Trends in Mineral Metabolism: Kidney Early Evaluation Program (KEEP) and the National Health and Nutrition Examination Survey (NHANES) 1999-2004

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Background: Chronic kidney disease (CKD) is associated with mineral metabolism dysregulation, cardiovascular disease, and premature mortality. No study specifically examined mineral metabolism trends in a generalizable sample of patients at increased CKD risk.

Methods: This cross-sectional analysis from November 1, 2005, to December 31, 2006, of calcium, phosphorus, and parathyroid hormone (PTH) includes 2,646 individuals with estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m^2 in the National Kidney Foundation Kidney Early Evaluation Program (KEEP), a community-based health-screening program targeting individuals 18 years and older with diabetes, hypertension, or family history of kidney disease, diabetes, or hypertension. A parallel analysis of National Health and Nutrition Examination Survey (NHANES) 1999-2004 data was performed.

Results: In KEEP, as eGFR decreased from 55 to less than 60 mL/min/1.73 m^2 to less than 30 mL/min/1.73 m^2, calcium level decreased (9.55 $\pm$ 0.47 to 9.34 $\pm$ 0.62 mg/dL; $P < 0.001$), phosphorus level increased (3.70 $\pm$ 0.59 to 4.15 $\pm$ 0.80 mg/dL; $P < 0.001$), and PTH level increased (66.3 $\pm$ 36.3 to 164 $\pm$ 109 pg/mL; mean, 80.8 $\pm$ 57.0 pg/mL; $P < 0.001$). NHANES 1999-2004 showed similar trends, with PTH values not as high. Individuals within opinion-based Kidney Disease Outcomes Quality Initiatives targets from the highest to the lowest eGFR group were as follows: calcium, 93.0% to 92.3% (KEEP) and 97.4% to 89.6% (NHANES); phosphorus, 90.4% to 90.3% (KEEP) and 91.6% to 87.1% (NHANES); and PTH, 46.1% to 31.2% (KEEP) and 56.4% to 36.1% (NHANES).

Conclusions: In a community-based CKD screening population, increased PTH level occurs early in patients with stage 3, typically with normal calcium and phosphorus levels. These findings support the importance of including PTH with calcium and phosphorus monitoring for individuals with eGFR less than 60 mL/min/1.73 m^2.
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INDEX WORDS: Calcium; chronic kidney disease; Kidney Early Evaluation Program (KEEP); mineral metabolism; National Health and Nutrition Examination Survey (NHANES); parathyroid hormone (PTH); phosphorus.

Chronic kidney disease (CKD) is associated with several complications, including mineral metabolism dysregulation, increased cardiovascular disease (CVD) morbidity, and premature mortality. Mineral metabolism abnormalities in dialysis patients present with persistently increased parathyroid hormone (PTH) levels, typically accompanied by hyperphosphatemia. More than half the patients with chronic kidney failure or end-stage renal disease treated with hemodialysis or peritoneal dialysis in several large observational studies showed hyperphosphatemia, a finding associated with increased mortality.[1-6] Observational and prospective data also show an

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Table 1. Characteristics of KEEP and NHANES Populations by Estimated Glomerular Filtration Rate

	Estimated Glomerular Filtration Rate (mL/min/1.73 m^2)					
	KEEP			NHANES 1999-2004*		
	55-<60	45-<55	<45	55-<60	45-<55	<45
No. of participants	768	1,082	796	430	571	437
Age (y)						
18-45	25.8	49.5	24.7	50.0	24.0	26.0
46-60	50.3	34.2	15.5	52.1	36.6	11.3
61-75	28.4	40.3	31.3	32.3	39.7	28.1
≥75	13.8	45.9	40.3	24.2	41.4	34.4
Sex						
Men	31.1	40.3	28.6	37.5	36.6	25.9
Women	28.1	41.2	30.7	32.4	40.0	27.6
Race						
White	29.2	41.3	29.5	35.6	39.1	25.3
African American	29.6	39.9	30.5	25.8	35.0	39.2
Other	26.9	40.2	32.9	29.3	37.8	32.9
Body mass index (kg/m^2)						
≥30	29.8	38.5	31.7	35.0	37.7	27.3
<30	28.3	43.0	28.7	35.2	39.5	25.3
Smoking status						
Current smoker	28.2	43.6	28.2	49.4	25.9	24.7
Nonsmoker	28.8	40.8	30.4	32.1	40.6	27.3
Education						
<High school	22.7	39.8	37.5	26.9	42.3	30.8
≥High school	30.5	41.1	28.4	37.5	37.1	25.4
Diabetes†						
Yes	22.7	41.0	36.3	26.8	35.3	38
No	33.9	40.8	25.3	36.1	39.4	24.5
Hypertension‡						
Yes	28.0	41.0	31.0	31.6	39.7	28.7
No	39.7	40.1	20.3	51.0	32.0	17.1
Anemia§						
Yes	15.4	34.6	50.0	17.6	27.2	55.2
No	33.2	42.8	24.0	37.0	40.5	22.6
Cardiovascular disease						
Yes	23.2	38.9	37.9	23.1	35.4	41.5
No	33.0	42.2	24.8	40.0	40.4	19.6
Albumin-creatinine ratio (mg/g)						
<30	32.7	42.6	24.7	40.3	40.7	18.9
30-300	19.8	38.0	42.2	25.6	40.3	34.1
>300	10.0	23.1	66.9	17.2	22.1	60.7

Note: Categorical values are expressed in percent.

Abbreviations: KEEP, Kidney Early Evaluation Program; NHANES, National Health and Nutrition Examination Survey.

*In NHANES, for analyses related to smoking status and self-reported cardiovascular disease, the study population is limited to participants 20 years and older.

†KEEP definition: self-reported or measured (glucose ≥ 126 mg/dL [≥7.0 mmol/L] fasting or ≥ 200 mg/dL [11.1 mmol/L] nonfasting); NHANES definition: self-reported.

