PTH and the Risks for Hip, Vertebral, and Pelvic Fractures Among Patients on Dialysis

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• ***Background:*** **Few investigations have described fracture risk and its relation to disorders in calcium (Ca), phosphorus (P), and parathyroid hormone (PTH) metabolism in the end-stage renal disease population.** ***Methods:*** **Laboratory values for Ca, P, and PTH were obtained from Dialysis Morbidity and Mortality Study (DMMS) Waves 1 to 4. Additional data available from the US Renal Data System were used to determine the incidence and associated costs of hip, vertebral, and pelvic fractures in 9,007 patients with nonmissing laboratory values and Medicare as primary payor. Cox proportional hazards and Poisson models were used to analyze time to first fracture and numbers of fractures, respectively.** ***Results:*** **There was no association between Ca or P values and risk for fracture; risks for vertebral and hip fractures and PTH concentrations were U shaped and weakly significant using Poisson regression ($P = 0.03$). The age- and sex-adjusted mortality rate after fracture was 2.7 times greater (580/1,000 person-years) than for general dialysis patients from the DMMS (217/1,000 person-years). Mean total episodic costs of hip, vertebral, and pelvic fractures were $20,810 ± $16,743 (SD), $17,063 ± $26,201, and $14,475 ± $19,209, respectively.** ***Conclusion:*** **Using data from the DMMS, there were no associations between Ca and P concentrations and risk for fracture. Risks for hip and vertebral fracture were associated weakly with PTH concentration, with the lowest risk observed around a PTH concentration of 300 pg/mL (ng/L). Fractures were associated with high subsequent mortality and costs. Prospective studies are needed to determine whether therapies that maintain PTH concentrations within or near the National Kidney Foundation–Kidney Disease Outcomes Quality Initiative range will result in fewer complications of disordered mineral metabolism.** ***Am J Kidney Dis*** **47:149-156.**

INDEX WORDS: Secondary hyperparathyroidism; dialysis; fractures; costs.

A SIGNIFICANT PROPORTION of patients on dialysis therapy experience secondary hyperparathyroidism accompanied by imbalances in serum calcium (Ca) and phosphorus (P) concentrations.[1] Prolonged secondary hyperparathyroidism is associated with an increased risk for adverse clinical consequences, such as soft-tissue and cardiovascular calcification[2-6] and calcific uremic arteriolopathy (calciphylaxis).[7-10]

Relationships among disordered Ca, P, and, to a lesser extent, parathyroid hormone (PTH) concentrations with increased risks for mortality and hospitalization caused by cardiovascular disease have been described previously.[3,11-15] However, the relation between disorders of mineral metabolism and fracture risk remains unclear. To date, few investigations have described fracture risk in the end-stage renal disease (ESRD) population,[16,17] and past investigations focused primarily on hip fracture in the dialysis population.[18-20] Published literature describing associations between actual values for Ca, P, and PTH and fracture risk also is scant.[18-20] We conducted the following analyses to determine whether abnormalities in serum Ca, P, and PTH concentrations were related to risk for hip, pelvic, and vertebral fractures. We hypothesized that elevated Ca and P concentrations were related to fracture risk and that fracture risk would vary across the spectrum of PTH concentrations, with the highest rates in the lowest and highest PTH concentration ranges.

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Received March 23, 2005; accepted in revised form September 19, 2005.

Originally published online as doi:10.1053/j.ajkd.2005.09.024 on November 22, 2005.

Support: Dr Chertow was supported by NIH RO1 DK58411, UO1 DK03005, and NO1 DK12450. Potential conflicts of interest: Dr Kim was employed by Amgen, Inc, at the time of this work. Drs Danese, Doan, Dylan, and Griffiths are consultants to Amgen, Inc. Dr Chertow has received research support and served as a scientific advisor to Amgen, Inc. Dr Chertow received no funding from Amgen, Inc, for his work on this project.

The data reported here have been supplied by the US Renal Data System (USRDS). The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy of the US government or the USRDS.

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0272-6386/05/4701-0018$30.00/0

doi:10.1053/j.ajkd.2005.09.024

We also aim to describe mortality and costs associated with and after fractures in the ESRD population.

