Laboratories, Rochester, MN). Parathyroid hormone (PTH) concentrations were measured using a two-site enzyme-linked immunoassay that detects the intact PTH peptide (Immutopics, San Clemente, CA) with coefficients of variation (CVs) of <6%. FGF23 concentrations were measured in duplicate using a two-site enzyme-linked immunoassay that detects two epitopes in the carboxyl-terminal portion of FGF23 (Immutopics, Santa Clara, CA,) with CVs of <5%. Creatinine clearance was measured from 24 hour urine collections.

Dietary intake data were derived from four-day food records. Information from each food record was manually entered into the Nutrition Data System for Research (NDSR) software system by a certified research nutritionist to estimate daily nutrient intake for each participant.

Assessment of Augmentation Index

Augmentation index is a validated surrogate measure of central arterial stiffness that estimates the relative incremental increase, or “augmentation,” that peripherally reflected arterial pressure waves contribute to the forward arterial pressure wave during systole.[21] Faster reflection of pressure waves from peripheral arterial sites, indicative of increased central arterial stiffness, increases the amplitude of the composite arterial waveform during systole (i.e., cardiac afterload pressure), resulting in an increase in the augmentation index. Importantly, elevated augmentation index has been shown to be an independent marker of morbidity and mortality in patients with CKD.[22]

Since peripheral arterial waveforms are a composite of a forward arterial pressure wave produced during systole and a later-arriving pressure wave reflected from the periphery, peripheral arteries, such as the radial artery, can be used to calculate the augmentation index.

A trained research assistant recorded radial artery waveforms of study participants using the Endopat2000 device (Itamar Medical, Caesarea, Israel). This device records pulsatile blood volume changes in the radial artery using a pneumatic plethysmograph finger probe that applies a uniform pressure field to the surface of the distal one-third of the finger. Radial pulse amplitude was measured from each fingertip for 5 minutes, during which changes in arterial wall tension were captured by changes in the pneumatic pressure field measured in the finger probe, producing a composite arterial waveform for analysis. Augmentation index was then calculated from the waveform using the following formula: $(P_2 - P_1)/\Delta P$, where P_2 is the late systolic peak pressure, representing the composite of the forward arterial pressure wave and the reflected arterial pressure wave; P_1 is the early systolic pressure wave, representing the forward arterial pressure wave alone; and ΔP represents the pulse pressure. Since heart rate has been shown to strongly influence augmentation index,[23] all calculated values were corrected to a heart rate of 75 beats per minute.

Statistical Analysis

Creatinine clearance was analyzed as a continuous variable and categorized as follows: > 60 ml/min, 45–60 ml/min, 30–44 ml/min, and < 30 ml/min. Augmentation index was analyzed on a continuous scale and categorized by tertiles according to the distribution of the variable in the study population. Demographic, clinical, laboratory, and dietary characteristics of study participants were compared across categories of creatinine clearance and augmentation index using tests for linear trend, Fisher's exact test, or Kruskal-Wallis test, as appropriate. Spearman coefficients were used to examine the correlations between FGF23, PTH and indices of phosphate and calcium metabolism. Linear regression models were fit to examine the associations between augmentation index and demographic, clinical, and laboratory variables. Variables that were significantly ($P < 0.05$) associated with augmentation index on univariate analysis were included in multivariable models to identify factors independently associated with augmentation index. A *P*-value less than 0.05 was considered significant. All analyses were performed using SAS software version 9.2 (SAS Institute, Cary, NC).

Results

Participant Characteristics

A total of 77 subjects with CKD were recruited for participation in the study. Augmentation index results were not able to be obtained in three subjects—two who withdrew from the study prior to plethysmograph testing because of illness, and one whose test results were not of sufficient quality to calculate the index. Therefore, a total of 74 subjects were included in the final analytic sample. Table 1 depicts the demographic and clinical characteristics of these participants.

