Fracture Risk after Parathyroidectomy among Chronic Hemodialysis Patients

Kyle D. Rudser,* Ian H. de Boer,† Annemarie Dooley,‡ Bessie Young,§ and Bryan Kestenbaum‖

*Department of Biostatistics, †Division of Nephrology, §Division of General Medicine, Puget Sound Veterans' Affairs Medical Center, and ‖Division of Nephrology, Harborview Medical Center, University of Washington, and ‡Northwest Health Services Research and Development Program, Veterans Affairs Puget Sound Health System, Seattle, Washington

ABSTRACT

The impact of parathyroidectomy (PTX) on the long-term risks for hip and other fractures is unknown. Uncontrolled case series have reported an increase in bone mineral density after PTX. However, very low serum parathyroid hormone levels have been associated with decreased bone mineral density, adynamic bone disease, and fractures. This study compared long-term fracture rates among hemodialysis patients who underwent PTX with a matched control group. Data were obtained from the US Renal Data System. Patients who underwent a first PTX while receiving hemodialysis were matched with up to three control patients by age, race, gender, year of dialysis initiation, primary cause of renal failure, and the dosage of intravenous vitamin D used before PTX. Patients with a history of fracture or renal transplantation were excluded. Study outcomes were incident hip, vertebral, and distal radius-wrist fractures identified using hospitalization codes. Incident hip fracture rates in the PTX and matched control groups were 6.0 and 9.3 fractures per 1000 person-years, respectively. After adjustment, PTX was associated with a significant 32% lower risk for hip fracture (95% confidence interval 0.54 to 0.86; $P = 0.001$) and a 31% lower risk for any analyzed fracture (95% confidence interval 0.57 to 0.83; $P < 0.001$) compared with matched control subjects. Fracture risks were lower among hemodialysis patients who underwent PTX compared with matched control subjects. Surgical amelioration of secondary hyperparathyroidism may outweigh the risk of parathyroid hormone oversuppression in terms of bone health.

J Am Soc Nephrol 18: 2401–2407, 2007. doi: 10.1681/ASN.2007010022

Secondary hyperparathyroidism (SHPTH) is a common problem among long-term dialysis patients and is associated with progressive bone disease, fracture, and vascular calcification.[1–4] Despite considerable advances in medical therapy for SHPTH, parathyroidectomy (PTX) remains an important tool for treating refractory disease. More than 1000 PTX procedures were performed among patients with ESRD in the United States in 1999.[5] In most cases, PTX dramatically reduces serum PTH levels, ameliorates symptoms of hyperparathyroidism, and leads to rapid accumulation of calcium and phosphate by the skeleton.[6–9]

The long-term impact of PTX on fracture risk remains unknown. Surgical case series have reported an increase in bone mineral density (BMD) after PTX, particularly in the lumbar spine and femoral neck.[10–12] These studies were uncontrolled, examined small numbers of selected patients at individual centers, and did not evaluate fractures. In contrast, very low levels of parathyroid hormone (PTH) and oversuppression of PTH using vitamin

Received January 5, 2007. Accepted May 3, 2007.

Published online ahead of print. Publication date available at www.jasn.org.

The data were provided by the USRDS, and the opinions of the authors do not necessarily represent government policy.

Correspondence: Dr. Bryan Kestenbaum, University of Washington, Division of Nephrology, Harborview Medical Center, Room 10EH11, Box 359764, Seattle, WA 98104-2499. Phone: 206-731-4029; Fax: 206-731-2252; E-mail: brk@u.washington.edu

D analogs have been linked with adynamic bone disease, decreased BMD, and a greater risk for fracture among long-term dialysis patients.[13–17] Furthermore, exogenous administration of PTH to postmenopausal women who do not have kidney disease significantly improves BMD.[18,19] These findings raise concern that PTX could have an adverse impact on bone health by oversuppressing PTH. Divergent conclusions from existing studies leave residual uncertainty as to whether PTX might lead to greater or lesser long-term fracture risks.

In this matched cohort study, we evaluated the risks for incident hip, vertebral spine, and distal radius fractures among long-term hemodialysis patients after PTX. We compared fracture rates among PTX patients with those from a control group, matched by age, race, gender, dialysis duration, primary cause of ESRD, and the dosage of intravenous vitamin D used during the 6-mo period before PTX.

RESULTS

From the source ESRD population, 7221 patients were identified on the basis of having undergone a first PTX while receiving hemodialysis. Among this group, 490 (6.8%) patients were excluded because of a history of renal transplantation, 295 (4.1%) because of a history of any of the study fracture outcomes, and 12 (0.2%) because of a fracture that occurred during the PTX hospitalization. Of the 5918 PTX procedures that were analyzed, 2067 were classified as "total parathyroidectomy" and 3851 were classified as "other parathyroidectomy." Three matched control patients were found for 4992 (77.6%) of the eligible PTX cohort, two matched control patients for 426 (6.6%), and one matched control patient for 500 (7.8%). No suitable match could be found for 518 (8.0%) PTX patients, resulting in exclusion. Compared with matched PTX patients, unmatched PTX patients tended to be younger (mean age 39.7 yr), were more likely to have glomerulonephritis, and tended to be of race other than white or black.