METHODS

Data Source and Patients

Clinical and claims data from the US Renal Data System (USRDS) were used. The USRDS contains claims data for all US patients eligible for the ESRD program under Medicare. Hospitalization claims files were used to identify the occurrence and quantify the costs of fracture events. The Dialysis Morbidity and Mortality Study (DMMS) in the USRDS was an observational study of randomly selected US dialysis patients. DMMS data were composed of 4 Waves, with each Wave composed of data modules containing additional information outside the usual data collection in the USRDS, such as laboratory data, nutrition, and quality of life.

The sample frame for Waves 1, 3, and 4 included patients who were alive and on hemodialysis therapy on December 31, 1993. The sample frame for Wave 2 included hemodialysis and peritoneal dialysis patients starting dialysis therapy on various dates between January 1, 1996, and December 31, 1997, with a few dates outside this range. Only patients with Medicare as primary payor designation at the study start date were included. A single set of laboratory values for serum Ca, P, and PTH was measured for each patient from the DMMS Waves during a 4-month window surrounding each subject's study start date. Adjusted serum Ca concentration (in milligrams per deciliter) was calculated by using the following formula: adjusted Ca = total Ca + 0.8 * (4 − albumin). These values were reported as close as possible to the study start date within 3 months before or 1 month after the start date. Laboratory specimens were analyzed at a variety of laboratories, with no calibration of results. Patients were excluded if they had missing laboratory data or a history of parathyroidectomy.

Fracture Identification

Hip, vertebral, and pelvic fractures were identified from the inpatient claims file of the USRDS by using *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM),* diagnosis, *ICD-9-CM* procedure, and *Current Procedural Terminology* codes (Appendix 1). All fractures identified from the hospitalization claims file were linked to the DMMS by using a unique identifier from the USRDS. We captured only hospitalized cases of closed fractures and excluded open fractures because they likely are related to trauma. Pelvic fracture included areas of the acetabulum, ilium, and ischium. Hip fracture is defined as located primarily at the neck of the femur.

Cost of Fracture

To estimate the episodic cost of each fracture type, we analyzed 2001 Medicare claims data. Costs represented the amount paid by Medicare adjusted to 2004 US dollars using the medical care component of the Consumer Price Index. The fully reimbursed amount of the claim was considered the cost if the fracture-related diagnosis and/or procedure codes were located in the first or second coding field.

Each fracture episode required a hospital admission. The start date of the episode was before the hospital admission date if there was an emergency department visit or a physician office visit for fracture the day before admission. Hospital readmission for fracture within 5 days of a prior admission was considered part of the identical episode. In such instances, any fracture-related inpatient and outpatient costs during the period between hospitalizations were included as part of the same episode. Any costs for a stay in a skilled nursing facility that immediately followed the hospital discharge were included. Costs for physician services provided during stays in the hospital and skilled nursing facility also were included. Any fracture-related services in the outpatient setting were included if they were incurred on or 1 day before the hospital admission or during the 5-day period between hospitalizations. Costs from long-term care facilities were not included because this information was not available.

Statistical Analysis

Associations among sociodemographic factors, clinical variables, and serum measures and fracture types were examined. Comparisons were made by using chi-square tests for categorical variables and Student *t*-tests for continuous variables. Two-sided probability *(P)* values were calculated with statistical significance set at $P \leq 0.05$.

Hip, pelvic, and vertebral fractures were end points in multivariable analyses. Cox proportional hazard models were used to analyze time to first fracture. Because multiple fractures in a single subject may occur and data for multiple events would better characterize the clinical burden of this condition, Poisson regression methods also were used to estimate crude and adjusted fracture rates.

For all modeling, the risk period was 3 years after the DMMS study start date for each patient. Claims occurring before the study start date were not considered for analysis. Patients were censored if they died or dialysis therapy was discontinued before the end of the observation period. The primary focus of the modeling is to evaluate independent associations of serum Ca, P, and intact PTH concentrations with fracture. Initially, risk models were constructed that parameterized biochemical markers as categorical variables that were consistent with the National Kidney Foundation–Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) Clinical Practice Guidelines on Bone Metabolism and Disease, using NKF-KDOQI laboratory-recommended ranges as reference groups. These models suggested that the relation between PTH concentration and fracture was curvilinear and neither Ca nor P concentration was associated significantly with different fracture outcomes. To address the curvilinear relation between fracture risk and PTH concentration, spline regressions were performed by using a linear term for PTH concentration and defining the knots for PTH at the NKF-KDOQI cutoff values of 150, 300, and 800 pg/mL (ng/L). The lower knot at PTH (150 pg/mL [ng/L]) and the Ca × P term were dropped from the final model because the model fit was not improved. Prior studies showed that advanced age, female sex, white race, and smoking history are important risk factors for hip fracture in