Associations of Diet Characteristics with Markers of Phosphorus Metabolism

Diet characteristics of study participants according to level of kidney function are summarized in Table 2. There was a trend toward lower caloric intake with lower categories of creatinine clearance. Consistent with previous studies,[24] total protein intake also decreased with decreasing creatinine clearance. This was primarily driven by animal protein, which significantly decreased with decreasing categories of creatinine clearance, whereas vegetable protein intake did not differ by category. In line with the decrease in protein intake, dietary phosphorus intake decreased with decreasing categories of creatinine clearance. Similarly, calcium intake substantially declined with decreasing creatinine clearance.

Table 3 depicts contemporaneous blood concentrations of phosphate, calcium, 25(OH)D, $1,25(OH)_2D$, PTH and FGF23, and 24-hour urinary phosphate and calcium excretion according to level of kidney function. Although average serum phosphate concentrations did not significantly differ as kidney function declined, 24-hour urinary phosphate excretion markedly decreased, with the percent decrease from highest to lowest category of creatinine clearance (60%) being substantially higher than the concurrent decrease in dietary phosphorus intake (31%). Plasma FGF23 concentrations were linearly correlated with serum phosphate concentrations (r = 0.24, $P = 0.03$) and inversely correlated with creatinine clearance (r= −0.4, $P = 0.001$), but had no significant associations with estimated daily phosphorus intake (r=0.01, $P = 0.9$) or with 24-hour urinary phosphate excretion (r= −0.15, $P = 0.2$). In addition, there were no significant associations of FGF23 with 25(OH)D or $1,25(OH)_2D$. PTH concentrations were not associated with serum phosphate, dietary phosphorus intake or 24-hour urinary phosphate excretion, but were inversely correlated with serum calcium (r= −0.36, $P < 0.001$) and urinary calcium excretion (r= −0.4, $P < 0.001$).

Mineral metabolism and augmentation index

Table 4 depicts demographic, clinical, and laboratory characteristics of study participants according to tertile of augmentation index. Increasing age, female gender, black race, decreasing creatinine clearance and increasing systolic blood pressure were significantly associated with increasing augmentation index. Mean 24-hour urinary phosphate excretion was the only parameter related to mineral metabolism that was significantly associated with tertiles of augmentation index. When these factors were included together as independent variables in a multivariable linear regression model with augmentation index as the dependent variable, older age (β 0.4, $P = 0.03$), female gender (β 11.0, $P = 0.02$), black race (β 14.0, $P = 0.04$), and higher systolic blood pressure (β 0.34, $P < 0.001$) remained independently associated with higher augmentation index, whereas there were no significant associations between creatinine clearance and urinary phosphate excretion with augmentation index. Black race was the covariate responsible for most of the attenuation of the association of lower 24-hour urinary phosphate excretion with higher augmentation index.

Discussion

In this cross-sectional analysis of 74 CKD patients not yet requiring hemodialysis, we found no associations of serum phosphate, urinary phosphate excretion, estimated daily phosphorus intake or FGF23 with augmentation index, a surrogate marker of arterial stiffness. Instead, our study confirms previous reports that older age, black race, and higher blood pressure are independent predictors of greater arterial stiffness in CKD.[25, 26] In addition, although dietary phosphorus strongly influences FGF23 secretion,[27–29] we found no associations of FGF23 with estimated dietary phosphorus intake or with 24-hour urinary phosphate excretion. These latter data may indicate that factors other than dietary phosphorus consumption are more important mediators of higher FGF23 levels in CKD. Alternatively, they may suggest that single estimates of phosphorus consumption may be inadequate to capture the impact of dietary phosphorus intake on FGF23 in CKD patients.