‡Self-reported or measured (systolic blood pressure ≥ 130 mm Hg or diastolic blood pressure ≥ 80 mm Hg if patient has diabetes or chronic kidney disease, otherwise systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg).

§As defined by the World Health Organization (hemoglobin < 13 g/dL [<130 g/L] for men and < 12 g/dL [<120 g/L] for women).

association between phosphorus level greater than 3.5 mg/dL and mortality in patients with CKD.[7,8] The direct or indirect mechanism by which greater serum phosphorus values and mortality are linked is not fully understood. Mineral metabolism dysregulation is a novel cardiovascular risk marker in patients with CKD because of associations with arterial stiffness,[9] vascular cal-

Table 2. Mean Parathyroid Hormone, Calcium, and Phosphorus in KEEP and NHANES 1999-2004 by Estimated Glomerular Filtration Rate

	Estimated Glomerular Filtration Rate (mL/min/1.73 m^2)					
	KEEP			NHANES		
	55-<60	45-<55	<45	55-<60	45-<55	<45
No. of participants	768	1,082	796	518	1,438	1,438
Parathyroid hormone*						
95th Percentile	129.0	155.0	268.0	99.0	132.5	236.6
Mean	66.3	73.7	104.5	51.3	59.4	84.4
Median	60.0	64.0	84.0	42.9	50.2	63.7
SD/SE	36.3	45.3	76.9	3.0	3.1	8.2
5th percentile	18.0	19.0	24.0	19.0	23.4	15.5
% Within range†	46.1	40.9	31.2	56.4	55.2	36.1
Calcium						
95th Percentile	10.3	10.4	10.3	10.1	10.3	10.5
Mean	9.6	9.6	9.5	9.5	9.5	9.5
Median	9.5	9.5	9.5	9.5	9.5	9.5
SD/SE	0.5	0.5	0.5	0.03	0.02	0.04
5th Percentile	8.8	8.8	8.6	8.9	8.8	8.5
% Within range‡	93.0	90.9	92.3	97.4	93.4	89.6
Phosphorus						
95th Percentile	4.7	4.8	4.9	4.6	4.5	5.4
Mean	3.7	3.7	3.8	3.7	3.7	3.9
Median	3.7	3.7	3.8	3.6	3.6	3.7
SD/SE	0.6	0.7	0.6	0.04	0.03	0.05
5th Percentile	2.8	2.8	2.8	2.8	2.7	2.9
% Within range§	90.4	91.1	90.3	91.6	92.2	87.1

Note: SD used in KEEP; SE used in NHANES. To convert estimated glomerular filtration rate in mL/min/1.73 m^2 to mL/s/1.73 m^2, multiply by 0.01667.

Abbreviations: KEEP, Kidney Early Evaluation Program; NHANES, National Health and Nutrition Examination Survey.

*Using NHANES 2003-2004 only.

†Parathyroid hormone, 35 to 70 pg/mL for patients with stage 3, 70 to 110 pg/mL for patients with stage 4, and 150 to 300 pg/mL for patients with stage 5 (values in ng/L are equivalent).

‡Calcium, 8.4 to 10.2 mg/dL (2.10 to 2.45 mmol/L) for patients with all stages.

§Phosphorus, 2.7 to 4.6 mg/dL (0.87 to 1.49 mmol/L) for patients with stages 3 and 4, and 3.5 to 5.5 mg/dL (1.13 to 1.78 mmol/L) for patients with stage 5.

cification,[9-11] myocardial infarction,[7] and cardiovascular mortality.[5] Even in individuals free of CKD and CVD in the community, greater serum phosphorus levels are associated with increased CVD risk.[12] However, no study specifically examined mineral metabolism trends in a generalizable sample of patients at increased risk of CKD. This study addresses these issues by using data from the National Kidney Foundation Kidney Early Evaluation Program (KEEP), a free voluntary community-based health screening program to raise kidney disease awareness and detect CKD for early disease intervention for high-risk individuals.

METHODS

This is a cross-sectional analysis of calcium, phosphorus, and PTH for the subset of KEEP participants with CKD stages 3, 4, and 5. KEEP enrolls people 18 years and older with a family history of kidney disease or a personal or family history of diabetes or hypertension.[13] Participants treated with dialysis or transplantation were excluded from these analyses. Parallel analyses using data from a sample population of the National Health and Nutrition Examination Survey (NHANES) 1999-2004 (n = 1,438) were performed. KEEP and the NHANES database are fully described elsewhere in this supplement.[14]

All participants provided informed consent before data collection. The Institutional Review Board at the Minneapolis Medical Research Foundation approved KEEP, including the research protocol, informed consent process, and data management procedures. A screening questionnaire was used to collect data for demographic characteristics, family and medical history, smoking habits, education level, access to physicians, and health insurance status. Detailed information for medication use was not obtained. The diagnostic panel included blood pressure, height and weight to calculate body mass index (BMI), and blood and urine collection. Estimated glomerular filtration rate (eGFR) was calculated

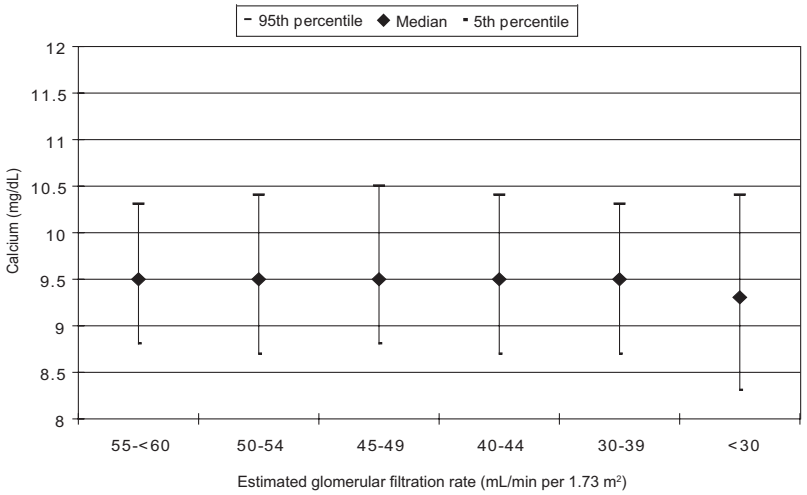

Figure 1. Distribution of calcium levels by estimated glomerular filtration rate (eGFR) in the Kidney Early Evaluation Program. Pearson correlation coefficient for eGFR and calcium, 0.0859; $P < 0.001$ for all. To convert eGFR in mL/min/1.73 m^2 to mL/s/1.73 m^2, multiply by 0.01667; calcium in mg/dL to mmol/L, multiply by 02495.

