Earlier Onset and Greater Severity of Disordered Mineral Metabolism in Diabetic Patients With Chronic Kidney Disease

PATRICIA WAHL, PHD[1]
HUILIANG XIE, PHD[2]
JULIA SCIALLA, MD, MHS[1]
CHERYL A.M. ANDERSON, PHD, MPH[3]
KEITH BELLOVICH, DO[4]
CAROLYN BRECKLIN, MD[5]
JING CHEN, MD, MMSC, MSCE[6,7]
HAROLD FELDMAN, MD, MSCE[8,9]
ORLANDO M. GUTIERREZ, MD, MMSC[10]
JIM LASH, MD[5]
MARY B. LEONARD, MD, MSCE[8,11]
LAVINIA NEGREA, MD[12]
SYLVIA E. ROSAS, MD, MSCE[9]
AMANDA HYRE ANDERSON, PHD, MPH[8]
RAYMOND R. TOWNSEND, MD[9]
MYLES WOLF, MD, MMSC[1]
TAMARA ISAKOVA, MD, MMSC[1]
ON BEHALF OF THE CHRONIC RENAL INSUFFICIENCY COHORT STUDY GROUP

OBJECTIVE—Disordered mineral metabolism is a common complication of chronic kidney disease (CKD) and a novel risk factor for CKD progression, cardiovascular disease, and mortality. Although diabetes is the leading cause of CKD and is associated with worse clinical outcomes than other etiologies, few studies have evaluated mineral metabolism in CKD according to diabetes status.

RESEARCH DESIGN AND METHODS—Using the Chronic Renal Insufficiency Cohort Study, we tested the hypothesis that diabetes is independently associated with lower serum calcium and higher serum phosphate, parathyroid hormone (PTH), and fibroblast growth factor 23 (FGF23).

RESULTS—Compared with participants without diabetes (n = 1,936), those with diabetes (n = 1,820) were more likely to have lower estimated glomerular filtration rate (eGFR), lower serum albumin, and higher urinary protein excretion (all $P < 0.001$). Unadjusted serum phosphate, PTH, and FGF23 levels were higher and calcium was lower among those with compared with those without diabetes (all $P < 0.001$). After multivariate adjustment, diabetes remained a significant predictor of serum phosphate, PTH, and FGF23 but not calcium. The eGFR cut point at which 50% of participants met criteria for secondary hyperparathyroidism or elevated FGF23 was higher in participants with diabetes compared with those without (PTH: eGFR 30–39 vs. 20–29, $P < 0.001$; FGF23: eGFR 50–59 vs. 40–49, $P < 0.001$).

CONCLUSIONS—Disordered mineral metabolism begins earlier in the course of CKD and is more severe among CKD patients with compared with those without diabetes. Future studies should explore mechanisms for these differences and whether they contribute to excess risks of adverse clinical outcomes among diabetic patients with CKD.

Diabetes Care 35:994–1001, 2012

From the [1]Division of Nephrology and Hypertension, Department of Medicine, University of Miami Miller School of Medicine, Miami, Florida; the [2]Department of Epidemiology and Public Health, University of Miami Miller School of Medicine, Miami, Florida; [3]The Welch Center for Prevention, Epidemiology, and Clinical Research and the Department of Epidemiology, Johns Hopkins University, Baltimore, Maryland; the [4]Division of Nephrology, Department of Medicine, St. John Hospital and Medical Center, Detroit, Michigan; the [5]Department of Medicine, University of Illinois at Chicago, Chicago, Illinois; the [6]Department of Medicine, Tulane University Health Sciences Center, New Orleans, Louisiana; the [7]Department of Epidemiology, Tulane University Health Sciences Center, New Orleans, Louisiana; [8]The Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; the [9]Department of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania; the [10]Division of Nephrology, Department of Medicine, University of Alabama at Birmingham, Birmingham, Alabama; the [11]Department of Pediatrics, The Children's Hospital of Philadelphia, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; and the [12]Division of Nephrology and Hypertension, Department of Medicine, Case Western Reserve University, Cleveland, Ohio.
Corresponding author: Tamara Isakova, tisakova@med.miami.edu.
Received 18 November 2011 and accepted 18 January 2012.
DOI: 10.2337/dc11-2235

An estimated 25.8 million people in the U.S. suffer from diabetes, a leading risk factor for cardiovascular disease (CVD) and the most common cause of chronic kidney disease (CKD) (1,2). Although improved understanding of diabetes-related complications has led to advances in clinical management of affected individuals, recent studies show that even with delivery of optimal care, high risks of CVD and CKD persist (3). Moreover, compared with patients without diabetes, those with diabetes experience faster progression to end-stage renal disease (ESRD) and higher rates of CVD events and mortality (2). Thus, identifying novel pathophysiologic mechanisms that may contribute to these differences and can be targeted for intervention is a critical priority for diabetes and CKD management.

Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD) refers to the clinical syndrome of laboratory abnormalities, bone disease, and extraskeletal calcification, including the arterial system (4). Among the earliest manifestations of CKD-MBD are vitamin D deficiency, disordered calcium and phosphate homeostasis, and secondary elevations of parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF23). Mounting experimental and epidemiologic data support these alterations in mineral metabolism as novel risk factors for ESRD, CVD, and mortality (5,6). The evidence is especially strong for elevated serum phosphate and FGF23, which independently predict risks of CKD progression, CVD, and mortality (7,8). Differences in mineral metabolism according to diabetes status have been described in patients with ESRD (9,10), but a detailed characterization of the syndrome according to diabetes status is lacking in earlier stages of CKD. We measured mineral metabolites in baseline samples from 3,756 participants in the Chronic Renal Insufficiency Cohort (CRIC) Study, a racially and ethnically diverse prospective CKD cohort with a high prevalence of diabetes. We hypothesized that individuals with diabetes

would have more severe abnormalities of mineral metabolism at comparable levels of renal dysfunction than patients without diabetes (lower serum calcium, higher serum phosphate, PTH, and FGF23 levels).

