Incidence and risk factors for hip or other bone fractures among hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study

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The available data on bone fractures in hemodialysis (HD) patients are limited to results of a few studies of subgroups of patients in the United States. This study describes the prevalence of hip fractures and the incidence and risk factors associated with hip and other fractures in representative groups of HD facilities ($n = 320$) and patients ($n = 12\,782$) from the 12 countries in the second phase of the Dialysis Outcomes and Practice Patterns Study (2002–2004). Among prevalent patients, 2.6% had a prior hip fracture. The incidence of fractures was 8.9 per 1000 patient years for new hip fractures and 25.6 per 1000 for any new fracture. Older age (relative risk $(RR)_{HIP} = 1.91$, $RR_{ANY} = 1.33$, $P < 0.0001$), female sex ($RR_{HIP} = 1.41$, $P = 0.02$; $RR_{ANY} = 1.59$, $P < 0.0001$), prior kidney transplant ($RR_{HIP} = 2.35$, $P = 0.04$; $RR_{ANY} = 1.76$, $P = 0.007$), and low serum albumin ($RR_{HIP} = 1.85$, $RR_{ANY} = 1.45$, per 1 g/dl lower, $P < 0.0001$) were predictive of new fractures. Elevated risk of new hip fracture was observed for selective serotonin reuptake inhibitors and combination narcotic medications (RR = 1.63, RR = 1.74, respectively, $P < 0.05$). Several medications were associated with risk of any new fracture: narcotic pain medications (RR = 1.67, $P = 0.02$), benzodiazepines (RR = 1.31, $P = 0.03$), adrenal cortical steroids (RR = 1.40, $P < 0.05$), and combination narcotic medications (RR = 1.72, $P = 0.001$). Parathyroid hormone (PTH) levels >900 pg/ml were associated with an elevated risk of any new fracture (RR = 1.72, $P < 0.05$) versus PTH 150–300. The results suggest that greater selectivity in prescribing several classes of psychoactive drugs and more efficient treatment of secondary hyperparathyroidism may help reduce the burden of fractures in HD patients.

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The available data on risk factors for hip and other bone fractures in hemodialysis (HD) patients remains restricted to a few studies on selected subgroups of patients in the United States (US).[1–4] We took advantage of the prospective gathering of data on this topic in the second phase of the Dialysis Outcomes and Practice Patterns Study (DOPPS II) to investigate this substantial cause of morbidity and mortality in HD patients across 12 countries. We hypothesized that both severe hyperparathyroidism and various drugs, especially psychoactive medications known to cause falls and fractures in elderly non-uremics, would be independent risk factors for bone fractures in HD patients.

RESULTS

Across all 12 countries participating in the DOPPS II, 2.6% of the prevalent cross-section of patients had a prior hip fracture, with less than a threefold difference between the highest (3.9% in France) and the lowest (1.4% in Germany) country prevalence of history of prior hip fracture (Table 1). In the US, 2.7% of patients had a prior hip fracture. The overall unadjusted incidence of new hip fracture events was 8.9 per 1000 patient years at risk (95% confidence interval (CI) = 8.4–9.4 per 1000 patient years), whereas the incidence of new fracture events of any type was 25.6 per 1000 patient years (95% CI = 24.4–27.0 per 1000 patient years). The incidence of these events in the US was modestly higher than the incidence overall, with 9.9 hip fractures per 1000 patient years (95% CI = 8.9–11.1 per 1000 patient years) and 24.8 fractures of any type per 1000 patient years (95% CI = 22.5–27.5 per 1000 patient years). Outside the US, the incidence of these events was 8.6 hip fractures per 1000 patient years (95% CI = 8.0–9.2 per 1000 patient years) and 25.9 fractures of any type per 1000 patient years (95% CI = 24.4–27.4 per 1000 patient years).