by using the isotope dilution mass spectrometry–traceable 4-variable Modification of Diet in Renal Disease (MDRD) Study equation ($175 \times$ [serum creatinine $(mg/dL)^{-1.154}$] $\times$ [age $(y)^{-0.203}$]) $\times$ (0.742 for women) $\times$ (1.21 for African Americans), as described elsewhere in this supplement.[15] Glucose and hemoglobin were also assessed.

For participants with eGFR less than 60 mL/min/1.73 m^2 (<1.0 mL/s/1.73 m^2) only, additional reflex testing for calcium, phosphorus, and PTH was done. Calcium and phosphorus levels were determined by using the Architect c8000 (Abbott Laboratories, Abbott Park, IL), with Arsenazo-III (Stanbio Laboratory, Boerne, TX) dye for calcium and ammonium molybdate for phosphorus. The intact PTH assay was performed using Immulite 2000 (Siemens Medical Solutions Diagnostics, Los Angeles, CA), a 2-site chemiluminescent enzyme-labeled immunometric assay. All laboratory tests were performed at Consolidated Laboratory Services, Van Nuys, CA. In NHANES 2003-2004 only, the PTH assay was performed in 518 individuals using the Elecsys 1010 analyzer (Roche Diagnostics, Basel, Switzerland).

Diabetes was defined as self-reported history of diabetes or retinopathy or increased blood glucose, defined as glucose level of 126 mg/dL or greater ($\geq$7.0 mmol/L) if fasting or 200 mg/dL or greater ($\geq$11.1 mmol/L) if nonfasting. Hypertension was defined as self-reported history of high blood pressure or increased blood pressure, defined as systolic blood pressure of 130 mm Hg or greater or diastolic blood pressure of 80 mm Hg or greater for persons with a history of diabetes or CKD, otherwise systolic blood pressure of 140 mm Hg or greater or diastolic blood pressure of 90 mm Hg or greater.[16] CVD was defined as self-reported heart attack, heart bypass surgery, heart angioplasty, stroke, heart failure, abnormal heart rhythm, or peripheral arterial disease (before May 2005). The slightly different definition of history of CVD in NHANES is self-reported history of coronary heart disease, angina/angina pectoris, heart attack, congestive heart failure, or stroke. World Health Organization (WHO) anemia is defined as hemoglobin level less than 13 g/dL ($<$130 g/L) for men and less than 12 g/dL ($<$120 g/L) for women. Normal PTH level (Kidney Disease Outcomes Quality Initiative [KDOQI] targets)[17] is 35 to 70 pg/mL for patients with CKD stage 3, 70 to 110 pg/mL for patients with stage 4, and 150 to 300 pg/mL for patients with stage 5 (values in ng/L are equivalent). Increased PTH level

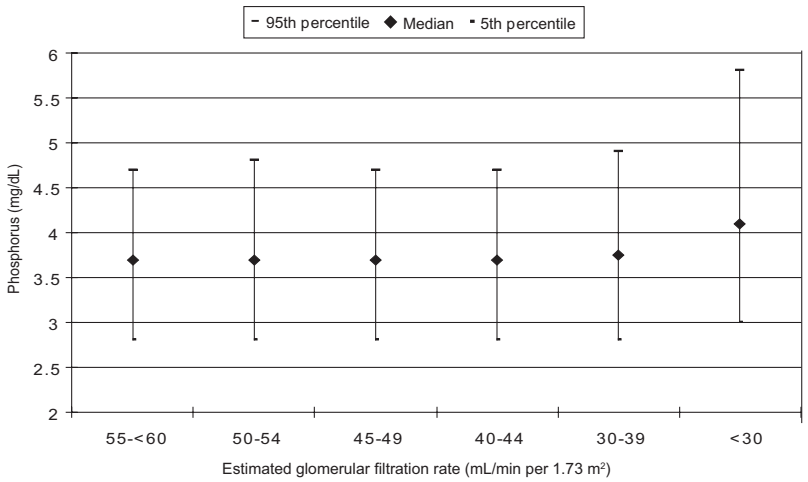

Figure 2. Distribution of phosphorus levels by estimated glomerular filtration rate (eGFR) in the Kidney Early Evaluation Program. Pearson correlation coefficient for eGFR and phosphorus, -0.1399; $P < 0.001$. To convert eGFR in mL/min/1.73 m^2 to mL/s/1.73 m^2, multiply by 0.01667; phosphorus in mg/dL to mmol/L, multiply by 0.3229.

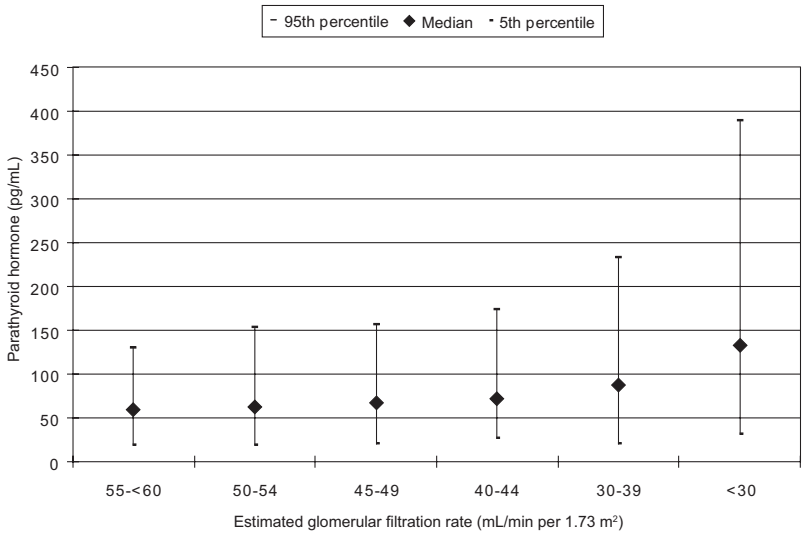

Figure 3. Distribution of parathyroid hormone levels by estimated glomerular filtration rate (eGFR) in the Kidney Early Evaluation Program. Pearson correlation coefficient for eGFR and intact parathyroid hormone, −0.3773; $P < 0.001$. To convert eGFR in mL/min/1.73 m^2 to mL/s/1.73 m^2, multiply by 0.01667; parathyroid hormone in pg/mL and ng/L are equivalent.