Table 1. Baseline Characteristics of Study Population

	Cohort With Laboratory Data (n = 9,007)	Cohort Without Laboratory Data (n = 3,529)	*P*
Male (%)	57.5	57.2	0.76
White race (%)	53.8	50.1	<0.001
Diabetes diagnosis (%)	39.8	37.6	0.023
Current smoker (%)	19.8	18.9	0.25
Previous smoker (%)	20.9	17.8	<0.001
Age (y)	61.7 ± 15.5	61.3 ± 15.9	0.20
Predialysis systolic blood pressure (mm Hg)	151.0 ± 24.4	150.3 ± 24.4	0.15
Hematocrit (%)	30.8 ± 4.9	30.5 ± 5.2	0.002
Dialysis vintage (y)	1.8 ± 3.0	1.7 ± 2.8	0.087
Hip fracture	3.61	4.10	0.19
Vertebral fracture (%)	1.42	1.39	<0.001
Pelvic fracture (%)	1.33	1.22	0.63

the general population.[21,22] In this study, adjustments were made using continuous (age, hematocrit, and predialysis systolic blood pressure) and dichotomous variables (sex, race, history of diabetes, current smoking status, previous smoking status, and history of any fracture). Because Wave 2 was conducted several years after Waves 1, 3, and 4, Wave 2 cohort status also was included as a categorical covariate. For the proportional hazards model, left truncation of data was performed to account for variation in dialysis vintage (ie, time since initiation of dialysis therapy) when serum markers were obtained. Dialysis vintage was included as a continuous covariate in companion analyses.

RESULTS

There were 9,007 patients included in this study from Waves 1 to 4 with nonmissing laboratory variables and Medicare as primary payor. The cohort of 3,529 patients with missing laboratory data was not different with regard to age, sex, current smoking status, dialysis vintage, and percentage with hip and pelvic fractures (Table 1). Approximately 42% of patients were women, 54% were white, 40% had a diagnosis of diabetes, 20% were current smokers, and 21% were previous smokers. Mean serum adjusted Ca, P, and PTH concentrations were 9.5 ± 2.1 mg/dL (2.4 ± 0.5 mmol/L), 5.9 ± 3.1 mg/dL (1.9 ± 1.0 mmol/L), and 375.2 ± 947.8 pg/mL (ng/L), respectively. Median PTH concentration was 146 pg/mL (ng/L; interquartile range, 54 to 369 pg/mL [ng/L]).

During the risk period, 175 hip fractures, 100 pelvic fractures, and 77 vertebral fractures were documented (Table 2). In bivariate analyses, only PTH concentration less than 50 pg/mL (ng/L) was associated with increased risk for hip and vertebral fracture.

The adjusted relative hazard for vertebral fracture associated with PTH concentration was U shaped. At less than 300 pg/mL (ng/L), risk for vertebral fracture increased by a factor of 1.45 for each 100-pg/mL (ng/L) decrease in PTH concentration. From 300 to 800 pg/mL (ng/L), vertebral fracture risk increased by a factor of 1.17 for each 100-pg/mL (ng/L) increase in PTH

Table 2. Patients With Hip, Vertebral, or Pelvic Fracture Within Serum Ca, P, and PTH Strata

	Hip Fracture (%)	Vertebral Fracture (%)	Pelvic Fracture (%)
PTH (pg/mL) strata (no. of patients)			
<50 (1,408)	4.1*	2.2*	1.6
50 to <150 (1,646)	3.4	1.4	1.2
150 to <300 (1,154)	2.7	1.4	1.6
300 to <800 (1,205)	2.6	0.7	1.2
≥800 (610)	3.4	1.5	1.2
Adjusted Ca (mg/dL) strata (no. of patients)			
<8.4 (945)	2.7	0.9	1.2
8.4 to <9.5 (3,158)	3.5	1.5	1.2
9.5 to <10.2 mg/dL (1,987)	3.8	1.4	1.3
≥10.2 (1,513)	4.0	1.7	1.9
P (mg/dL) strata (no. of patients)			
<3.5 (669)	3.6	2.1	1.5
3.5 to <5.5 (3,238)	3.8	1.4	1.1
≥5.5 (4,385)	3.4	1.3	1.4