RESEARCH DESIGN AND METHODS

—The CRIC study is a multicenter prospective cohort study of risk factors for CVD and CKD progression (11). The ancillary Hispanic CRIC study recruited additional Hispanic participants (12). Adult patients aged 21–74 years with mild to moderate CKD, defined as an age-stratified estimated glomerular filtration rate (eGFR) at the screening visit between 20 and 70 mL/min/1.73 m^2, were enrolled between May 2003 and August 2008. Individuals who were eligible based on their screening eGFR but whose eGFR at the first study visit was found to be outside the range of 20–70 mL/min/1.73 m^2 were retained in the study. Patients were excluded for pregnancy, New York Heart Association class III–IV heart failure, HIV, cirrhosis, myeloma, renal cancer, recent chemotherapy or immunosuppressive therapy, polycystic kidney disease, organ transplantation, or prior treatment with dialysis for >1 month. The CRIC study protocol was approved by the institutional review boards at each of the 13 recruitment sites. All participants provided written informed consent. After the baseline visit, participants are followed annually.

We studied 3,756 CRIC study participants who had measurements of the primary dependent variables at the baseline study visit (serum calcium, phosphate, PTH, and FGF23). Diabetes was defined as current use of diabetes medications or documented laboratory evidence of diabetes (random plasma glucose >200 mg/dL or a fasting plasma glucose level >126 mg/dL).

Data collection and measurements

We analyzed the following covariate data collected at the baseline visit: demographics, medical history, use of phosphate binders and activated vitamin D, blood pressure, BMI, and dietary phosphate, calcium, and caloric intake estimated from the National Cancer Institute's Diet History Questionnaire (13). Dietary data were available for 2,817 participants. Serum 25-hydroxyvitamin D and 1,25-hydroxyvitamin D levels were available from the year 1 follow-up visit in 1,457 (605 diabetic participants; 852 nondiabetic participants) and 1,480 (615 diabetic participants; 865 nondiabetic participants) participants, respectively.

Baseline fasting blood samples, spot urine samples for assessment of the albumin-to-creatinine ratio, and 24-h urine collections were assayed using standard methods. Twenty-four-hour urinary data were available for 3,554 participants. In addition to total 24-h urinary mineral content (mg/day), we analyzed fractional urinary mineral excretion (fractional excretion of calcium = [urine calcium × serum creatinine]/[serum calcium × urine creatinine] × 100%; fractional excretion of phosphate = [urine phosphate × serum creatinine]/[serum phosphate × urine creatinine] × 100%). Plasma FGF23 was measured using the second-generation COOH-terminal assay that detects two epitopes in the C-terminus of FGF23 (coefficient of variation [CV] <5%; Immutopics, San Clemente, CA). Plasma PTH was measured using a total PTH assay, which includes the 1–84 PTH molecule and 7–84 fragments (CV <5%; Scantibodies, Santee, CA). Serum 25-hydroxyvitamin D was measured using liquid chromatography–mass spectroscopy (CV<5%), and serum 1,25-dihydroxyvitamin D was measured by competitive chemiluminescent immunoassay (CV <12%; Heartland Assays, Ames, IA). Serum 25-hydroxyvitamin D and eGFR were based on the modified Modification of Diet in Renal Disease (MDRD) equation (14). A subset of 1,351 participants (650 with diabetes; 701 without diabetes) had GFR measured directly using ^{125}I iothalamate clearance (iGFR).

Statistical analysis

We defined hyperphosphatemia as serum phosphate ≥4.6 mg/dL, secondary hyperparathyroidism as PTH ≥65 pg/mL, and FGF23 excess as FGF23 ≥100 RU/mL (15,16). We compared baseline characteristics, levels of mineral metabolites, and prevalence of abnormalities by diabetes status using two-sample *t* tests or Wilcoxon rank-sum tests for continuous variables and χ^2 tests for categorical variables. CRIC study participants with diabetes had lower eGFR at baseline, and eGFR is a well-established determinant of disordered mineral metabolism in CKD (16). Therefore, we examined differences in mean or median levels of mineral metabolites in diabetic subgroups stratified by levels of eGFR (15–29, 30–44, 45–59, and ≥60 mL/min/1.73 m^2). Participants with diabetes also had greater degrees of proteinuria, which has been linked to lower vitamin D levels (17), so we examined correlations between 24-h urinary protein excretion and mineral metabolites among participants with diabetes. To evaluate the role of glycemic control in disordered mineral metabolism, we examined correlations between mineral metabolism markers and hemoglobin A_{1c} within the group of participants with diabetes.

Next, we performed multivariable regression analyses to investigate the independent association between diabetes status and mineral metabolites. PTH and FGF23 were not normally distributed and were natural log-transformed for the analyses. For ease of interpretation, we report adjusted means that were back transformed into conventional scale. Separate regression analyses were performed for each of the dependent variables (calcium, phosphate, log PTH, and log FGF23). In all models, we included diabetes status as the primary predictor and adjusted for demographics (age, sex, black race, and Hispanic ethnicity), clinical characteristics (current smoking, BMI, and systolic blood pressure), clinical center, and laboratory values (eGFR and serum albumin). Higher BMI in diabetic participants would suggest differences in dietary exposure. Therefore, in addition to including BMI in the multivariable models, we performed supplementary analyses that adjusted for BMI, dietary phosphate, calcium, and total caloric intakes. To assess whether diabetes was associated with mineral metabolites independent of vitamin D status, we performed additional analyses that further adjusted for 25-hydroxyvitamin D levels in the subset in whom these data were available. We also repeated the adjusted analyses in the subcohort of participants with iGFR and substituted iGFR for MDRD eGFR. Finally, we compared the onset of disordered mineral metabolism in relation to eGFR according to diabetes status by calculating the prevalence of hyperphosphatemia, secondary hyperparathyroidism, and FGF23 excess within ascending groups of eGFR (<20, 20–29, 30–39, 40–49, 50–59, 60–69, and ≥70 mL/min/1.73 m^2). We summarized these data by comparing the eGFR range at which one-half of the participants within each study group had these abnormalities and tested for significance of the stratified two-by-two table using the Cochran-Mantel-Haenszel statistic. Two-sided *P* values <0.05 were considered statistically significant. All statistical analyses were performed using SAS software (version 9.2; SAS Institute, Cary, NC).