was defined as greater than 70 pg/mL for patients with CKD stage 3, greater than 110 pg/mL for patients with stage 4, and greater than 300 pg/mL for patients with stage 5. Normal phosphorus levels are 2.7 to 4.6 mg/dL (0.87 to 1.49 mmol/L) for patients with CKD stages 3 and 4 and 3.5 to 5.5 mg/dL (1.13 to 1.78 mmol/L) for patients with CKD stage 5. Normal calcium level is 8.4 to 10.2 mg/dL (2.10 to 2.45 mmol/L). Obesity was defined as BMI of 30 kg/m^2 or greater.

This analysis includes 3,022 of 21,107 participants (14.3%) with an eGFR less than 60 mL/min/1.73 m^2 (<1.0 mL/s/1.73 m^2). After excluding 376 participants for whom calcium, phosphorus, and PTH testing results were unavailable for the study period of November 1, 2005, to December 31, 2006, a total of 2,646 participants remained. Data are presented as mean ± SD (SE for NHANES data) unless specified otherwise. Kruskal-Wallis test was used to test mean differences among eGFR groups. Multiple linear regressions were used to estimate the effect of each predictor on mean values for PTH, phosphorus, and calcium with and without control for eGFR. Predictors were age, sex, race, obesity, smoking status, education level, diabetes, hypertension, anemia, CVD, urinary albumin-creatinine ratio, normal phosphorus level, and normal calcium level. Logistic regression was used for odds ratios of increased PTH, increased phosphorus, and increased calcium levels. Predictors were the same as in multiple linear regressions, except for the interaction term between diabetes and obesity for PTH level only. Pearson correlation coefficients were calculated for eGFR with PTH, calcium, and phosphorus levels, respectively.

RESULTS

Demographically, the overall KEEP population compared with NHANES 1999-2004 included older participants, more women (68.5% versus 54.7%), fewer whites (46.7% versus 72.3%), more African Americans (34.1% versus 12.1%), and similar health insurance coverage (81.8% versus 84%).[14] Characteristics of the KEEP and NHANES population subsets with eGFR less than 60 mL/min/1.73 m^2 (<1.0 mL/s/1.73 m^2) show remarkable similarities (Table 1). The distribution of mean, median, and upper and lower 5% results for calcium, phosphorus, and PTH measures by eGFR categories in KEEP and NHANES 1999-2004 population are listed in Table 2. PTH data are available for only NHANES 2003-2004. CKD stage 3 included almost 95% of KEEP subjects in this study, with the remainder in stages 4 and 5. In both populations, most calcium and phosphorus results were within normal or opinion-based targets[17] from the highest eGFR group (55 to <60 mL/min/1.73 m^2 [0.92 to <1.00 mL/s/1.73 m^2]) to the lowest group (eGFR < 45 mL/min/1.73 m^2 [<0.75 mL/s/1.73 m^2]); calcium, 93.0% to 92.3% in KEEP and 97.4% to 89.6% in NHANES; and phosphorus, 90.4% to 90.3% in KEEP and 91.6% to 87.1% in NHANES. Conversely, PTH values within the KDOQI target range using the same eGFR groups decreased from 46.1% to 31.2% in KEEP and 56.4% to 36.1% in NHANES. As eGFR decreased in KEEP from 55 to less than 60 mL/min/1.73 m^2 [0.92 to <1.00 mL/s/1.73 m^2] to less than 30 mL/min/1.73 m^2, mean calcium level decreased from 9.55 ± 0.47 to 9.34 ± 0.62 mg/dL (2.38 ± 0.12 to 2.33 ± 0.15 mmol/L; $P <$ 0.001), mean phosphorous level increased from 3.70 ± 0.59 to 4.15 ± 0.80 mg/dL (1.19 ± 0.19 to 1.34 ± 0.26 mmol/L; $P < 0.001$), and mean

Table 3. Multiple Linear Regression of Mean Parathyroid Hormone as a Continuous Variable Unadjusted and Adjusted for Estimated Glomerular Filtration Rate

	Model			
	Unadjusted		Adjusted for Estimated Glomerular Filtration Rate	
Variable	Estimate	Pr > t	Estimate	Pr > t
Intercept	84.05	<0.0001	72.42	<0.0001
Age (y)				
18-45	−15.64	0.0114	−13.05	0.0262
46-60	−14.89	<0.0001	−10.28	0.0013
61-75	−6.74	0.0136	−4.69	0.0709
≥75 (reference)	0.00		0.00	
Sex				
Women (reference)	0.00		0.00	
Men	1.34	0.5816	2.97	0.1989
Race				
White (reference)	0.00		0.00	
African American	19.94	<0.0001	22.25	<0.0001
Other	2.01	0.5913	3.59	0.3131
Body mass index (kg/m^2)				
<30 (reference)	0.00		0.00	
≥30	11.21	<0.0001	11.10	<0.0001
Smoking status				
Nonsmoker (reference)	0.00		0.00	
Current smoker	1.24	0.7844	2.32	0.5914
Education				
<High school (reference)	0.00		0.00	
≥High school	−4.06	0.1704	−3.59	0.201
Diabetes*	−8.62	0.0003	−8.29	0.0002
Hypertension†	−4.88	0.2171	−5.74	0.1259
Anemia‡	17.62	<0.0001	7.30	0.0068
Cardiovascular disease	10.15	<0.0001	7.77	0.0004
Albumin-creatinine ratio (mg/g)				
<30 (reference)	0.00		0.00	
30-300	17.25	<0.0001	9.58	0.0006
>300	46.95	<0.0001	21.85	<0.0001
Normal phosphorus§	−4.84	0.1984	−1.35	0.7056
Normal calcium‖	−4.19	0.3039	−1.93	0.618
	$R^2 = 0.1171$		$R^2 = 0.2065$	

*Self-reported or measured (glucose ≥ 126 mg/dL [≥7.0 mmol/L] fasting or ≥ 200 mg/dL [≥11.1 mmol/L] nonfasting).