NOTE. To convert PTH in pg/mL to ng/L, multiply by 1; Ca in mg/dL to mmol/L, multiply by 0.2495; P in mg/dL to mmol/L, multiply by 0.3229.

*$P < 0.05$ for chi-square test.

Table 3. Results of Cox Proportional Hazards Models of Hip, Vertebral, and Pelvic Fracture With Right Censored Left Truncated Splines

	Hip	Vertebral	Pelvic
Age (y)	1.03 (1.02-1.04)	1.04 (1.02-1.06)	1.05 (1.03-1.07)
Male	0.63 (0.46-0.86)	0.55 (0.34-0.89)	0.32 (0.19-0.53)
White race	2.28 (1.59-3.25)	1.92 (1.1-3.35)	1.55 (0.92-2.61)
Diabetes diagnosis	1.98 (1.44-2.73)	0.76 (0.45-1.29)	1.4 (0.86-2.29)
Predialysis systolic blood pressure	1.00 (0.99-1.01)	0.99 (0.98-1)	1 (0.99-1.01)
Hematocrit	0.99 (0.96-1.03)	0.99 (0.94-1.04)	1.01 (0.96-1.06)
Current smoker	1.2 (0.81-1.77)	1.42 (0.78-2.57)	1.27 (0.67-2.4)
Previous smoker	0.81 (0.54-1.2)	1.05 (0.59-1.87)	1.35 (0.77-2.36)
DMMS Wave 2	0.90 (0.87-0.93)	0.97 (0.93-1.02)	0.89 (0.85-0.94)
History of any fracture	8.33 (5.04-13.74)	7.32 (3.41-15.71)	2.1 (0.65-6.8)
PTH (/100 pg/mL)			
1-300 pg/mL	0.96 (0.8-1.16)	**0.69 (0.51-0.93)**	1.02 (0.77-1.34)
300-800 pg/mL	1.06 (0.93-1.21)	1.17 (0.93-1.45)	0.94 (0.76-1.16)
>800 pg/mL	1.00 (0.98-1.02)	0.99 (0.95-1.04)	1.02 (1-1.03)

NOTE. Values expressed as hazard ratio (95% confidence interval). Hazard ratios are per 100-pg/mL (ng/L) increase within the category listed. For hazard ratios less than 1, this indicates greater risk with lower PTH concentration. For example, for hip fracture, the hazard ratio per 100-pg/mL (ng/L) decrease in PTH concentration can be expressed as 1/0.96, or 1.04. Corresponding values for vertebral and pelvic fracture are 1/0.69 = 1.45 and 1/1.02 = 0.98, respectively. Significant associations between PTH concentration and fracture risk are shown in bold.

concentration. For PTH concentration greater than 800 pg/mL (ng/L), the additional risk of vertebral fracture per 100-pg/mL (ng/L) increase in PTH concentration was unchanged (ie, risk was increased, but constant at >800 pg/mL [ng/L]). Age, sex, and race were significantly associated with risk for vertebral fracture (Table 3). There did not appear to be a temporal association when including incident patients in Wave 2 of the DMMS. Finally, previous vertebral fracture was associated with more than a 7-fold increase in risk for subsequent fracture, independent of other risk factors.

Hip fracture also showed a U-shaped relation with PTH concentration, albeit somewhat weaker than with vertebral fracture. There was essentially no association between PTH concentration and pelvic fracture (Table 3).

The Poisson models estimated that median rates of hip, vertebral, and pelvic fracture were 18.1, 4.8, and 5.1 events/1,000 person-years in the dialysis population, respectively. Similar to findings derived from proportional hazard models, Poisson models also suggested a U-shaped relation between PTH concentration and vertebral fracture (Table 4). The association between hip fracture and PTH concentration also was curvilinear, but less marked. Poisson models fit with and without PTH terms showed significantly better fit with inclusion of PTH terms ($P = 0.03$). Longer dialysis vintage was associated with a greater fracture risk for vertebral fracture only (19%/y).