RESULTS—The mean (±SD) eGFR among the 3,756 CRIC study participants included in this study was 42.7 ± 13.5 mL/min/1.73 m^2. Forty-eight percent had diabetes, 41.5% were black, and 12.9% were Hispanic. Table 1 shows the baseline characteristics of the participants according to diabetes status. Because of the large sample size, many comparisons yielded significant but not clinically meaningful differences. Age and sex were similar across the groups; however, a greater percentage of participants with diabetes were black or Hispanic. Systolic blood pressure and BMI were significantly higher in those with diabetes versus those without diabetes. In contrast to previous reports of greater urinary phosphate excretion in diabetes (18,19), both 24-h urinary phosphate and fractional excretion of phosphate were comparable between the groups. Compared with those without diabetes, participants with diabetes had significantly lower eGFR and higher urinary protein excretion ($P < 0.001$ for both) (Table 1). There were no significant differences in use of phosphate binders or activated vitamin D, and frequency of use of these medications was low in both groups.

Serum phosphate, PTH, and FGF23 levels were significantly higher, and serum calcium, 25-hydroxyvitamin D, and 1,25-hydroxyvitamin D were significantly lower among those with diabetes compared with those without diabetes ($P < 0.001$ for all) (Table 1). Hyperphosphatemia (serum phosphate ≥4.6 mg/dL), secondary hyperparathyroidism (PTH ≥65 pg/mL), and FGF23 excess (FGF23 ≥100 RU/mL) were more prevalent in the diabetic group ($P < 0.001$ for all) (Table 1).

Given significant differences in eGFR between the groups, we examined levels of mineral metabolites according to diabetes status within four strata of eGFR (Table 2). Although differences between the study groups were detectable in each parameter, the most consistent differences were observed in FGF23 levels, which were significantly higher in the diabetic group in each stratum of eGFR. Of importance, caloric intake, dietary phosphate and calcium intake, and urinary phosphate and calcium excretion were comparable in both groups across all categories of eGFR (Table 2). Within the eGFR >60 mL/min/1.73 m^2 stratum, only FGF23 was significantly different in diabetic compared with nondiabetic participants.

Because diabetes was associated with a greater amount of proteinuria, we examined the correlations between degree of proteinuria and the severity of abnormalities in mineral metabolism within the diabetic

Table 1—*Characteristics of the study population*

Variable	With diabetes	Without diabetes	*P*
n	1,820	1,936	
Age (years)	59.5 ± 9.8	57.0 ± 11.9	<0.001
Women (%)	43.4	45.7	0.15
Black (%)	44.1	39.1	0.002
Hispanic (%)	17.9	8.3	<0.001
Systolic blood pressure (mmHg)	133.7 ± 22.8	123.8 ± 20.5	<0.001
BMI (kg/m^2)	34.0 ± 8.0	30.4 ± 7.2	<0.001
Current smoking (%)	11.5	13.8	0.04
Activated vitamin D use (% treated)	3.7	2.6	0.07
Binder use (% treated)	7.5	6.3	0.18
eGFR (mL/min/1.73 m^2)	40.7 ± 12.8	44.7 ± 13.8	<0.001
24-h urine protein (g/day)	0.38 (0.1–1.8)	0.11 (0.1–0.47)	<0.001
Urine albumin-to-creatinine ratio (μg/mg)	151.4 (19.3–1,018.6)	21.6 (6.0–197.7)	<0.001
24-h urine calcium (mg/day)	32.7 (15.0–66.4)	49.4 (21.7–106.3)	<0.001
24-h urine phosphate (mg/day)	710.3 (512.0–942.1)	717.7 (518.2–965.1)	0.63
Fractional excretion of calcium (%)	0.52 (0.28–1.0)	0.68 (0.33–1.3)	<0.001
Fractional excretion of phosphate (%)	26.0 (18.8–35.7)	24.8 (18.7–33.9)	0.01
Dietary calcium intake (mg/day)	646.4 (442.4–912.5)	592.2 (412.1–846.0)	<0.001
Dietary phosphate intake (mg/day)	1,110.3 (789.9–1,497.2)	1,024.0 (729.2–1,380.2)	<0.001
Total caloric intake (kcal/day)	1,670.9 (1,205.7–2,272.2)	1,626.6 (1,252.2–2,276.7)	0.70
Serum albumin (g/dL)	3.8 ± 0.5	4.0 ± 0.4	<0.001
Serum calcium (mg/dL)	9.1 ± 0.5	9.2 ± 0.5	<0.001
Serum phosphate (mg/dL)	3.9 ± 0.7	3.5 ± 0.6	<0.001
PTH (pg/mL)	60.3 (38.0–102.5)	49.5 (33.0–78.9)	<0.001
FGF23 (RU/mL)	172.4 (114.3–277.2)	121.9 (84.0–198.8)	<0.001
25-hydroxyvitamin D (ng/mL)	23.9 ± 13.3	31.0 ± 14.8	<0.001
1,25-dihydroxyvitamin D (ng/mL)	25.8 ± 18.4	33.5 ± 20.3	<0.001
Secondary hyperparathyroidism (%)	45.9	35.0	<0.001
Hyperphosphatemia (%)	16.8	5.1	<0.001
FGF23 excess (%)	82.1	63.4	<0.001

Data are percent, means ± SD, or medians (interquartile range). 25-hydroxyvitamin D and 1,25-hydroxyvitamin D levels measured from the year 1 visit were available in 1,457 (605 with diabetes; 852 without diabetes) and 1,480 (615 with diabetes; 865 without diabetes) participants, respectively. Twenty-four-hour urinary data were available for 3,554 (1,718 with diabetes; 1,836 without diabetes) participants. Dietary data were available for 2,817 (1,261 with diabetes; 1,556 without diabetes) participants. Fractional mineral excretion data were available for 3,621 (1,751 with diabetes; 1,870 without diabetes) participants.