†Self-reported or measured (systolic blood pressure ≥ 130 mm Hg or diastolic blood pressure ≥ 80 mm Hg if diabetes or chronic kidney disease, otherwise systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg).

‡As defined by the World Health Organization (hemoglobin < 13 g/dL [<130 g/L] for men and < 12 g/dL [<120 g/L] for women).

§Phosphorus, 2.7 to 4.6 mg/dL (0.87 to 1.49 mmol/L) for patients with stages 3 and 4, and 3.5 to 5.5 mg/dL (1.13 to 1.78 mmol/L) for patients with stage 5.

‖Calcium, 8.4 to 10.2 mg/dL (2.10 to 2.45 mmol/L).

PTH level increased from 66.3 ± 36.3 to 163.6 ± 109.8 pg/mL (values expressed in ng/L are equivalent; $P < 0.001$; Figs 1 to 3). Mineral metabolism parameters in KEEP and NHANES show a gradual increase in phosphorus and slow decrease in calcium values associated with lower levels of kidney function, whereas PTH level was associated with a steady increase. In the KEEP analysis, Pearson correlation coefficients (shown in legends to Figs 1 to 3) confirmed that lower eGFR was associated with increased phosphorus and PTH and lower calcium levels.

Multiple linear regression of mean PTH as a continuous variable in KEEP by using 2 models (1 adjusted for eGFR) showed significantly greater PTH levels by the following characteris-

tics: African American, older, obese, diabetes absent, WHO anemia, CVD, and albuminuria (Table 3). Adjustment for level of kidney function decreased the coefficients for age, anemia, CVD, and albuminuria, but had little impact on obesity, African American race, and nondiabetic status. Increased PTH level was not significantly associated with sex, education level, tobacco use, or hypertension. Odds ratios for increased PTH levels were significantly increased for older participants, men, African Americans, obese participants, participants with lower eGFR, and participants with CVD (Table 4). The association of obesity with greater PTH level was dependent on diabetes. For patients without diabetes, obesity was significantly associated with increased PTH level; for patients with diabetes, the association of obesity and increased PTH level was not significant. The relationship of obesity without diabetes and increased PTH level was independent of eGFR and race (data not shown).

Multiple linear regression of mean phosphorus level (Table 5) as a continuous variable in KEEP by using 2 models (1 adjusted for eGFR) showed weaker associations than PTH level (Table 3). Odds ratios for increased phosphorus levels were significantly greater for participants younger than 60 years, women, participants with high school education or less, and participants with lower eGFR (Table 6). Similarly, multiple linear regression of mean calcium level (Table 7) showed weaker associations than those for PTH level. Odds ratios for increased calcium level were significantly increased for women, nonobese participants, diabetic participants, participants with hypertension, and participants without anemia (Table 8).

DISCUSSION

These data confirm that as eGFR decreases, PTH level increases in a unique, large, community-based CKD screening program. Phosphorus level increase and calcium level decrease with kidney function loss is more gradual. The PTH level increase may be the result of end-organ resistance affecting normal feedback inhibition, minute increases in serum phosphorus levels within the normal range, or low vitamin D levels (not measured in this study).[18-20] These trends in calcium, phosphorus, and PTH by eGFR level are consistent with physiological expectations and previous studies.[18-20] Small phosphorus level

Table 4. Odds Ratios of Increased Parathyroid Hormone

Variable	Odds Ratio (95% confidence interval)	*P*
Age (y)		
18-45 (reference)	0.52 (0.32-0.85)	0.009
46-60	0.63 (0.48-0.81)	<0.001
61-75	0.78 (0.63-0.96)	0.02
≥75	1	
Sex		
Women (reference)	1	
Men	1.33 (1.10-1.59)	0.003
Race		
White (reference)	1	
African American	2.33 (1.85-2.93)	<0.001
Other	1.18 (0.89-1.57)	0.3
Smoking status		
Nonsmoker (reference)	1	
Current smoker	1.06 (0.75-1.51)	0.7
Education		
<High school (reference)	1	
≥High school	0.88 (0.71-1.11)	0.3
Hypertension*	1.11 (0.82-1.52)	0.5
Anemia†	1.11 (0.89-1.37)	0.4
Cardiovascular disease	1.33 (1.11-1.58)	0.002
Estimated glomerular filtration rate (mL/min/1.73 m^2)		
50-59 (reference)	1	
40-49	1.28 (1.05-1.56)	0.01
30-39	2.36 (1.79-3.11)	<0.001
<30	1.83 (1.22-2.73)	0.003
Normal phosphorus‡	1.19 (0.89-1.60)	0.3
Normal calcium§	1.34 (0.98-1.85)	0.07
Diabetes-BMI (kg/m^2) interaction		
No diabetes, BMI < 30 (reference)	1	
Diabetes, BMI < 30	0.95 (0.74-1.21)	0.7
No diabetes, BMI ≥ 30	1.75 (1.37-2.23)	<0.001
Diabetes, BMI ≥ 30	0.96 (0.76-1.21)	0.7

Note: n = 2,362 after excluding patients with missing predictor values. Increased parathyroid hormone level defined as greater than 70 pg/mL for patients with chronic kidney disease stage 3, greater than 110 pg/mL for patients with stage 4, and greater than 300 pg/mL for patients with stage 5 (values in ng/L are equivalent). To convert estimated glomerular filtration rate in mL/min to mL/s, multiply by 0.01667.