The matched PTX study population tended to be relatively young (mean age 49.7 yr), with a higher proportion of black patients and patients without diabetes than would be expected from the general prevalent hemodialysis population (Table 1). The matching process successfully balanced the distribution of demographic characteristics and intravenous vitamin D dosage between PTX and control groups. Unmatched comorbid conditions also tended to be similar comparing PTX patients with matched control patients. For example, the Charlson comorbidity index was 3.1 and 3.3 for PTX and matched control patients, respectively.

The interquartile range of follow-up time was 0.7 to 3.4 yr, with maximum follow-up of 13.5 yr. There were 90 observed incident hip fractures in the PTX group (6.0 fractures per 1000 person-years) and 370 observed hip fractures in the matched control group (9.3 fractures per 1000 person-years). Hip fracture rates in the PTX group were higher during the 90-d postoperative period compared with the remainder of follow-up (Table 2). However, the small number of postoperative fractures ($n = 18$) and wide confidence intervals (CI) surrounding the estimate of postoperative fracture rate limit conclusions regarding temporal trends. Exploration of characteristics of the 18 PTX patients who experienced a postoperative fracture did not reveal notable differences in measured characteristics, except for modestly older age (mean 54.4 *versus* 49.0 yr) and a higher proportion of white race (55.6 *versus* 43.0%).

Table 1. Baseline characteristics of the PTX and matched control groups[a]

Characteristic	Mean ± SD or *n* (%)	
	PTX Group (*n* = 5918)	Matched Control Group (*n* = 16,328)
Age (yr)	49.0 ± 15.6	50.0 ± 15.4
Female	3306 (55.9)	9082 (55.6)
Race		
white	2547 (43.0)	7168 (43.9)
black	3230 (54.6)	8861 (54.3)
other	141 (2.38)	299 (1.83)
Dialysis duration (yr)	4.0 ± 2.5	3.7 ± 2.4
Cause of ESRD		
diabetes	1476 (24.9)	4263 (26.1)
hypertension	2229 (37.7)	6244 (38.2)
glomerulonephritis	1045 (17.7)	2691 (16.5)
other	1168 (19.7)	3130 (19.2)
Intravenous vitamin D use[b]	3452 (66.1)	9.276 (64.9)
Calcitriol dosage (μg)[c]	49.4 ± 44.4	48.1 ± 37.8
Paricalcitol dosage (μg)[c]	421.0 ± 414.0	406.5 ± 389.0
Prevalent cardiovascular disease	1965 (33.2)	5037 (30.9)
Hospitalized days during previous year	12.8 ± 21.3	14.1 ± 25.3
Charlson comorbidity index	3.1 ± 1.6	3.3 ± 1.9

[a]PTX, parathyroidectomy.
[b]Calculated during the 6-mo period before PTX. Proportions based on PTX procedures beginning in 1995, corresponding to widespread intravenous vitamin D use.
[c]Six-month vitamin D dosage calculated among patients who received any calcitriol or paricalcitol.

After the postoperative period, unadjusted hip facture rates remained consistently lower among PTX patients, compared with matched control patients, throughout the duration of follow-up (Table 2, Figure 1). The estimated cumulative incidence of hip fracture after 10 yr was 5.3% in the PTX group and 8.5% in the matched control group. Before adjustment, PTX was associated with a 27% lower risk for hip fracture during follow-up (crude hazard ratio 0.73; 95% CI 0.58 to 0.91; $P = 0.006$). After adjustment for the matching variables, prevalent coronary heart disease (CHD) status, the number of previous hospitalized days, and the Charlson comorbidity index, PTX was associated with a significant 32% lower risk for hip fracture (Table 3). Neither intravenous calcitriol nor paricalcitol use during the 6-mo period before PTX was significantly associated with hip fracture risk. Longer term exposure to vitamin D use was further explored by calculation of the cumulative vita-

Table 2. Hip fracture rates in the PTX and matched control groups[a]

Time from PTX	PTX Group		Matched Control Group		Adjusted HR (95% CI)[c]	*P*
	No. of Patients	Fracture Rate (Fractures)[b]	No. of Patients	Fracture Rate (Fractures)[b]		
0 to 90 d	5918	13.0 (18)	16,328	7.7 (30)	1.78 (0.99 to 3.20)	0.056
90 d to 1 yr	5233	4.4 (15)	14,894	9.5 (92)	0.50 (0.29 to 0.86)	0.013
1 to 3 yr	3966	5.0 (28)	11,005	9.4 (141)	0.54 (0.36 to 0.81)	0.003
>3 yr	1857	6.3 (29)	4768	9.5 (107)	0.72 (0.47 to 1.09)	0.116

[a]CI, confidence interval; HR, hazard ratio.
[b]Hip fracture rates per 1000 person-years at risk.
[c]Models adjusted for the matching covariates plus prevalent coronary heart disease, the number of hospitalized days during the 1-yr period before PTX, and the Charlson comorbidity index.