Total episodic costs of hip, vertebral, and pelvic fracture were \$20,810 ± \$16,743, \$17,063 ± \$26,201, and \$14,475 ± \$19,209, respectively (Table 5). Most fracture-related costs were attributed to stays at inpatient facilities. Approximately 65% to 74% of the total episodic cost was caused by hospitalization, and 11% to 21% was accounted for by care in skilled nursing facilities, depending on fracture type. Costs for inpatient physician services and outpatient services consisted of approximately 14% to 16% and less than 1% of the total cost, respectively.

When the crude mortality rate in the fracture population was adjusted to reflect the same age and sex distribution as the overall DMMS population by using direct adjustment, it declined from 778 deaths/1,000 person-years to 580 deaths/1,000 person-years. The age- and sex-adjusted mortality rate was 2.7-fold greater than the overall DMMS rate of 217 deaths/1,000 person-years.

DISCUSSION

In this study, we found no significant associations among serum Ca, P, and Ca × P values and

Table 4. Results of Poisson Models of Hip, Vertebral, and Pelvic Fractures

	Hip	Vertebral	Pelvic
Age (y)	1.03 (1.02-1.04)	1.05 (1.02-1.08)	1.06 (1.03-1.09)
Male	0.64 (0.46-0.87)	0.37 (0.2-0.65)	0.32 (0.17-0.56)
White race	2.2 (1.53-3.22)	2.56 (1.34-5.31)	1.10 (0.63-1.94)
Diabetes diagnosis	1.79 (1.3-2.46)	0.83 (0.43-1.54)	1.79 (1.04-3.07)
Predialysis systolic blood pressure	1.00 (1-1.01)	1.00 (0.99-1.01)	1.01 (1-1.02)
Hematocrit	1.00 (0.97-1.04)	0.99 (0.94-1.05)	1.01 (0.95-1.07)
Current smoker	1.32 (0.87-1.96)	2.01 (1-3.83)	1.10 (0.5-2.21)
Previous smoker	1.15 (0.78-1.67)	1.32 (0.65-2.53)	1.21 (0.62-2.24)
DMMS Wave 2	0.90 (0.86-0.93)	0.93 (0.87-0.99)	0.91 (0.86-0.96)
Time on dialysis	1.02 (0.96, 1.08)	1.19 (1.11, 1.28)	1.03 (0.91-1.15)
History of any fracture	6.07 (3.6-9.69)	9.44 (4.15-19.08)	1.83 (0.34, 5.72)
PTH (/100 pg/mL)			
1-300 pg/mL	0.91 (0.75-1.10)	0.74 (0.51-1.05)	1.02 (0.75-1.37)
300-800 pg/mL	**1.15 (1.01-1.31)**	**1.33 (1.06-1.66)**	0.91 (0.71-1.16)
>800 pg/mL	0.99 (0.97-1.02)	0.99 (0.95-1.04)	1.01 (0.98-1.03)

NOTE. Values expressed as rate ratio (95% confidence interval). Rate ratios are per 100-pg/mL (ng/L) increase within the category listed. For hazard ratios less than 1, this indicates greater risk with lower PTH concentration. For example, for hip fracture, the rate ratio per 100-pg/mL (ng/L) decrease in PTH concentration can be expressed as 1/0.91, or 1.10. Corresponding values for vertebral and pelvic fracture are 1/0.74 = 1.343 and 1/1.02 = 0.98, respectively. Significant associations between PTH concentration and fracture risk are shown in bold. Overall *P* for comparing models with PTH terms for vertebral and hip fracture versus models without PTH terms is $P = 0.03$.

fracture outcomes, contrary to our stated hypothesis. Abnormalities in these biochemical parameters have been associated strongly with increased risk for other clinical outcomes, such as overall mortality, cardiac mortality, and cardiac valvular procedures.[3,13,23] A study of hemodialysis patients from a large US provider showed a significant association between higher serum P concentration (relative risk [RR], 1.12/1-mg/dL [0.323-mmol/L] increase in P concentration) and risk for hospitalization for hip and femur fractures. Advanced age, female sex, white race, longer hemodialysis vintage, and lower serum creatinine concentration also were associated with a higher fracture risk; higher PTH concentration was associated weakly with fracture in this study,[24] although specific cutoff values and curvilinear relations using splines were not explored. We may have missed the association between greater serum P concentration and fracture because of limited power (ie, smaller sample size in DMMS Waves) and misclassification (ie, a single P concentration was used to define exposure, rather than the average during 3 months, with the latter more likely to accurately reflect the exposure).