Abbreviation: BMI, body mass index.

*Self-reported or measured (systolic blood pressure ≥ 130 mm Hg or diastolic blood pressure ≥ 80 mm Hg if patient has diabetes or chronic kidney disease, otherwise systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg).

†As defined by the World Health Organization (hemoglobin < 13 g/dL [<130 g/L] for men and < 12 g/dL [<120 g/L] for women).

‡Phosphorus, 2.7 to 4.6 mg/dL (0.87 to 1.49 mmol/L) for patients with stages 3 and 4, and 3.5 to 5.5 mg/dL (1.13 to 1.78 mmol/L) for patients with stage 5.

§Calcium, 8.4 to 10.2 mg/dL (2.10 to 2.45 mmol/L) for patients with all stages.

Table 5. Multiple Linear Regression of Mean Phosphorus as a Continuous Variable Unadjusted and Adjusted for Estimated Glomerular Filtration Rate

	Model			
	Unadjusted		Adjusted for Estimated Glomerular Filtration Rate	
Variable	Estimate	Pr > t	Estimate	Pr > t
Intercept	4.01	<0.0001	3.97	<0.0001
Age (y)				
18-45	0.17	0.0272	0.18	0.022
46-60	0.12	0.0024	0.14	0.0009
61-75	0.01	0.6691	0.02	0.5342
≥75 (reference)	0		0	
Sex				
Women (reference)	0		0	
Men	−0.29	<0.0001	−0.28	<0.0001
Race				
White (reference)	0		0	
African American	0.03	0.3672	0.04	0.2317
Other	0.05	0.304	0.05	0.2385
Body mass index (kg/m^2)				
<30 (reference)	0		0	
≥30	−0.06	0.0339	−0.06	0.0368
Smoking status				
Nonsmoker (reference)	0		0	
Current smoker	0.13	0.0202	0.14	0.0152
Education				
<High school (reference)	0		0	
≥High school	−0.05	0.1655	−0.05	0.1737
Diabetes*	−0.07	0.0248	−0.06	0.0322
Hypertension†	0.04	0.4725	0.03	0.502
Anemia‡	0.1	0.003	0.05	0.1185
Cardiovascular disease	0.05	0.0783	0.04	0.1466
Albumin-creatinine ratio (mg/g)				
<30 (reference)	0		0	
30-300	0.01	0.7056	−0.02	0.5699
>300	0.21	0.0017	0.08	0.2302
Normal parathyroid hormone§	0.04	0.1321	0.05	0.0549
Normal calcium‖	−0.26	<0.0001	−0.24	<0.0001
	R^2 = 0.0698		R^2 = 0.0847	

*Self-reported or measured (glucose ≥ 126 mg/dL [≥7.0 mmol/L] fasting or ≥ 200 mg/dL [≥11.1 mmol/L] nonfasting).

†Self-reported or measured (systolic blood pressure ≥ 130 mm Hg or diastolic blood pressure ≥ 80 mm Hg if patient has diabetes or chronic kidney disease, otherwise systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg).

‡As defined by the World Health Organization (hemoglobin < 13 g/dL [<130 g/L] for men and < 12 g/dL [<120 g/L] for women).

§Parathyroid hormone, 35 to 70 pg/mL for patients with stage 3, 70 to 110 pg/mL for patients with stage 4, and 150 to 300 pg/mL for patients with stage 5 (values in ng/L are equivalent).

‖Calcium, 8.4 to 10.2 mg/dL (2.10 to 2.45 mmol/L).

increases from baseline ranging from 0.1 to 0.6 mg/dL (0.16 to 0.32 mmol/L) across kidney function levels independent of diet were found in more than 17,000 individuals using NHANES III (1988-1994) data.[21] This study did not evaluate PTH and used a generally less accurate Cockcroft-Gault creatinine clearance to assess kidney function. Cross-sectional data from a study of more than 1,800 patients, predominantly in primary-care clinics, showed that PTH level increases early in the course of CKD, accompanied by gradual alterations in calcium and phosphorus levels, with the important additional information that low 1,25-dihydroxyvitamin D_3 (calcitriol)

Table 6. Odds Ratios of Increased Phosphorus

Variable	Odds Ratio (95% confidence interval)	*P*
Age (y)		
18-45	4.80 (2.28-10.10)	<0.001
46-60	2.56 (1.49-4.25)	<0.001
61-75	1.32 (0.82-2.12)	0.3
≥75 (reference)	1	
Sex		
Women (reference)	1	
Men	0.58 (0.38-0.88)	0.01
Race		
White (reference)	1	
African American	1.08 (0.69-1.69)	0.7
Other	1.22 (0.72-2.08)	0.5
Body mass index (kg/m^2)		
<30 (reference)	1	
≥30	1.07 (0.75-1.54)	0.7
Smoking status		
Nonsmoker (reference)	1	
Current smoker	1.24 (0.68-2.26)	0.5
Education		
<High school (reference)	1	
≥High school	0.649 (0.43-0.99)	0.05
Diabetes*	0.72 (0.50-1.04)	0.08
Hypertension†	0.85 (0.48-1.50)	0.6
Anemia‡	1.01 (0.65-1.56)	0.9
Cardiovascular disease	1.32 (0.92-1.88)	0.1
Estimated glomerular filtration rate (mL/min/1.73 m^2)		
50-59 (reference)	1	
40-49	1.07 (0.69-1.64)	0.8
30-39	1.84 (1.08-3.13)	0.02
<30	4.62 (2.55-8.35)	<0.001
Normal parathyroid hormone§	1.52 (1.07-2.15)	0.02
Normal calcium‖	0.29 (0.18-0.45)	<0.001

Note: n = 2,362 after excluding patients with missing predictor values. Increased phosphorus level defined as greater than 4.6 mg/dL for patients with chronic kidney disease stage 3 and 4 and greater than 5.5 mg/dL for patients with stage 5. To convert estimated glomerular filtration rate in mL/min/1.73 m^2 to mL/s/1.73 m^2, multiply by 0.01667.