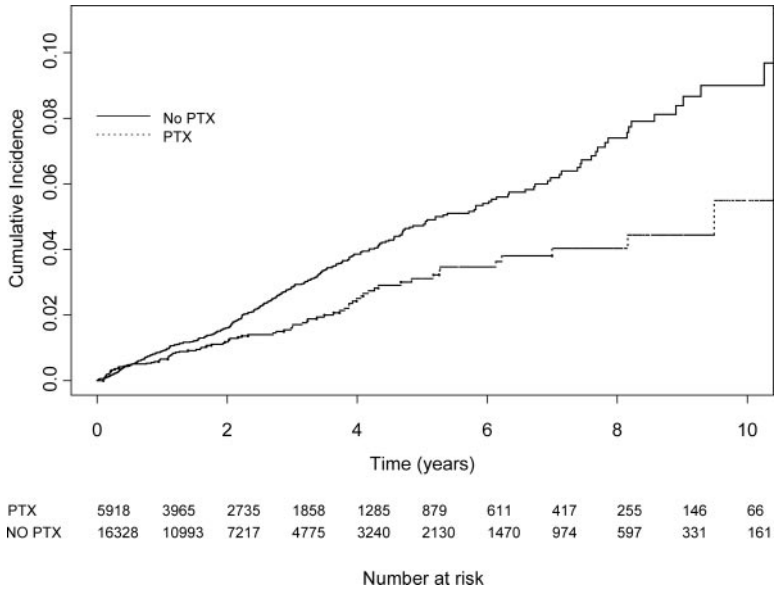


Figure 1. Cumulative incidence of hip fracture in parathyroidectomy (PTX) and matched control groups.

min D dosage from the start of dialysis to the PTX date or to the PTX index date for matched control patients. In adjusted analyses, neither cumulative calcitriol nor paricalcitol dosage was related to the risk for incident hip fracture.

Incidence rates of vertebral and distal radial-wrist fracture were lower than rates of hip fracture (Table 4). The estimated relative risks for vertebral, radial, and combined fractures associated with PTX were similar to those observed for hip fracture (Table 4).

Sensitivity analyses were performed to assess whether study findings were robust. A total of 155 (2.6%) PTX patients required a repeat PTX procedure during follow-up. Removal of these patients and their respective control patients from analysis did not alter the estimated relative risk for combined fracture associated with PTX (adjusted hazard ratio 0.69; 95% CI 0.57 to 0.84). The relative risk for combined fracture was modestly lower for procedures that were classified as total PTX (adjusted hazard ratio 0.58; 95% CI 0.42 to 0.81), compared with those that were classified as other PTX (adjusted hazard ratio 0.74; 95% CI 0.60 to 0.91). The estimated association of PTX with combined fracture remained unaltered when restricted to patients who received any intravenous vitamin D during the 6-mo preoperative period (adjusted hazard ratio 0.71; 95% CI 0.55 to 0.90).

We also examined postoperative intravenous vitamin D use as a potential explanation for the lower predicted risk for fracture among PTX patients. This was done among matched groups for which the PTX date was no earlier than January 1, 1995, corresponding to widespread intravenous vitamin D use across US dialysis centers. After PTX, the prevalence of intravenous vitamin D use declined in the surgery group but remained relatively constant among the control group (Figure 2). However, neither postoperative intravenous calcitriol nor paricalcitol use, modeled as time-dependent covariates, was found to be associated with hip fracture, and inclusion of these variables in the multivariate models did not appreciably alter the estimated association of PTX with any incident fracture (adjusted hazard ratio 0.61; 95% CI 0.58 to 0.64).

Finally, we explored whether the association of PTX with incident fracture might differ across subgroups defined by age, race, gender, diabetes status, and geographic region (Figure 3). None of these factors significantly altered the association of PTX with fracture risk ($P > 0.15$ for all interactions tested).

DISCUSSION

We found PTX to be associated with lower long-term risks for hip and combined fractures, compared with a matched control group. To our knowledge, this is the first description of long-term fracture rates after PTX in the setting of dialysis-related SHPTH.