These analyses suggest that PTH concentrations less than 150 pg/mL (ng/L) may increase the RR for hip or vertebral fracture compared with PTH concentrations within the NKF-KDOQI

Table 5. Episodic Cost of Hip, Vertebral, and Pelvic Fractures

	Hip Fracture		Vertebral Fracture		Pelvic Fracture	
	Mean	SD	Mean	SD	Mean	SD
Hospitalization ($)	14,343	14,255	12,678	22,568	9,365	16,852
Physician component of hospitalization ($)	2,957	2,042	2,233	3,027	1,681	1,819
SNF ($)	3,122	5,814	1,900	4,739	3,083	5,440
Physician component of SNF ($)	329	1,086	209	791	295	1,113
Outpatient ($)	59	305	44	245	51	260
Total ($)	20,810	16,743	17,063	26,201	14,475	19,209

NOTE. Costs are adjusted by the medical care component of the Consumer Price Index and expressed in 2004 US dollars.
Abbreviation: SNF, skilled nursing facility.

recommended range of 150 to 300 pg/mL (ng/L). Previously published research on PTH concentration and fracture in dialysis patients showed conflicting results. Coco and Rush[18] reported that PTH concentrations less than 195 pg/mL (ng/L) were associated with a 5.8-fold increase in hip fracture risk during a 10-year period, adjusted for age, race, and the concentrations of alkaline phosphatase, albumin, and PTH. Atsumi et al[19] reported that male Japanese dialysis patients with low PTH concentrations (range, 5 to 61 pg/mL [ng/L]) were 2.4- and 1.6-fold more likely to have had vertebral fractures compared with patients with PTH concentrations in the ranges of 62 to 202 and 203 to 1,818 pg/mL (ng/L), respectively. The analyses presented here confirm the finding of Atsumi et al[19] that the shape of the PTH-fracture (vertebral and hip) relation was U shaped. However, a potentially important distinction was the absence of a marked increase in fracture rates associated with extremely low PTH concentrations. Our findings lend support to the current NKF-KDOQI guidelines, which warn against overzealous suppression of PTH.[25] Greater awareness of the consequences of elevated PTH concentrations on hip and vertebral fractures also should be emphasized.

Stehman-Breen et al[20] reported that PTH concentration was not associated significantly with hip fracture from an analysis of USRDS data (adjusted RR = 1.16 for PTH >300 pg/mL (ng/L); $P = 0.66$; RR = 1.17 for PTH <100 pg/mL; $P = 0.59$). It is noteworthy that these investigators used Wave 1 only, rather than Waves 1 to 4, and examined only hip fracture, rather than hip, pelvic, and vertebral fracture; therefore, the power to detect the associations we observed was considerably less. Moreover, spline techniques were not used.

The estimated rate of vertebral fracture was similar to rates reported by the USRDS, suggesting that the DMMS cohort is similar to the overall dialysis population.[26] One study reported that overall incidences of hip fracture were 7.45 and 13.63/1,000 person-years for white males and females, respectively.[16] These rates corresponded to RRs for hip fracture 4.44 and 4.40 times that of the general population. Results from this study confirm the associations of age, sex, race, and diabetes with fracture.

The costs of fractures are high. The direct medical cost alone can range from $14,475 to $20,810 per fracture event. The major component of each episodic cost was hospitalization and accounted for approximately two thirds to three quarters of the total cost.

In this study, occurrence of fracture in dialysis patients was associated with an increased mortality rate compared with the general DMMS population. Any fracture type studied was associated with an approximately 2.7-fold increase in 1-year mortality independent of age and sex. Although adjustment for age and sex may be incomplete and residual confounding might increase or decrease the mortality risk estimate, the qualitative inference is unlikely to change. Increased risk for death after hip fracture (~23.7% at 1 year in the general population) was documented by other investigators.[27,28] For dialysis patients, a 1-year mortality rate of 64% was reported after hip fracture, a figure similar to our estimates.[18] Given the high postfracture mortality rate and considerable morbidity associated with fracture in persons often already physically limited by ESRD, strategies for fracture prevention should be included among the highest priority activities for care providers in ESRD.