*Self-reported or measured (glucose ≥ 126 mg/dL [≥7.0 mmol/L] fasting or ≥ 200 mg/dL [≥11.1 mmol/L] nonfasting).

†Self-reported or measured (systolic blood pressure ≥ 130 mm Hg or diastolic blood pressure ≥ 80 mm Hg if patient has diabetes or chronic kidney disease, otherwise systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg).

‡As defined by the World Health Organization (hemoglobin < 13 g/dL [<130 g/L] for men and < 12 g/dL [<120 g/L] for women).

§Parathyroid hormone, 35 to 70 pg/mL for patients with stage 3, 70 to 110 pg/mL for patients with stage 4, and 150 to 300 pg/mL for patients with stage 5 (values in ng/L are equivalent).

‖Calcium, 8.4 to 10.2 mg/dL (2.10 to 2.45 mmol/L).

precedes PTH level increase and 25 hydroxyvitamin D (calcidiol) is consistently less than recommended values across all levels of kidney function. Additional strengths of this study include detailed medication assessment with exclusion of those treated with prescription-based vitamin D therapies.[19] Its limitations include lack of serum creatinine calibration to the reference standard and an elderly population with a mean age older than 70 years. Data from 2 large outpatient nephrology clinics in Spain also showed similar trends in mineral metabolism parameters by eGFR.[20]

The early increase in PTH level as eGFR decreases is significant enough to support PTH monitoring in patients with CKD. In this analysis of KEEP data, older age, African American race, obesity, nondiabetic status, anemia, CVD, and albuminuria with albumin-creatinine ratio of 30 mg/g or greater were associated with greater PTH levels, suggesting the need for more aggressive monitoring for these subgroups. Speculation is that low vitamin D levels contribute to these associations, as shown in other studies of patients with CKD.[19,20,22] In our study, adjustment for eGFR had little impact on the association of obesity, African American race, and nondiabetic status with increased PTH levels, whereas relationships of age, anemia, CVD, and albuminuria with greater PTH levels remained significant. These findings support the role of an independent variable, such as vitamin D levels, in those subgroups. Although the association of obesity with increased PTH level was independent of African American race and eGFR, it was dependent on the absence of diabetes. The relationship of obesity and PTH level in patients with CKD was also shown in a recent US Veteran's Administration study of adult men, which showed that higher BMI was associated with greater PTH level independently of age, race, diabetes status, serum calcium level, or serum phosphorus level.[23]

Although the increase in phosphorus level is relatively small in both KEEP and NHANES, 2 other studies showed that similar increases of 0.5 to 1.0 mg/dL (0.16 to 0.32 mmol/L) were associated with increased mortality.[7,8] In the prospective African American Study of Hypertension and Kidney Disease and a Veteran's Administration retrospective study, minute increases in phosphorus levels also were associated with CKD progression, both loss of kidney function deter-

Table 7. Multiple Linear Regression of Mean Calcium as a Continuous Variable Unadjusted and Adjusted for Estimated Glomerular Filtration Rate

	Model			
	Unadjusted		Adjusted for Estimated Glomerular Filtration Rate	
Variable	Estimate	Pr > t	Estimate	Pr > t
Intercept	9.49	<0.0001	9.49	<0.0001
Age (y)				
18-45	0.04	0.4715	0.04	0.4639
46-60	0.1	0.0009	0.1	0.0009
61-75	0.08	0.0017	0.08	0.0017
≥75 (reference)	0		0	
Sex				
Women (reference)	0		0	
Men	−0.14	<0.0001	−0.14	<0.0001
Race				
White (reference)	0		0	
African American	0.11	<0.0001	0.11	<0.0001
Other	0.04	0.2763	0.04	0.2962
Body mass index (kg/m^2)				
<30 (reference)	0		0	
≥30	−0.08	0.0004	−0.08	0.0004
Smoking status				
Nonsmoker (reference)	0		0	
Current smoker	0.04	0.3365	0.04	0.3635
Education				
<High school (reference)	0		0	
≥High school	−0.02	0.4365	−0.02	0.4399
Diabetes*	0.05	0.029	0.05	0.0359
Hypertension†	0.16	<0.0001	0.16	<0.0001
Anemia‡	−0.17	<0.0001	−0.17	<0.0001
Cardiovascular disease	−0.02	0.3671	−0.02	0.3854
Albumin-creatinine ratio (mg/g)				
<30 (reference)	0		0	
30-300	−0.07	0.014	−0.06	0.0225
>300	−0.16	0.0012	−0.14	0.0058
Normal parathyroid hormone§	0.05	0.0145	0.05	0.0176
Normal phosphorus‖	−0.08	0.016	−0.09	0.0124
	$R^2 = 0.0739$		$R^2 = 0.0747$	

*Self-reported or measured (glucose ≥ 126 mg/dL [≥7.0 mmol/L] fasting or ≥ 200 mg/dL [≥11.1 mmol/L] nonfasting).

†Self-reported or measured (systolic blood pressure ≥ 130 mm Hg or diastolic blood pressure ≥ 80 mm Hg if patient has diabetes or chronic kidney disease, otherwise systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg).

‡As defined by the World Health Organization (hemoglobin < 13 g/dL [<130 g/L] for men and < 12 g/dL [<120 g/L] for women).

§Parathyroid hormone, 35 to 70 pg/mL for patients with stage 3, 70 to 110 pg/mL for patients with stage 4, and 150 to 300 pg/mL for patients with stage 5 (values in ng/L are equivalent).