Our findings are complementary to observations from single-center surgical case series, which reported an increase in BMD among dialysis patients who underwent PTX.[10–12,20] For example, Yano *et al.*[12] reported an approximately 5 and 15% increase in radial and lumbar spine BMD, respectively, as assessed by dual-energy x-ray absorptiometry 3 yr after PTX among 15 long-term hemodialysis patients. Improvement was apparent as early as 3 mo after surgery and tended to be greatest

Table 3. Adjusted relative hazard of hip fracture after PTX

Parameter	Adjusted HR (95% CI)[a]	*P*
PTX	0.68 (0.54 to 0.86)	0.001
Age (per 10 yr)	1.05 (1.05 to 1.06)	<0.001
Gender		
male	Reference	
female	1.22 (1.00 to 1.50)	0.051
Race		
white	Reference	
black	0.47 (0.38 to 0.58)	<0.001
other	1.02 (0.56 to 1.88)	0.938
Cause of ESRD		
diabetes	Reference	
hypertension	1.18 (0.92 to 1.51)	0.203
glomerulonephritis	1.00 (0.72 to 1.39)	0.986
other	1.22 (0.92 to 1.63)	0.168
Dialysis duration (per mo)	1.01 (1.00 to 1.01)	<0.001
Intravenous calcitriol dosage (μg)[b]		
none	Reference	
>0 to 36	1.02 (0.80 to 1.31)	0.869
>36 to 72	0.87 (0.64 to 1.18)	0.385
>72	0.88 (0.60 to 1.30)	0.528
Intravenous paricalcitol dosage (μg)[b]		
none	Reference	
>0 to 180	1.15 (0.80 to 1.64)	0.454
>180 to 360	1.27 (0.85 to 1.89)	0.250
>360	1.30 (0.87 to 1.94)	0.195
Prevalent coronary heart disease	1.14 (0.93 to 1.41)	0.209
Hospital days in previous 6 mo (per 10 d)	1.04 (1.00 to 1.09)	0.048

[a]Adjusted for all variables in the table plus the Charlson comorbidity index.
[b]Intravenous vitamin D dosage calculated during 6-mo period before PTX.

for patients who had the highest preoperative serum PTH levels. Abdelhadi and Nordenstrom[10] observed similar 18 and 15% increases in lumbar spine and femoral neck BMD, respectively, 3 yr after PTX among 10 long-term hemodialysis patients with SHPTH. Chou *et al.*[11] reported increases of 11 and 14% in lumbar spine and femoral neck BMD, respectively, 6 mo after PTX among dialysis patients who were classified as having osteoporosis. Of interest, similar improvements in BMD after PTX have also been reported among nonrenal patients who had primary hyperparathyroidism.[21,22] Despite potential beneficial effects of PTX on BMD, no available data link BMD with fracture risk in the ESRD setting, in which metabolic bone disturbances are complex.

PTX may reduce fractures *via* a number of mechanisms. PTX rapidly lowers serum PTH levels in the majority of cases.[7,8] Serum PTH excess is classically linked with pathologic findings of osteitis fibrosa, characterized by marrow fibrosis, and increased osteoblast and osteoclast activity.[23] Amelioration of the high-turnover bone lesion by PTX could improve bone quality and decrease long-term fracture risks. PTX also triggers the hungry bone syndrome, characterized by rapid uptake of calcium and phosphate by the skeleton.[9] It is possible that these changes in mineral distribution lead to long-term protective effects on fracture. Finally, it is possible that reduction in bone pain and improvement of anemia after PTX could increase the capacity and desire for exercise, which could increase BMD and lower the risk for fracture.[6,24] Consistent with this hypothesis are reports documenting improvement in muscle strength and measured nutritional parameters among dialysis patients after PTX.[25–27]

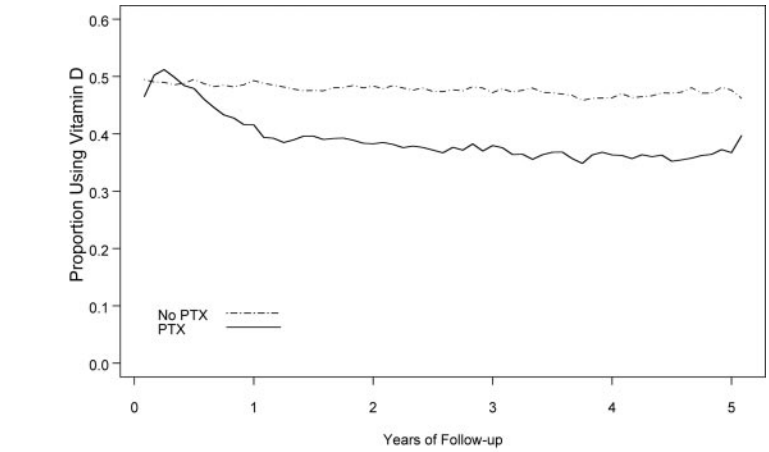
The association of PTX with lower fracture risk in this study is interesting given previously described associations of very low PTH levels with reduced BMD, adynamic bone disease, and a higher risk for fracture among long-term hemodialysis patients.[1,13,14,17,28] It is possible that previous associations represent residual confounding by unmeasured characteristics of dialysis patients who have lower PTH levels and not specific effects of inadequate circulating PTH levels on bone. It is also possible that PTH levels rise to acceptable levels after PTX. Although postoperative PTH levels were not available in this study, our findings do not support a protective role for residual PTH in dialysis because (*1*) estimated associations of PTX with fracture were qualitatively stronger among patients who underwent total *versus* subtotal PTX and (*2*) excluding patients who required repeat PTX, who would be expected to have high residual PTH levels, did not alter associations of PTX with fracture.