Table 2—*Laboratory and dietary values by diabetes status and eGFR cut points*

	eGFR 15–29 (n = 727)		eGFR 30–44 (n = 1,432)		eGFR 45–59 (n = 1,210)		eGFR >60 (n = 382)	
	With diabetes	Without diabetes	With diabetes	Without diabetes	With diabetes	Without diabetes	With diabetes	Without diabetes
n	400	327	778	654	517	693	123	259
eGFR (mL/min/1.73 m^2)	24.6 ± 3.6	25.2 ± 3.3	37.6 ± 4.1	38.1 ± 4.2	51.3 ± 4.1	51.8 ± 4.3	67.9 ± 8.4	67.6 ± 7.1
24-h urine protein (g/day)	0.9 (0.2–3.3)	0.4 (0.1–1.2)	0.4 (0.1–1.9)	0.1 (0.1–0.7)	0.2 (0.1–0.8)	0.1 (0.1–0.2)	0.1 (0.1–0.5)	0.1 (0.1–0.15)
Urine albumin-to-creatinine ratio (μg/mg)	525.9 (72.8–2,144.9)	187.9 (27.9–654.1)	212.6 (23.5–1,199.6)	37.6 (6.9–311.1)	53.1 (10.0–363.0)	11.2 (4.9–65.9)	21.0 (5.3–246.1)	7.9 (4.1–32.3)
Serum albumin (g/dL)	3.7 ± 0.5	4.0 ± 0.4	3.8 ± 0.5	4.0 ± 0.5	3.9 ± 0.4	4.1 ± 0.4	3.9 ± 0.5	4.1 ± 0.4
Dietary calcium intake (mg/day)	658.3 (425.5–913.1)	597.2 (394.1–885.3)	608.9 (415.0–904.5)	574.3 (409.1–809.5)	655.6 (488.7–916.5)	602.0 (419.4–850.4)	712.9 (469.7–966.4)	640.0 (435.8–864.9)
Dietary phosphate intake (mg/day)	1,091.3 (765.9–1,476.8)	974.2 (682.2–1,388.2)	1,072.4 (741.9–1,455.9)	981.3 (700.8–1,342.1)	1,156.3 (833.4–1,533.2)	1,033.5 (756.7–1,405.7)	1,148.3 (887.0–1,654.2)	1,082.9 (782.6–1,387.8)
Caloric intake (kcal/day)	1,583 (1,196–2,298)	1,581 (1,209–2,219)	1,645 (1,160–2,224)	1,600 (1,199–2,271)	1,729 (1,252–2,288)	1,681 (1,272–2,303)	1,818 (1,310–2,472)	1,688 (1,359–2,275)
24-h urine calcium (mg/day)	24.0 (12.0–41.1)	26.6 (13.5–50.0)	28.5 (14.0–56.0)	36.7 (17.3–79.2)	44.5 (22.0–91.8)	67.8 (31.7–128.5)	68.7 (33.0–138.8)	105.0 (58.2–183.1)
24-h urine phosphate (mg/day)	656.2 (473.2–875.6)	618.1 (454.7–794.0)	693.5 (498.0–912.3)	679.0 (497.5–882.0)	779.9 (554.0–1,025.0)	768.0 (566.8–1,026.5)	768.7 (606.2–1,118.0)	852.1 (597.2–1,104.7)
FECa (%)	0.61 (0.33–1.1)	0.65 (0.33–1.3)	0.48 (0.25–0.91)	0.58 (0.26–1.2)	0.54 (0.27–1.0)	0.72 (0.37–1.3)	0.70 (0.33–1.2)	0.90 (0.55–1.5)
FEPi (%)	35.3 (26.3–47.2)	35.2 (26.4–46.7)	26.6 (19.9–35.5)	26.8 (20.6–35.4)	22.0 (16.8–29.0)	22.7 (17.4–28.8)	18.6 (14.1–23.7)	18.8 (13.9–23.9)
Serum calcium (mg/dL)	9.0 ± 0.6*	9.2 ± 0.6	9.1 ± 0.5*	9.3 ± 0.6	9.2 ± 0.5	9.2 ± 0.5	9.2 ± 0.4	9.2 ± 0.4
PTH (pg/mL)	105.7 (68.7–170.5)	101.1 (62.0–172.4)	61.9 (40.0–99.0)*	55.4 (36.7–82.7)	45.0 (31.1–68.0)*	41.0 (31.0–61.0)	34.3 (26.0–53.3)	35.9 (27.6–48.5)
Serum phosphate (mg/dL)	4.3 ± 0.8*	3.9 ± 0.7	3.9 ± 0.6*	3.5 ± 0.5	3.7 ± 0.6*	3.4 ± 0.5	3.5 ± 0.5	3.4 ± 0.5
FGF23 (RU/mL)	279.0 (193.4–401.3)*	226.7 (153.3–356.6)	179.6 (125.5–269.2)*	138.5 (98.7–214.2)	128.4 (96.0–180.3)*	99.9 (73.3–146.7)	99.2 (74.2–131.5)*	84.4 (61.7–111.9)

Data are percent, means ± SD, or medians (interquartile range). Twenty-four-hour urinary data were available for 3,554 (1,718 with diabetes; 1,836 without diabetes) participants. Dietary data were available for 2,817 (1,261 with diabetes; 1,556 without diabetes) participants. Fractional mineral excretion data were available for 3,621 (1,751 with diabetes; 1,870 without diabetes) participants. Five individuals with eGFR <15 are not included. FECa, fractional excretion of calcium; FEPi, fractional excretion of phosphate. *$P < 0.05$ vs. participants without diabetes.

group. Greater 24-h urinary protein correlated with serum phosphate ($r = 0.2$, $P < 0.001$), PTH ($r = 0.3$, $P < 0.001$), FGF23 ($r = 0.2$, $P < 0.001$), and 25-hydroxyvitamin D ($r = –0.2$, $P < 0.001$) levels. Correlation between glycemic control and mineral metabolites was even weaker (data not shown).