‖Phosphorus, 2.7 to 4.6 mg/dL (0.87 to 1.49 mmol/L) for patients with stages 3 and 4 and 3.5 to 5.5 mg/dL (1.13 to 1.78 mmol/L) for patients with stage 5.

mined by doubling of serum creatinine and incidence of end-stage renal disease.[8,24] These data suggest that small increases in phosphorus levels within normal or target ranges are clinically significant. Physicians may not recognize such subtle changes in phosphorus levels for individual patients. Moreover, mineral metabolism parameters generally are not assessed in patients with CKD, whereas dialysis patients have high rates of evaluation. Annual testing probabilities in 2005 of 29% for calcium and phosphorus and 11% for PTH[25] provide evidence of low rates of

Table 8. Odds Ratios of Increased Calcium

Variable	Odds Ratio (95% confidence interval)	*P*
Age (y)		
18-45	0.38 (0.09-1.64)	0.2
46-60	1.51 (0.93-2.47)	0.1
61-75	1.26 (0.83-1.92)	0.3
≥75 (reference)	1	
Sex		
Women (reference)	1	
Men	0.46 (0.30-0.69)	<0.001
Race		
White (reference)	1	
African American	1.13 (0.73-1.74)	0.6
Other	1.11 (0.65-1.89)	0.7
Body mass index (kg/m^2)		
<30 (reference)	1	
≥30	0.63 (0.44-0.89)	0.01
Smoking status		
Nonsmoker (reference)	1	
Current smoker	1.14 (0.60-2.15)	0.7
Education		
<High school (reference)	1	
≥High school	1.03 (0.67-1.58)	0.9
Diabetes*	1.54 (1.09-2.17)	0.01
Hypertension†	2.36 (1.12-4.99)	0.03
Anemia‡	0.42 (0.25-0.70)	<0.001
Cardiovascular disease	0.93 (0.66-1.31)	0.7
Estimated glomerular filtration rate (mL/min/1.73 m^2)		
50-59 (reference)	1	
40-49	1.13 (0.77-1.65)	0.5
30-39	0.99 (0.57-1.70)	0.9
<30	1.15 (0.52-2.57)	0.7
Normal parathyroid hormone§	0.85 (0.61-1.20)	0.4
Normal phosphorus‖	0.39 (0.25-0.60)	<0.001

Note: n = 2,362 after excluding patients with missing predictor values. Increased calcium level defined as greater than 10.2 mg/dL for patients with all chronic kidney disease stages. To convert estimated glomerular filtration rate in mL/min/1.73 m^2 to mL/s/1.73 m^2, multiply by 0.01667.

*Self-reported or measured (glucose ≥ 126 mg/dL [≥7.0 mmol/L] fasting or ≥ 200 mg/dL [≥11.1 mmol/L] nonfasting).

†Self-reported or measured (systolic blood pressure ≥ 130 mm Hg or diastolic blood pressure ≥ 80 mm Hg if patient has diabetes or chronic kidney disease, otherwise systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg).

‡As defined by the World Health Organization (hemoglobin < 13 g/dL [<130 g/L] for men and < 12 g/dL [<120 g/L] for women).

§Parathyroid hormone, 35 to 70 pg/mL for patients with stage 3, 70 to 110 pg/mL for patients with stage 4, and 150 to 300 pg/mL for patients with stage 5 (values in ng/L are equivalent).

‖Phosphorus, 2.7 to 4.6 mg/dL (0.87 to 1.49 mmol/L) for patients with stages 3 and 4 and 3.5 to 5.5 mg/dL (1.13 to 1.78 mmol/L) for patients with stage 5.

mineral metabolism evaluation in patients with CKD enrolled in Medicare before dialysis therapy. Conversely, abstraction of randomly selected charts for 300 hemodialysis and 180 peritoneal dialysis patients in a 2-month interval in 2006 showed calcium and phosphorus assessments in 90% or more of patients,[26] with no PTH evaluation in the report.

The strengths of this KEEP analysis include a large community-based population and reliable laboratory methods. Previously published studies of mineral metabolism in patients with CKD included patients from dialysis units, nephrology CKD practices, or primary care clinics. This description of trends in mineral metabolism for a community-based population at increased risk of CKD is unique. Serum creatinine was calibrated to the MDRD Study central laboratory to increase the accuracy of eGFR, as described elsewhere in this supplement.[15] Calcium and phosphorus laboratory methods generally are reliable. Although this analysis does not include serum calcium corrected for albumin level, total serum calcium level may be as accurate an assessment of calcium status as corrected calcium formulas.[27] PTH assays have important interassay variability owing to antibody specificity and standardization reasons.[28] The PTH assays in KEEP Immulite 2000 and NHANES Elecsys 1010 behave similarly in published interassay comparison data, including a total of 14 assays.[28] The similar trends in mineral metabolism dysregulation with decreasing eGFR between KEEP and NHANES support the overall generalizability of the KEEP cohort. Greater PTH levels may reflect more African Americans with characteristically greater PTH levels in the KEEP cohort.[22,23]

Study limitations include the absence of outcomes data because incidences of death and end-stage renal disease are too low to be assessed meaningfully within the study period. The KEEP database was started August 1, 2000, but data for mineral metabolism parameters are available only beginning November 1, 2005. The association of small, but significant, increases in phosphorus levels with mortality and CKD progression in other studies raises the potential contribution of progression bias and competing death bias with these cross-sectional results, which cannot be assessed using the currently available data.

A single assessment in this study has limitations for the reproducibility of eGFR to detect

CKD, particularly at or near the diagnostic threshold of 60 mL/min/1.73 m^2 (1.0 mL/s/1.73 m^2), because 2 evaluations 3 or more months apart are required to define the condition. Individuals with eGFR at this level or greater were excluded from the analysis so that isolated albuminuria was not used to define CKD. KEEP has limited medication data, but the prevalence of drug therapy relevant to mineral metabolism in a population with 6.7% awareness of CKD is likely to be low. Last, KEEP includes no assessment of diet or vitamin D levels.

In a community-based CKD screening population, increased PTH levels occur early in patients with CKD stage 3, typically in the presence of normal calcium and phosphorus levels. Early abnormalities in mineral metabolism support early dietary phosphorus restriction to maintain homeostasis[29] and the need for PTH monitoring even in the presence of normal calcium and phosphorus levels.

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