Some important limitations should be discussed. Patients who underwent PTX, an elective surgical procedure, may have been healthier than control patients in terms of unmeasured comorbidity, such as the burden of chronic disease and physical activity level. In this regard, weaker, more frail individuals may be less likely to undergo elective PTX and more likely to fall and fracture, possibly accounting for the observed higher

Table 4. Hip and other fractures in the PTX and matched control groups

Parameter	PTX Group		Matched Control Group		Adjusted HR (95% CI)[a]
	No. of Fractures	Rate per 1000 Person-Years	No. of Fractures	Rate per 1000 Person-Years	
Hip	90	6.0	370	9.3	0.68 (0.54 to 0.86)
Vertebral	47	3.1	167	4.2	0.79 (0.57 to 1.10)
Distal radius-wrist	10	0.7	45	1.1	0.64 (0.32 to 1.27)
All fractures[b]	140	9.4	559	14.2	0.69 (0.57 to 0.84)

[a]Models adjusted for the matching covariates plus prevalent coronary heart disease, the number of hospitalized days during the 6-mo period before PTX, and the Charlson comorbidity index.
[b]Total fractures will be slightly higher than the sum of individual fractures as a result of censoring at first fracture.



At Risk						
No PTX	14302	9412	5977	3768	2418	1508
PTX	5733	3806	2570	1645	1049	668

Data censored at the time of first fracture.

Any vitamin D use for a given month defined by ≥ 3 ug of calcitriol or 15 ug of paricalcitol.

Figure 2. Proportion of intravenous vitamin D use after PTX.

fracture risk among control patients. We attempted to account for differences in comorbidity by matching on age, race, gender, dialysis duration, and cause of ESRD and adjusting for hospitalized conditions, intravenous vitamin D use, and Charlson comorbidity index. It is interesting that fracture risk was found to be higher among PTX patients in the early postoperative period, suggesting that PTX patients may have actually been at greater preoperative fracture risk. A higher fracture rate in the first 90 d after PTX may be due to longstanding toxic effects of SHPTH, acute metabolic derangements that occur immediately after PTX, or a higher risk for falling during the postoperative period. Specific laboratory data were not available for this population-based study, precluding analyses of whether the impact of PTX might differ according to the preoperative PTH level or whether the extent of PTH lowering after surgery is related to subsequent fracture risk. Confounding by intravenous vitamin D use seems unlikely because groups were matched on preoperative vitamin D dosage and because intravenous vitamin D was not related to fracture in this study. Oral vitamin D use was not measured and may represent a residual confounding variable. Strengths of the study include evaluation of clinical fractures, rather than a surrogate marker such as BMD, and the use of a general study population that is not biased by practice patterns of a particular health care center.

We observed a lower long-term risk for fractures among a national cohort of long-term hemodialysis patients who underwent PTX, compared with a matched control group. These data, in combination with previous reports describing improved BMD after PTX, provide suggestive evidence that amelioration of biochemical consequences of SHPTH by PTX may outweigh potential risks of long-term PTH oversuppression in terms of bone health. Further studies are needed to address this important hypothesis. These findings also demonstrate the long-term safety of PTX with regard to fracture risk.

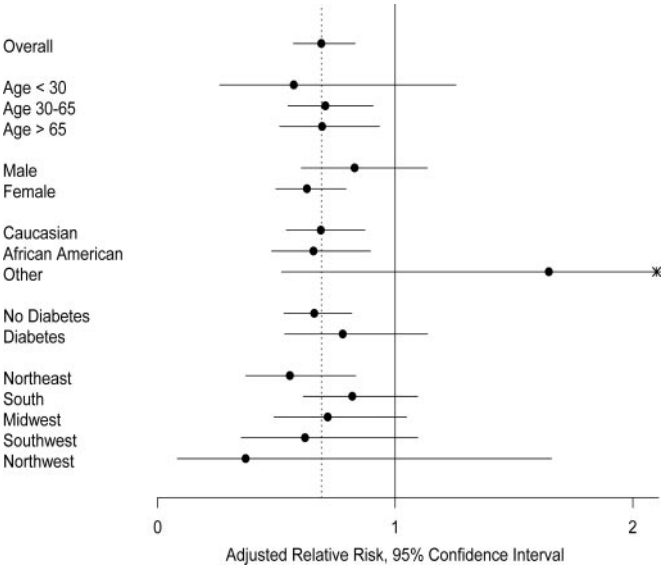


Figure 3. Association of PTX with any fracture among selected subgroups.