Disorders of phosphorus metabolism are strongly associated with vascular stiffness. Prior studies showed significant associations of higher serum phosphate and FGF23 levels with vascular calcification and surrogate markers of arterial stiffness in individuals with largely preserved kidney function and in CKD patients.[19, 30, 31] In contrast, we did not detect any associations between serum phosphate or FGF23 and arterial stiffness in this study. The most likely explanation for this is that the sample size of this study was insufficient to detect associations of phosphate or FGF23 with arterial stiffness that were as modest as were

observed in previous studies conducted in larger, population-based cohorts. Importantly, our study is the first to our knowledge to examine the associations of other key components of phosphorus metabolism such as dietary phosphorus intake and 24-hour urinary phosphate excretion with arterial stiffness in CKD patients. Similar to phosphate and FGF23, we found no independent associations of these parameters with arterial stiffness, suggesting that obtaining these measurements may not add any diagnostic information with respect to predicting subclinical vascular disease above and beyond established risk factors such as blood pressure in CKD patients. Studies in large population-based cohorts are needed to confirm this possibility. Interestingly, we found that black race was the variable most responsible for attenuation of the association of lower urinary phosphate excretion with higher augmentation index, likely because black individuals excrete less urinary phosphate than whites in kidney disease and have higher prevalence of arterial stiffness.[32] This finding suggests that black race is an important confounder of the association of urinary phosphate excretion with cardiovascular disease that should be accounted for in future studies evaluating associations of urinary phosphate excretion with clinical outcomes.

Small physiologic studies of healthy human volunteers demonstrated that several days of high phosphorus intake resulted in increased FGF23 levels, and conversely that low phosphorus diets decreased FGF23 levels.[27–29] Although no large-scale studies exist in CKD, a single study of 16 pre-dialysis patients showed that significant elevations in FGF23 (53% rise) occurred in response to 2 weeks of a 1500 mg per day phosphorus diet.[33] Further, several studies have shown that restriction of dietary phosphorus absorption, either through the use of oral phosphorus binders or the consumption of vegetable sources of phosphorus with low bioavailability, lowered FGF23 levels in CKD patients.[34–36] Our results expand on existing data by capturing contemporaneous dietary data from detailed four-day food records, 24-hour urinary phosphate excretion, and FGF23 levels in free-living individuals from across a broad range of CKD. Interestingly, although previous studies clearly showed that gut phosphorus absorption modulates FGF23 in CKD,[34–36] we found no significant associations of FGF23 with dietary phosphorus or with 24-hour urinary phosphate excretion. This may be because other factors, such as decreased kidney function itself, may be more important stimulants of higher FGF23 levels than dietary phosphorus consumption. Alternatively, these data may indicate that an association of dietary phosphorus intake with FGF23 may not be adequately captured via single measurements in time, but instead multiple measurements over a longer period of time may be necessary.

Regardless of the root reason for the lack of an association of FGF23 with dietary phosphorus intake or urinary phosphorus excretion, this finding has important clinical relevance. There is mounting evidence that phosphorus excess is associated with increased cardiovascular risk and mortality, and that increased FGF23 may be the earliest biochemical marker of phosphorus excess in CKD patients.[37] These data suggest that FGF23 may be a more sensitive biomarker for identifying patients who might benefit from phosphorus-reduction strategies such as dietary phosphorus restriction in early CKD. However, the poor correlation between dietary phosphorus and FGF23 in this study might make it difficult to utilize this as a target of therapy for lowering FGF23 levels in clinical practice. This is especially true given the observation that individuals with lowest creatinine clearance in this study had the lowest dietary phosphorus intake (mean ~1018 mg per day) and lowest 24-hour urinary phosphate excretion (377 mg/day), yet had the highest FGF23 levels. In a clinical setting, this might suggest that there is little room for improvement with respect to dietary phosphorus reduction in the very individuals who may need it the most since they have the highest FGF23, posing a dilemma for nutritional counseling of these patients. Further studies are needed to determine whether utilizing FGF23 in place of or along with dietary phosphorus intake or urinary phosphate excretion may provide a better guide for managing dietary phosphorus intake in CKD patients than diet estimates alone.