In multivariable analyses that adjusted for age, sex, black race, Hispanic ethnicity, eGFR, serum albumin, systolic blood pressure, BMI, and clinical center, diabetes remained a significant predictor of phosphate, PTH, and FGF23 but not calcium (Table 3). Of note, the direction of association for diabetes and PTH levels was reversed in the multivariable models, with diabetes associated with lower PTH levels (Fig. 1). Additional adjustment for dietary phosphate, calcium, and total caloric intakes did not change the findings (Table 3, *model 2*). Further adjustment for 25-hydroxyvitamin D levels in the subset of participants with measured levels did not alter the results (Table 3, *model 3*). In the adjusted models, lower 25-hydroxyvitamin D levels were independently associated with higher levels of serum phosphate, PTH, and FGF23. Finally, when we examined the correlation between eGFR and iGFR in the entire CRIC and within each of the study groups, we found that the correlations were high in the entire study sample ($r = 0.82$, $P < 0.001$) and among diabetic ($r = 0.78$, $P < 0.001$) and nondiabetic ($r = 0.84$, $P < 0.001$) participants. Moreover, the results of the adjusted models remained qualitatively unchanged following substitution of iGFR for eGFR (data not shown).

To further compare the prevalence of abnormalities of mineral metabolism according to presence of diabetes across the spectrum of eGFR, we examined the eGFR at which one-half of the participants had elevated levels of mineral metabolites. The eGFR cut point at which 50% of participants met criteria for secondary hyperparathyroidism (PTH ≥65 pg/mL) was higher in patients with diabetes (eGFR 30–39) compared with those without diabetes (eGFR 20–29, $P < 0.001$). Likewise, among those with diabetes, 50% already had elevated FGF23 (≥100 RU/mL) at an eGFR of 50–59 compared with an eGFR of 40–49 for those without diabetes ($P < 0.001$). The prevalence of hyperphosphatemia did not reach 50% except in the lowest eGFR cut point only in the diabetes group, and hyperphosphatemia was more prevalent among those with diabetes compared with those without diabetes at every 10-point range of eGFR ($P < 0.001$).

CONCLUSIONS—In this large descriptive study of patients with CKD stages 2–4, participants with diabetes had higher levels of serum phosphate, PTH, and FGF23 levels and lower vitamin D levels compared with those without diabetes. Moreover, hyperphosphatemia, secondary hyperparathyroidism, and FGF23 excess occurred earlier in the course of CKD in individuals with diabetes compared with those without diabetes. Although the direction for the association of PTH and diabetes reversed in multivariable models, serum phosphate and FGF23 levels remained higher in participants with diabetes compared with those without diabetes, independent of demographic, clinical, and laboratory values. These findings extend the previously reported differences in mineral metabolism found in small studies of predialysis CKD (20,21) and emphasize the potential need for greater surveillance of mineral metabolism in diabetic patients with early CKD.

Abnormalities in bone and mineral metabolism have been reported in patients with diabetes across the spectrum of kidney disease and even in those with normal kidney function. Previous studies reported that patients with diabetes and normal renal function have lower PTH levels, reduced bone formation rates, decreased bone mass, and greater risk of fractures compared with those without diabetes (22–28). Likewise, patients with diabetes who are undergoing dialysis are more likely to develop low-turnover bone disease and relatively low PTH levels compared with patients with nondiabetic ESRD (9,10). In patients with earlier stages of CKD, the prevalence of vitamin D deficiency is higher in diabetes than in CKD as a result of other etiologies (29), perhaps in part because of greater urinary loss of vitamin D–binding protein in proteinuria (17). Our findings of lower 25-hydroxyvitamin D levels in participants with diabetes, and the inverse association between proteinuria and 25-hydroxyvitamin D levels, are consistent with this observation.

Although greater prevalence of vitamin D deficiency should predispose CKD patients with diabetes to greater severity of secondary hyperparathyroidism than patients with CKD as a result of other etiologies, previous small studies reported lower PTH levels in patients with CKD as a result of diabetes (18,19). Our findings are not in complete agreement with these reports. Although we found that unadjusted PTH levels were higher in patients with diabetes compared with those without diabetes, and that the prevalence of secondary hyperparathyroidism reached the 50% threshold at a higher eGFR (earlier in the course of disease) in the diabetic group, multivariable adjustment reversed the direction of the relationship, and the association between diabetes and lower PTH levels emerged, as has been described previously (18,19). Although additional studies are needed to explain the mechanism for the finding of lower adjusted PTH levels in diabetic CRIC study participants, unadjusted PTH levels, which are measured in clinical practice, are typically higher in diabetic patients with CKD, likely because this group possesses a greater number of characteristics predisposing them to secondary hyperparathyroidism (lower eGFR, higher BMI, greater proteinuria, and lower 25-hydroxyvitamin D levels). Closer surveillance of PTH may be needed in diabetes.

Table 3—*Multivariate-adjusted associations between mineral metabolism markers and diabetes*

	Model 1		Model 2		Model 3	
	β	*P*	β	*P*	β	*P*
Serum calcium	0.01	0.44	0.004	0.83	0.03	0.16
Log PTH	−0.06	0.002	−0.06	0.02	−0.10	0.001
Serum phosphate	0.31	<0.001	0.29	<0.001	0.25	<0.001
Log FGF23	0.15	<0.001	0.16	0.005	0.09	0.01

The regression coefficients are calculated for the effect of diabetes on each individual mineral metabolism marker. Model 1: adjusted for demographics (age, sex, black race, and Hispanic ethnicity), clinical characteristics (current smoking, BMI, and systolic blood pressure), clinical center, and laboratory values (eGFR and serum albumin). Model 2: same covariates as in model 1, plus dietary phosphate, calcium, and total caloric intakes. Model 3: same covariates as in model 1 plus 25-hydroxyvitamin D, restricted to those with 25-hydroxyvitamin D levels ($n = 1,453$).