CONCISE METHODS

Source Population

Data were obtained from the US Renal Data System (USRDS), which collects detailed information on patients who receive long-term renal replacement therapy in the United States.[29] Further details of the USRDS can be found at http://www.usrds.org. For this analysis, the source population included all patients who initiated long-term renal replacement therapy between January 1, 1990, and December 31, 2003; were at least 18 yr of age; and were receiving fee-for-service Medicare as their primary insurance payer within 90 d after initiating dialysis.

PTX Cohort

From the source population, all patients who had ESRD and underwent a first PTX while receiving hemodialysis were identified. Peritoneal dialysis patients were not studied because vitamin D dosing information could not be accurately ascertained using institutional claims data. PTX was defined by *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) hospital procedure codes 06.81 (total PTX) or 06.89 (other PTX). The first PTX that occurred after dialysis initiation was retained for primary analyses. Repeat PTX procedures were also collected for sensitivity analyses. PTX patients who had a history of any of the study fracture outcomes (hip, vertebral, distal radius, or wrist fracture) or a history of renal transplantation before PTX were excluded. Previous fractures were assessed using hospitalization data from the ESRD period before PTX. We chose to exclude conservatively the few PTX patients (n =

12) who received a diagnosis of a first fracture during the same hospitalization as PTX, because hospital claims cannot distinguish which of these events occurred first.

Control Cohort

For each eligible PTX patient, up to three control patients who were also receiving hemodialysis on the PTX date and who had no history of fracture or renal transplantation at that time were identified. Control patients were individually matched to each PTX patient by age ($\pm$2 yr), race (black, white, or other), gender, duration of dialysis ($\pm$1 yr), primary cause of ESRD (diabetes, hypertension, glomerulonephritis, or other), and the cumulative dosage and type of intravenous vitamin D product used during the 6-mo period before the PTX date (both calcitriol and Zemplar dosage: no use, dosage $\pm$ 36 μg for calcitriol, or dosage $\pm$ 180 μg for Zemplar). Whenever possible, three control patients were matched to each PTX patient. When three qualified control patients could not be identified, the maximum number of qualifying control patients were used. PTX patients who were unable to be matched ($n = 518$) were excluded from analyses.

Ascertainment of the Outcome

The primary study outcome was hip fracture, defined by ICD-9-CM codes 820.xx and 733.14, which correspond to fractures of the femoral neck. We also examined other fracture types that have been related to osteoporosis in the general population, specifically vertebral fractures excluding the cervical spine (ICD-9-CM codes 805.2x to 805.7x and 733.13) and fractures of the distal radius and wrist (ICD-9-CM codes 813.4x to 813.5x, 814.0x to 814.1x, and 733.12).[30,31] Hospitalization data were complete through 2003.

Ascertainment of Other Study Data

Demographics; baseline clinical information; and longitudinal data regarding dialysis modality, Medicare payer status, and hospitalizations were obtained from USRDS Standard Analysis Files. To account further for preoperative comorbidity status, we ascertained prevalent CHD and the total number of hospitalized days during the 1-yr period before PTX. CHD was defined as a previous hospitalizations for myocardial infarction, angina, ischemic heart disease, percutaneous transluminal coronary angioplasty, or coronary artery bypass grafting from the start of dialysis. Potential differences in comorbidity between PTX and matched control groups were further examined by calculation of the Charlson comorbidity index from hospitalization discharge data during the year before the PTX date.[32] The Charlson index differentially weighs 17 diagnostic categories to create a continuous comorbidity score.

Intravenous vitamin D use was determined from monthly Medicare institutional claims obtained from the USRDS. Calcitriol and paricalcitol were defined by Healthcare Common Procedure Coding System codes J0635 and J2500, respectively. The date and number of billed units of each intravenous vitamin D preparation were abstracted from each monthly claim. Intravenous vitamin D use was calculated for PTX procedures beginning in 1995, corresponding to widespread use of intravenous vitamin D in US dialysis centers.

Determination of Risk Time

Each matched group, consisting of one PTX patient and up to three matched control patients, began accruing risk time on the PTX date. Patients were considered at risk until the first occurrence of a fracture outcome or their data were censored as a result of death, loss to follow-up, or loss of Medicare coverage or the study ended on December 31, 2003. Patients were considered to be lost to follow-up by the USRDS when they received no dialysis billing claims for 1 consecutive year without a notification of death. For patients who were determined to be lost to follow-up, the last date of dialysis billing claims was considered to be the last date of follow-up.