We acknowledge several limitations. Clinical estimates of central arterial stiffness are often derived from the calculation of AI. While there is ongoing debate about whether AI appropriately captures arterial stiffness, multiple studies have shown AI to be independently predictive of cardiovascular events and mortality.[18, 38, 39] Second, the cross-sectional nature only allows for a single measurement in time. Future studies will need to determine whether measuring dynamic changes in augmentation index in response to dietary interventions may reveal an association of dietary phosphorus with arterial stiffness. Additionally, we did not request that participants stop taking vasoactive blood pressure medications on the day of AI measurement, a factor that could have affected the resulting data. An additional component to consider is the accuracy of the dietary software. The nutritional software available (NDSR) was developed based on nutrient composition tables that usually do not include phosphorus additives. Manufacturers often consider phosphorus content proprietary information and do not quantify this on the label, leading to underestimation of total phosphorus consumption by nutritional software.[40] Consequently, the software may have inaccurately captured dietary phosphorus due to the inability to account for phosphorus additives commonly used by manufacturers, which could contribute to a lack of an association between FGF23 and dietary phosphorus.

In summary, we found that traditional cardiovascular risk factors but not markers of phosphorus metabolism were associated with increased arterial stiffness as assessed by AI in community-living patients with pre-dialysis CKD. In addition, FGF23 was not associated with estimated dietary phosphorus intake or urinary phosphate excretion in these patients. This latter finding necessitates additional research to define the association of phosphorus intake with FGF23 levels, with specific attention paid to the utility of FGF23 vs. standard clinical measures of phosphorus intake in managing disordered phosphorus metabolism in CKD patients.

Practical Application

There were no significant associations between FGF23 and estimated dietary phosphorus intake or 24-hour urinary phosphate excretion in 74 chronic kidney disease patients across the spectrum of kidney function. These findings may suggest that the association between FGF23 and dietary phosphorus intake is poorly captured using single measurements in time, with important potential implications for the integration of FGF23 into the management of dietary phosphorus intake in clinical practice.

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Table 1

Demographic and clinical characteristics of study participants. Results are depicted as means ± standard deviation or frequencies.

N	74
Age	64 ± 12
Female Gender (%)	36
Black (%)	12
Creatinine clearance (ml/min)	51 ± 19
Blood pressure (mm Hg)	
Systolic	140 ± 21
Diastolic	75 ± 10
Co-morbidities (%)	
Diabetes	29
Coronary artery disease	26
Congestive heart failure	17
Hypertension	90
Stroke	6
Medications (%)	
Anti-hypertensive medications *	88
Diuretics	47
Calcium supplements	30
Ergocalciferol supplements	24

* Includes angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, β-blockers, α-blockers, and calcium channel blockers.

Table 2

Diet characteristics of study participants by categories of creatinine clearance. Results are depicted as means ± standard deviation or median (interquartile range).

	Crcl > 60	Crcl 45–60	Crcl 30–44	Crcl < 30	P (trend)
N	**17**	**18**	**20**	**10**	
Kilocalories	2409 (1665, 3071)	1524 (1359, 2007)	1763 (1644, 1938)	1852 (1075, 2292)	0.07
% Fat	37 ± 9	31 ± 5	35 ± 7	33 ± 6	0.2
% Carbohydrates	44 ± 12	51 ± 7	48 ± 7	49 ± 10	0.1
% Protein	17 ± 4	18 ± 3	16 ± 3	15 ± 4	0.3
Protein (g/d)	99 ± 38	71 ± 19	75 ± 23	68 ± 27	0.01
Animal	72 ± 36	47 ± 17	50 ± 16	44 ± 21	0.01
Vegetable	27 ± 7	24 ± 7	25 ± 10	24 ± 12	0.38
Sodium (mg/d)	3904 ± 1652	2760 ± 1076	3041 ± 848	2884 ± 1460	0.07
Potassium (mg/d)	3012 ± 785	2585 ± 686	2588 ± 806	2248 ± 889	0.02
Phosphorus (mg/d)	1469 ± 491	1103 ± 286	1214 ± 297	1018 ± 449	0.01
Calcium (mg/d)	905 ± 473	772 ± 202	832 ± 296	607 ± 216	0.04
Cholesterol (mg/d)	402 ± 250	293 ± 131	248 ± 85	287 ± 156	0.06

Table 3

Blood and urine markers of mineral metabolism by categories of creatinine clearance. Results are depicted as means ± standard deviation or median (interquartile range).