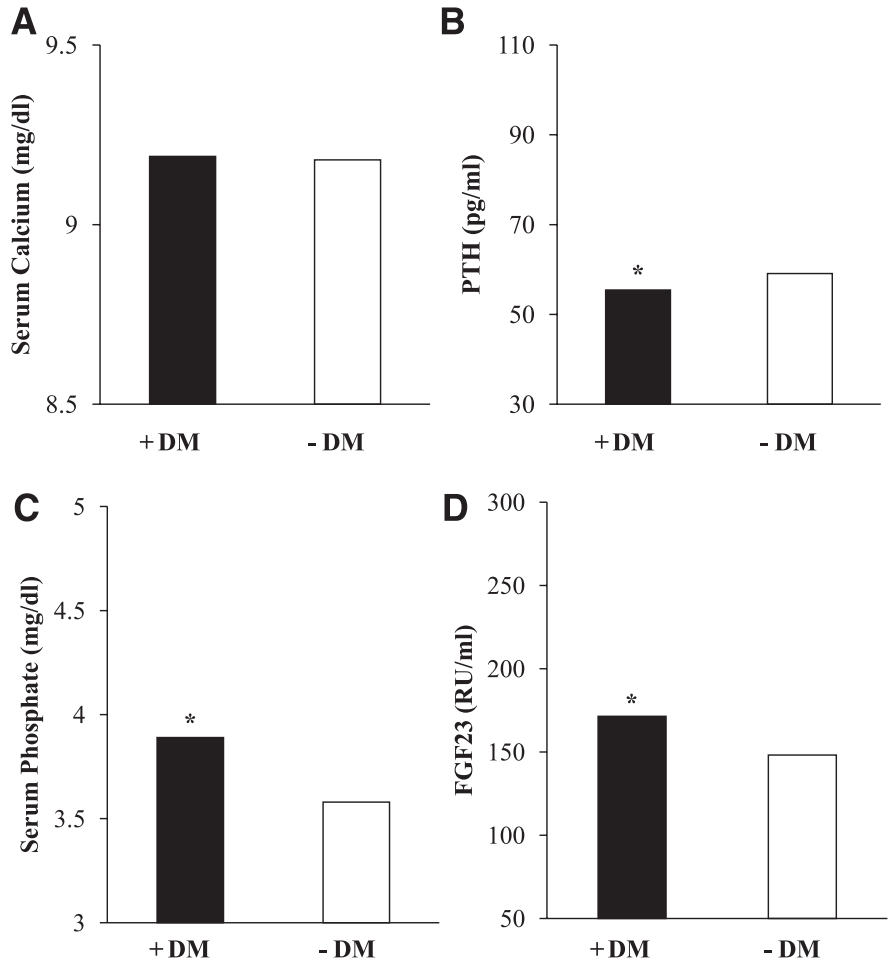

Figure 1—*Adjusted levels of calcium* (A)*, PTH* (B)*, phosphate* (C)*, and FGF23* (D) *according to diabetes status. Values are means that were estimated from generalized linear models that adjusted for age, sex, black race, Hispanic ethnicity, current smoking, BMI, systolic blood pressure, clinical center, eGFR, and serum albumin.* ■*, values obtained in the diabetic group;* □*, group without diabetes. *Significant differences between the two groups* ($P < 0.05$)*. +DM, participants with diabetes; −DM, participants without diabetes.*

We also found higher levels of FGF23 in participants with diabetes, which may explain previous reports of the independent association of diabetes with lower 1,25-dihydroxyvitamin D levels in patients with earlier stages of CKD, consistent with our data (16). FGF23 is the most recently discovered hormonal regulator of mineral metabolism, and elevated levels may be the earliest manifestation of disordered mineral metabolism in CKD (15). In healthy individuals, FGF23 is secreted by osteocytes in response to dietary phosphate loading or an increase in 1,25-dihydroxyvitamin D levels, and it stimulates phosphaturia and reduces 1,25-dihydroxyvitamin D and PTH levels (30). In patients with CKD, FGF23 levels are thought to increase as a compensatory response to maintain normal phosphate balance as the capacity for renal phosphate excretion declines. In conjunction with elevated PTH levels, elevated FGF23 levels help to maintain normal serum phosphate concentrations in the vast majority of patients with early and intermediate stages of CKD (30). Data comparing FGF23 in CKD attributed to diabetes versus other causes are sparse and conflicting. In three previous studies of 89–224 participants, some studies reported higher FGF23 in diabetes and others reported lower levels (20,21,31). Inconsistencies in the range of kidney function, small sample size, and use of medications that affect mineral metabolism may have accounted for these disparate results (20,21,31).

In this highly powered study, we found that diabetes was independently associated with elevated median FGF23 levels overall and at every level of eGFR and that FGF23 excess was more prevalent earlier in the course of CKD among those with diabetes versus those without diabetes. Although higher serum phosphate levels in the diabetic group may be one potential explanation for this difference, the cross-sectional design of our study limited our ability to assess directionality of associations or to delineate mechanisms for our findings. Nonetheless, we speculate two possibilities based on prior literature. First, patients with diabetes have decreased bone formation rates, which has been proposed as a stimulus for FGF23 secretion (32). Thus, diabetes may inhibit bone formation, thereby resulting in early and more severe elevations in FGF23 levels. Second, human and animal data suggest that patients with diabetes may have early tubular injury, prior to a measurable decrement in eGFR or onset of microalbuminuria (33,34). Therefore, it is possible that at an equivalent eGFR, patients with diabetes actually have greater severity of kidney disease and, thus, higher FGF23 levels compared with those without diabetes. Emerging reports of FGF23 elevation in the setting of definite kidney injury but prior to an appreciable rise in serum creatinine in humans and animals support this hypothesis (35,36).