Statistical Analyses

Baseline patient characteristics were tabulated with respect to PTX status. Unadjusted fracture rates were calculated as the number of incident fractures divided by the number of person-years of risk. Fracture rates were examined separately for categories of elapsed time from PTX. A 0- to 90-d category was chosen *a priori* to reflect the early postoperative period. A square-root variance stabilizing transformation was used to obtain variance estimates and 95% CI for fracture rates.[33] The cumulative incidence of hip fracture was plotted for PTX patients and matched control patients as a function of follow-up time using the Kaplan-Meier method for censored data.

Separate Cox proportional hazards models were used to evaluate the association of PTX with the relative risk for each fracture type. To account for potential residual differences in continuous variables from the matching process and for possible differences that arise as a result of variation in the number of matched control patients, we adjusted models for the matching covariates, along with prevalent CHD status, the number of hospitalized days during the year before PTX, and the Charlson comorbidity index. Patients were analyzed according to their dialysis modality at the time of PTX (hemodialysis) regardless of subsequent changes in modality.

Sensitivity analyses evaluated whether the estimated association of PTX with fracture risk remained consistent after (*1*) exclusion of patients who required a repeat PTX, (*2*) restriction of analyses to PTX patients and matched control patients who used any intravenous vitamin D during the 6-mo period before PTX, and (*3*) adjustment for vitamin D dosage after PTX as a time-varying covariate. For the last, intravenous calcitriol and paricalcitol use during the previous 6 mo were updated monthly, then lagged by 1 mo to avoid potential altered patterns of vitamin D use as a result of impending deterioration of health status. The difference in partial likelihoods from nested Cox models was used to evaluate whether the association of PTX with fracture differed according to age, gender, race, diabetes, and geographic region. Analyses were performed using Stata version 8 (Stata Corp, College Station, TX), SAS version 8.2 (SAS Institute, Cary, NC), and S-PLUS version 6.1 (Insightful, Seattle, WA).

DISCLOSURES

This study was supported by National Institutes of Health Career Development Award K23 DK63274-01 Amgen Corp. grant "Hip Fracture Rates among Chronic Dialysis Patients."