	Crcl > 60	Crcl 45–60	Crcl 30–44	Crcl < 30	P (trend)
N	**20**	**21**	**22**	**11**	
Serum phosphorus (mg/dl)	2.7 ± 0.4	3.1 ± 0.6	3.3 ± 0.6	3.0 ± 0.6	0.12
Urinary phosphate excretion (mg/d)	993 ± 324	627 ± 141	654 ± 211	377 ± 139	<0.001
Serum calcium (mg/dl)	9.7 ± 0.5	9.7 ± 0.4	9.5 ± 0.5	9.5 ± 0.4	0.25
Urinary calcium excretion (mg/d)	123 ± 83	81 ± 76	43 ± 39	28 ± 15	<0.001
25-hydroxyvitamin D (ng/ml)	29 ± 12	31 ± 14	28 ± 9	39 ± 14	0.04
1,25-dihydroxyvitamin D (pg/ml)	40 ± 18	39 ± 17	30 ± 13	33 ± 10	0.09
Parathyroid hormone (pg/ml)	47 (23, 69)	43 (23, 82)	68 (44, 128)	92 (62, 157)	0.01
Fibroblast growth factor 23 (RU/ml)	70 (37, 92)	98 (47, 118)	112 (55, 174)	118 (96, 154)	0.04

Table 4

Demographic and clinical characteristics of study participants by tertiles of augmentation index. Results are depicted as means ± standard deviation, median (interquartile range), or frequencies.

	Tertile 1 (< 4)	Tertile 2 (4–20)	Tertile 3 (> 20)	P (trend)
N	**24**	**24**	**24**	
Age	58 ± 14	68 ± 9	66 ± 12	0.02
Female (%)	25	29	58	0.02
Black (%)	4	8	25	0.03
Creatinine Clearance (ml/min)	57 ± 22	47 ± 16	45 ± 18	0.03
Blood Pressure (mm Hg)				
Systolic	129 ± 21	142 ± 18	148 ± 19	0.001
Diastolic	73 ± 10	76 ± 12	77 ± 9	0.29
Co-morbidities (%)				
Hypertension	91	88	92	0.92
Diabetes	17	42	29	0.39
Prior cardiovascular disease	8	54	29	0.12
Medications (%)				
ACE inhibitors	57	38	42	0.32
ARB	43	38	38	0.72
β-blockers	43	54	63	0.19
Serum Laboratory Data				
Calcium (mg/dl)	9.7 ± 0.5	9.6 ± 0.4	9.5 ± 0.5	0.19
Phosphate (mg/dl)	2.9 ± 0.6	3.2 ± 0.6	3.0 ± 0.6	0.96
25-hydroxyvitamin D (ng/ml)	31 ± 11	31 ± 13	31 ± 15	0.94
1,25-dihydroxyvitamin D (pg/ml)	33 ± 14	31 ± 12	41 ± 15	0.05
Parathyroid hormone (pg/ml)	42 (23, 67)	52 (29, 128)	69 (39, 89)	0.12
Fibroblast growth factor 23 (RU/ml)	74 (35, 121)	110 (65, 159)	93 (52, 114)	0.23
Urine Laboratory Data				
Urinary phosphate excretion (mg/d)	851 ± 373	661 ± 222	551 ± 191	<0.001
Urinary calcium excretion (mg/d)	87 ± 77	54 ± 42	64 ± 77	0.25