Our finding of higher serum phosphate levels in the diabetic versus the nondiabetic group is consistent with previous studies (21). Although we did not observe marked differences in dietary intake of phosphate or 24-h urinary phosphate excretion across the groups, factors other than dietary intake or urinary excretion may have contributed to our findings. We speculate reduced uptake of phosphate by bone attributed to decreased bone-formation rates (37) or diminished intracellular phosphate flux attributed to insulin resistance in diabetes led to increased serum phosphate (38). Although the latter was not supported by exploratory analyses of the association between glycemic control and serum phosphate, hemoglobin A_{1c} may be less accurate in CKD (39). Additional studies are needed to clarify mechanisms of elevated serum phosphate in diabetes complicated by CKD.

We acknowledge several limitations of our study beyond its cross-sectional design. First, the CRIC study intentionally oversampled blacks and Hispanics; therefore, our study population may not be entirely representative of others with

diabetes and CKD. Second, lack of information on diabetes type precludes conclusions of differences in mineral metabolism between type 1 and type 2 diabetes. Third, the MDRD equation used to estimate GFR in the full CRIC has been shown to perform less accurately in diabetic patients compared with those without diabetes (40). However, the sensitivity analyses with iGFR substituted for MDRD eGFR confirmed our main findings, and the correlations between iGFR and eGFR were high in both study groups. Finally, because vitamin D levels were only available at the year 1 follow-up visit in a subset of participants, and not concurrently with the rest of the mineral metabolism measurements, residual confounding by incomplete adjustment for vitamin D may be a possibility.

We conclude that disordered mineral metabolism is more severe and develops earlier in the course of CKD in patients with diabetes compared with those without diabetes. Future studies should explore mechanisms for these differences and whether they contribute to the worse clinical outcomes experienced by CKD patients with diabetes. Although long-term trials targeting mineral metabolism in diabetic patients with CKD are needed, in the interim our data support closer surveillance of mineral metabolism markers in this population.

Acknowledgments—This CRIC ancillary study was supported by National Institutes of Health Grants R01-DK-081374 (to M.W.), K23-DK-087858 (to T.I.), and R01-DK-077128 (to M.B.L.). The CRIC study is supported by cooperative agreement project grants 5U01-DK-060990, 5U01-DK-060984, 5U01-DK-06102, 5U01-DK-061021, 5U01-DK-061028, 5U01-DK-60980, 5U01-DK-060963, and 5U01-DK-060902 from the National Institute of Diabetes and Digestive and Kidney Diseases and by grants UL1-RR-024134, UL1-RR-025005, M01-RR-16500, UL1-RR-024989, M01-RR-000042, UL1-RR-024986, UL1-RR-029879, RR-05096, and UL1-RR-024131 from the National Institutes of Health.

No potential conflicts of interest relevant to this article were reported.

P.W. and T.I. wrote the manuscript. H.X. and T.I. researched data and reviewed and edited the manuscript. J.S., C.A.M.A., K.B., C.B., J.C., H.F., O.M.G., J.L., M.B.L., L.N., S.E.R., A.H.A., and R.R.T. contributed to the discussion and reviewed and edited the manuscript. M.W. was actively involved in the analyses and interpretation of data and reviewed and critically revised the manuscript. T.I. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Centers for Disease Control and Prevention. National Diabetes Fact Sheet: National Estimates and General Information on Diabetes and Prediabetes in the United States. Atlanta, GA, U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2011
2. U.S. Renal Data System. *USRDS 2010 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States*. Bethesda, MD, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2010
3. de Boer IH, Rue TC, Hall YN, Heagerty PJ, Weiss NS, Himmelfarb J. Temporal trends in the prevalence of diabetic kidney disease in the United States. JAMA 2011;305:2532–2539
4. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). Kidney Int Suppl 2009;113:S1–S130
5. Kestenbaum B, Sampson JN, Rudser KD, et al. Serum phosphate levels and mortality risk among people with chronic kidney disease. J Am Soc Nephrol 2005;16:520–528
6. Schwarz S, Trivedi BK, Kalantar-Zadeh K, Kovesdy CP. Association of disorders in mineral metabolism with progression of chronic kidney disease. Clin J Am Soc Nephrol 2006;1:825–831
7. Isakova T, Xie H, Yang W, et al.; Chronic Renal Insufficiency Cohort (CRIC) Study Group. Fibroblast growth factor 23 and risks of mortality and end-stage renal disease in patients with chronic kidney disease. JAMA 2011;305:2432–2439
8. Bellasi A, Mandreoli M, Baldrati L, et al. Chronic kidney disease progression and outcome according to serum phosphorus in mild-to-moderate kidney dysfunction. Clin J Am Soc Nephrol 2011;6:883–891
9. Andress DL, Hercz G, Kopp JB, et al. Bone histomorphometry of renal osteodystrophy in diabetic patients. J Bone Miner Res 1987;2:525–531
10. Vincenti F, Arnaud SB, Recker R, et al. Parathyroid and bone response of the diabetic patient to uremia. Kidney Int 1984;25:677–682
11. Feldman HI, Appel LJ, Chertow GM, et al.; Chronic Renal Insufficiency Cohort (CRIC) Study Investigators. The Chronic Renal Insufficiency Cohort (CRIC) Study: design and methods. J Am Soc Nephrol 2003;14(Suppl. 2):S148–S153
12. Fischer MJ, Go AS, Lora CM, et al.; CRIC and H-CRIC Study Groups. CKD in Hispanics: baseline characteristics from the CRIC (Chronic Renal Insufficiency Cohort) and Hispanic-CRIC studies. Am J Kidney Dis 2011;58:214–227
13. Subar AF, Thompson FE, Kipnis V, et al. Comparative validation of the Block, Willett, and National Cancer Institute food frequency questionnaires : the Eating at America's Table Study. Am J Epidemiol 2001;154:1089–1099
14. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D; Modification of Diet in Renal Disease Study Group. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Ann Intern Med 1999;130:461–470
15. Isakova T, Wahl P, Vargas GS, et al. Fibroblast growth factor 23 is elevated before parathyroid hormone and phosphate in chronic kidney disease. Kidney Int 2011;79:1370–1378
16. Levin A, Bakris GL, Molitch M, et al. Prevalence of abnormal serum vitamin D, PTH, calcium, and phosphorus in patients with chronic kidney disease: results of the study to evaluate early kidney disease. Kidney Int 2007;71:31–38
17. Thrailkill KM, Jo CH, Cockrell GE, Moreau CS, Fowlkes JL. Enhanced excretion of vitamin D binding protein in type 1 diabetes: a role in vitamin D deficiency? J Clin Endocrinol Metab 2011;96:142–149
18. Martínez I, Saracho R, Moina I, Montenegro J, Llach F. Is there a lesser hyperparathyroidism in diabetic patients with chronic renal failure? Nephrol Dial Transplant 1998;13(Suppl. 3):9–11
19. Aubia J, Bosch J, Lloveras J, Chine M, Hojman L, Masramon J. Relative hyperphosphaturia in diabetic chronic renal failure: a protective factor of hyperparathyroidism. Miner Electrolyte Metab 1987;13:311–315
20. Manghat P, Fraser WD, Wierzbicki AS, Fogelman I, Goldsmith DJ, Hampson G. Fibroblast growth factor-23 is associated with C-reactive protein, serum phosphate and bone mineral density in chronic kidney disease. Osteoporos Int 2010;21:1853–1861
21. Tanaka H, Hamano T, Fujii N, et al. The impact of diabetes mellitus on vitamin D metabolism in predialysis patients. Bone 2009;45:949–955
22. Schwartz AV, Sellmeyer DE, Ensrud KE, et al.; Study of Osteoporotic Features Research Group. Older women with diabetes have an increased risk of fracture: a prospective study. J Clin Endocrinol Metab 2001;86:32–38
23. Nicodemus KK, Folsom AR; Iowa Women's Health Study. Type 1 and type 2 diabetes and incident hip fractures in postmenopausal women. Diabetes Care 2001;24:1192–1197