REFERENCES

1. Danese MD, Kim J, Doan QV, Dylan M, Griffiths R, Chertow GM: PTH and the risks for hip, vertebral, and pelvic fractures among patients on dialysis. *Am J Kidney Dis* 47: 149–156, 2006
2. Goodman WG, Goldin J, Kuizon BD, Yoon C, Gales B, Sider D, Wang Y, Chung J, Emerick A, Greaser L, Elashoff RM, Salusky IB: Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. *N Engl J Med* 342: 1478–1483, 2000
3. Jadoul M, Albert JM, Akiba T, Akizawa T, Arab L, Bragg-Gresham JL, Mason N, Prutz KG, Young EW, Pisoni RL: Incidence and risk factors for hip or other bone fractures among hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study. *Kidney Int* 70: 1358–1366, 2006
4. Raggi P, Boulay A, Chasan-Taber S, Amin N, Dillon M, Burke SK, Chertow GM: Cardiac calcification in adult hemodialysis patients. A link between end-stage renal disease and cardiovascular disease? *J Am Coll Cardiol* 39: 695–701, 2002
5. Kestenbaum B, Seliger SL, Gillen DL, Wasse H, Young B, Sherrard DJ, Weiss NS, Stehman-Breen CO: Parathyroidectomy rates among United States dialysis patients: 1990–1999. *Kidney Int* 65: 282–288, 2004
6. Stracke S, Jehle PM, Sturm D, Schoenberg MH, Widmaier U, Beger HG, Keller F: Clinical course after total parathyroidectomy without autotransplantation in patients with end-stage renal failure. *Am J Kidney Dis* 33: 304–311, 1999
7. Coen G, Calabria S, Bellinghieri G, Pecchini F, Conte F, Chiappini MG, Ferrannini M, Lagona C, Mallamace A, Manni M, DiLuca M, Sardella D, Taggi F: Parathyroidectomy in chronic renal failure: Short- and long-term results on parathyroid function, blood pressure and anemia. *Nephron* 88: 149–155, 2001
8. Gagne ER, Urena P, Leite-Silva S, Zingraff J, Chevalier A, Sarfati E, Dubost C, Drueke TB: Short- and long-term efficacy of total parathyroidectomy with immediate autografting compared with subtotal parathyroidectomy in hemodialysis patients. *J Am Soc Nephrol* 3: 1008–1017, 1992
9. Brasier AR, Nussbaum SR: Hungry bone syndrome: Clinical and biochemical predictors of its occurrence after parathyroid surgery. *Am J Med* 84: 654–660, 1988
10. Abdelhadi M, Nordenstrom J: Bone mineral recovery after parathyroidectomy in patients with primary and renal hyperparathyroidism. *J Clin Endocrinol Metab* 83: 3845–3851, 1998
11. Chou FF, Chen JB, Lee CH, Chen SH, Sheen-Chen SM: Parathyroidectomy can improve bone mineral density in patients with symptomatic secondary hyperparathyroidism. *Arch Surg* 136: 1064–1068, 2001
12. Yano S, Sugimoto T, Tsukamoto T, Yamaguchi T, Hattori T, Sekita KI, Kaji H, Hattori S, Kobayashi A, Chihara K: Effect of parathyroidectomy on bone mineral density in hemodialysis patients with secondary hyperparathyroidism: Possible usefulness of preoperative determination of parathyroid hormone level for prediction of bone regain. *Horm Metab Res* 35: 259–264, 2003
13. Hercz G, Pei Y, Greenwood C, Manuel A, Saiphoo C, Goodman WG, Segre GV, Fenton S, Sherrard DJ: Aplastic osteodystrophy without aluminum: The role of "suppressed" parathyroid function. *Kidney Int* 44: 860–866, 1993
14. Taal MW, Masud T, Green D, Cassidy MJ: Risk factors for reduced bone density in haemodialysis patients. *Nephrol Dial Transplant* 14: 1922–1928, 1999
15. Wang M, Hercz G, Sherrard DJ, Maloney NA, Segre GV, Pei Y: Relationship between intact 1-84 parathyroid hormone and bone histomorphometric parameters in dialysis patients without aluminum toxicity. *Am J Kidney Dis* 26: 836–844, 1995
16. Atsumi K, Kushida K, Yamazaki K, Shimizu S, Ohmura A, Inoue T: Risk factors for vertebral fractures in renal osteodystrophy. *Am J Kidney Dis* 33: 287–293, 1999
17. Coco M, Rush H: Increased incidence of hip fractures in dialysis patients with low serum parathyroid hormone. *Am J Kidney Dis* 36: 1115–1121, 2000
18. Black DM, Bilezikian JP, Ensrud KE, Greenspan SL, Palermo L, Hue T, Lang TF, McGowan JA, Rosen CJ: One year of alendronate after one year of parathyroid hormone (1-84) for osteoporosis. *N Engl J Med* 353: 555–565, 2005
19. Cosman F, Nieves J, Zion M, Woelfert L, Luckey M, Lindsay R: Daily and cyclic parathyroid hormone in women receiving alendronate. *N Engl J Med* 353: 566–575, 2005
20. Abugassa S, Nordenstrom J, Eriksson S, Mollerstrom G, Alveryd A: Skeletal remineralization after surgery for primary and secondary hyperparathyroidism. *Surgery* 107: 128–133, 1990
21. Silverberg SJ, Gartenberg F, Jacobs TP, Shane E, Siris E, Staron RB, McMahon DJ, Bilezikian JP: Increased bone mineral density after parathyroidectomy in primary hyperparathyroidism. *J Clin Endocrinol Metab* 80: 729–734, 1995
22. Nordenstrom E, Westerdahl J, Bergenfelz A: Recovery of bone mineral density in 126 patients after surgery for primary hyperparathyroidism. *World J Surg* 28: 502–507, 2004
23. Hruska KA, Teitelbaum SL: Renal osteodystrophy. *N Engl J Med* 333: 166–174, 1995
24. Rault R, Magnone M: The effect of parathyroidectomy on hematocrit and erythropoietin dose in patients on hemodialysis. *ASAIO J* 42: M901–M903, 1996
25. Chou FF, Lee CH, Chen JB: General weakness as an indication for parathyroid surgery in patients with secondary hyperparathyroidism. *Arch Surg* 134: 1108–1111, 1999
26. Peters BS, Jorgetti V, Martini LA: Body composition changes in haemodialysis patients with secondary hyperparathyroidism after parathyroidectomy measured by conventional and vector bioimpedance analysis. *Br J Nutr* 95: 353–357, 2006
27. Yasunaga C, Nakamoto M, Matsuo K, Nishihara G, Yoshida T, Goya T: Effects of a parathyroidectomy on the immune system and nutritional condition in chronic dialysis patients with secondary hyperparathyroidism. *Am J Surg* 178: 332–336, 1999
28. Malluche HH, Monier-Faugere MC: Risk of adynamic bone disease in dialyzed patients. *Kidney Int Suppl* 38: S62–S67, 1992
29. US Renal Data System: *Annual Data Report Atlas*, Bethesda, National Institute of Diabetes and Digestive and Kidney Disease, National Institutes of Health, 2001
30. Gage BF, Birman-Deych E, Radford MJ, Nilasena DS, Binder EF: Risk of osteoporotic fracture in elderly patients taking warfarin: Results from the National Registry of Atrial Fibrillation 2. *Arch Intern Med* 166: 241–246, 2006
31. Johnell O, Kanis J: Epidemiology of osteoporotic fractures. *Osteoporos Int* 16[Suppl 2]: S3–S7, 2005
32. Deyo RA, Cherkin DC, Ciol MA: Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol* 45: 613–619, 1992
33. Fisher VB: *Biostatistics: A Methodology for the Health Sciences*, New York, Wiley, 1993