This study has several important limitations. We attempted to characterize fracture risk during a period based on a single measurement of Ca, P, and PTH. Because these parameters vary over time, we cannot claim that the reported value for PTH will remain elevated (or normal or decreased) throughout the risk period. These models are subject to nondifferential misclassification bias because patients are not likely to stay in the same PTH concentration group as initially "assigned."

Second, the accuracy and completeness of diagnosis and procedure codes from claims data can be questioned. However, because fracture events are serious and are defined by hospitalization, it is unlikely for these events to be consistently coded incorrectly. Moreover, underascertainment of events likely would bias associations toward the null.

Third, the association between PTH concentration and fracture outcomes may be influenced by medications (eg, vitamin D) that can alter biochemical levels.

Fourth, because of limitations in DMMS Wave data, we were unable to adjust adequately for several potential confounding variables. More complete adjustment might have altered the RR estimates.

Finally, estimates of costs in this study have not captured the total economic impact because costs from long-term care facilities, rehabilitation facilities, and home care and opportunity costs for younger patients who might have been employed or working at home were not included. One study reported that 27% and 14% of elderly patients treated for hip fracture were discharged to home and rehabilitation facilities, respectively; therefore, continued care in these settings may contribute to the episodic cost.[29] The cost of vertebral fracture, in particular, may have been underestimated because the vertebral fracture episode was defined artificially by a narrow time frame that began with a hospitalization. Defining the start of the fracture episode with hospitalization may hold true for such discrete events as hip or pelvic fracture, but may not be valid for vertebral fracture. Vertebral fracture can present as back pain or in a subacute form; thus, it is possible to incur substantial costs related to vertebral fracture from days to weeks before the diagnosis appears on medical claims. Patients with vertebral fractures typically are not hospitalized; therefore, we may have overestimated the cost per episode by simply focusing on hospitalized patients, although inclusion of less severe fractures would have provided additional power to identify clinical correlates. Given these caveats, our cost estimates may reflect only services delivered in hospitals and skilled nursing facilities.

In summary, using data from USRDS DMMS Waves 1 to 4, we show no association between Ca, P, or Ca $\times$ P values and fracture risk. We identified a weak association between PTH concentration and risk for vertebral and hip fractures that was U shaped, with the lowest risk observed around a PTH concentration of 300 pg/mL (ng/L). Fracture in patients with ESRD was associated with high subsequent mortality and considerable attributable costs. Prospective studies are required to determine whether therapies aimed at maintaining PTH concentrations within or near the NKF-KDOQI target range will result in fewer hospitalizations for fracture, fewer and less devastating fractures, and decreases in rates of other complications of hyperphosphatemia, hypercalcemia, and secondary hyperparathyroidism.

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APPENDIX 1: DIAGNOSIS AND PROCEDURE CODES TO IDENTIFY HIP, VERTEBRAL, AND PELVIC FRACTURES

	ICD-9-CM Diagnosis Code	*ICD-9-CM* Procedure Code	*CPT* Procedure Code
Hip fracture	733.14, 820.0x, 820.2x, 820.8	79.05, 79.15, 79.25, 79.35	27220, 27222, 27224, 27225, 27226, 27227, 27228, 27230, 27232, 27234, 27235, 27236, 27238, 27240, 27242, 27244, 27245, 27246, 27248
Vertebral fracture	733.13, 805.0x, 805.2x, 805.4x, 805.6x, 805.8x, 806.0x, 806.2x, 806.4, 806.6x, 806.8	03.53	22305, 22310, 22315, 22318, 22319, 22325, 22326, 22327, 22328, 22520, 22521, 22522
Pelvic fracture	808.0, 808.2, 808.4x, 808.8	None	27190, 27191, 27193, 27194, 27210, 27211, 27212, 27214, 27215, 27216, 27217, 27218

Abbreviation: *CPT*, *Current Procedural Terminology*.