24. Forsén L, Meyer HE, Midthjell K, Edna TH. Diabetes mellitus and the incidence of hip fracture: results from the Nord-Trøndelag Health Survey. Diabetologia 1999;42:920–925
25. Ottenbacher KJ, Ostir GV, Peek MK, Goodwin JS, Markides KS. Diabetes mellitus as a risk factor for hip fracture in Mexican American older adults. J Gerontol A Biol Sci Med Sci 2002;57: M648–M653
26. Keegan TH, Kelsey JL, Sidney S, Quesenberry CP Jr. Foot problems as risk factors of fractures. Am J Epidemiol 2002;155: 926–931
27. McNair P, Christensen MS, Madsbad S, Christiansen C, Transbøl I. Hypoparathyroidism in diabetes mellitus. Acta Endocrinol (Copenh) 1981;96:81–86
28. McNair P, Madsbad S, Christensen MS, et al. Bone mineral loss in insulin-treated diabetes mellitus: studies on pathogenesis. Acta Endocrinol (Copenh) 1979;90: 463–472
29. Ureña-Torres P, Metzger M, Haymann JP, et al.; NephroTest Study Group. Association of kidney function, vitamin D deficiency, and circulating markers of mineral and bone disorders in CKD. Am J Kidney Dis 2011;58:544–553
30. Wolf M. Forging forward with 10 burning questions on FGF23 in kidney disease. J Am Soc Nephrol 2010;21:1427–1435
31. Kojima F, Uchida K, Ogawa T, Tanaka Y, Nitta K. Plasma levels of fibroblast growth factor-23 and mineral metabolism in diabetic and non-diabetic patients on chronic hemodialysis. Int Urol Nephrol 2008;40: 1067–1074
32. Samadfam R, Richard C, Nguyen-Yamamoto L, Bolivar I, Goltzman D. Bone formation regulates circulating concentrations of fibroblast growth factor 23. Endocrinology 2009;150:4835–4845
33. Vaidya VS, Niewczas MA, Ficociello LH, et al. Regression of microalbuminuria in type 1 diabetes is associated with lower levels of urinary tubular injury biomarkers, kidney injury molecule-1, and N-acetyl-β-D-glucosaminidase. Kidney Int 2011;79: 464–470
34. Singh DK, Winocour P, Summerhayes B, Viljoen A, Sivakumar G, Farrington K. Are low erythropoietin and 1,25-dihydroxyvitamin D levels indicative of tubulo-interstitial dysfunction in diabetes without persistent microalbuminuria? Diabetes Res Clin Pract 2009;85:258–264
35. Pavik I, Jaeger P, Kistler AD, et al. Patients with autosomal dominant polycystic kidney disease have elevated fibroblast growth factor 23 levels and a renal leak of phosphate. Kidney Int 2011;79:234–240
36. Hasegawa H, Nagano N, Urakawa I, et al. Direct evidence for a causative role of FGF23 in the abnormal renal phosphate handling and vitamin D metabolism in rats with early-stage chronic kidney disease. Kidney Int 2010;78:975–980
37. Andress DL. Adynamic bone in patients with chronic kidney disease. Kidney Int 2008;73:1345–1354
38. Markowitz J. The relationship of phosphate and carbohydrate metabolism.III. The effect of glucose on the excretion of phosphate in depancreatized dogs. Am J Physiol 1926;76:525
39. Ng JM, Cooke M, Bhandari S, Atkin SL, Kilpatrick ES. The effect of iron and erythropoietin treatment on the A1C of patients with diabetes and chronic kidney disease. Diabetes Care 2010;33:2310–2313
40. Rognant N, Lemoine S, Laville M, Hadj-Aïssa A, Dubourg L. Performance of the chronic kidney disease epidemiology collaboration equation to estimate glomerular filtration rate in diabetic patients. Diabetes Care 2011;34:1320–1322