In multivariable logistic regression models, a variety of baseline patient characteristics and treatment parameters were significantly associated with having a prior hip fracture (Table 2). After controlling for an array of demographic, comorbidity, and laboratory factors, Spain and Sweden had significantly lower adjusted odds ratios (AORs) of a patient having a prior hip fracture (AOR = 0.41 and 0.45, respectively, $0.05 < P < 0.01$) compared with the US; no countries exhibited a significantly greater likelihood of a patient having a prior hip fracture than the US (data not shown). Among the demographic factors associated with a higher likelihood of having a prior hip fracture were greater age (AOR = 1.17 per 10 years older, $P = 0.02$), female sex (AOR = 1.56, $P = 0.002$), non-black versus black race (AOR = 1.96, $P = 0.02$), lower body mass index (BMI) (1.05 per 1 unit lower, $P = 0.004$), and a greater number of years on dialysis (AOR = 1.07 per 1 year longer, $P < 0.0001$). Patients who needed assistance to walk or who resided in a nursing home also had a higher likelihood of having a prior hip fracture (AOR = 3.05, $P < 0.0001$ and AOR = 1.75, $P = 0.02$, respectively). Examining categories of age by sex revealed that the adjusted odds of prior hip fracture did not differ significantly in older male subjects compared with male subject aged 18–54. However, among female subjects, the adjusted odds of having a prior hip fracture were progressively greater with age, becoming significantly greater for females aged 65–74 and $\geqslant 75$ (AOR = 1.89 and 2.69, respectively, $P < 0.05$) compared with females aged 18–54.

In general, comorbid conditions were not found to correlate with prior hip fracture, although the occurrence of certain prior events such as prior parathyroidectomy (AOR = 1.70, $P = 0.02$) and the presence of specific conditions such as carpal tunnel syndrome or β2-microglobulin disorder (AOR = 1.79, $P = 0.007$) were associated with higher odds of prior hip fracture. With respect to serum phosphorus levels, associations with prior hip fracture were only observed among patients with a phosphorus level of $\geqslant 5.5$ mg/dl (AOR = 0.67 versus 3.5–4.49 mg/dl, $P = 0.03$). Similarly, with serum calcium, the overall trend was not significant; however, patients with calcium of $\geqslant 10.2$ mg/dl had greater odds of having had a prior hip fracture (AOR = 1.57 versus 8.4–9.5 mg/dl, $P = 0.02$). Significantly greater odds of prior hip fracture were observed among patients with a serum albumin $\leqslant 3.3$ g/dl (AOR = 1.65 versus > 4.0 g/dl, $P = 0.05$). As a continuous predictor, lower albumin tended to be associated with higher odds of hip fracture, although the results only approached statistical significance (AOR = 1.23 per 1 g/dl lower, $P = 0.12$). Compelling baseline factors that were not associated with prior hip fracture were PTH and bicarbonate levels, and prior kidney transplant.

Throughout follow-up in all 12 countries, there were 174 new hip fracture events and 489 reported fractures of any type. Using this information along with the corresponding hospital admission or event occurrence dates, we analyzed the time from enrollment to first reported occurrence of either hip fracture or fracture of any type. Eleven percent of new hip fracture events occurred among patients with a reported prior hip fracture before enrollment. Model results were substantially equivalent regardless of whether the prospective analyses controlled for a patient's history of hip fracture or were restricted to patients without a prior hip fracture. The results presented herein are those from prospective analyses controlling for patient's history of hip fracture. Not surprisingly, prior hip fracture was highly correlated with greater risk of a new hip fracture (RR = 4.52, $P < 0.0001$) and fracture of any type (RR = 3.17, $P < 0.001$) (Table 3).

Older age ($RR_{HIP} = 1.91$, $P < 0.0001$; $RR_{ANY} = 1.33$, $P < 0.0001$) and female sex ($RR_{HIP} = 1.41$, $P = 0.02$; $RR_{ANY} = 1.59$, $P < 0.0001$) were highly predictive of both new hip fractures and fractures of any type. Analyzing age by sex confirmed these findings and also demonstrated that the RR of new fractures with older age was especially pronounced

Table 1 | Prevalence of prior hip fracture and incidence of new hip fracture and fracture of any type

	Hip fracture		
Country	Prevalence[a] of history of hip fracture (%)	Incidence[b] of new hip fracture (95% CI)	Incidence[b] of any new fracture (95% CI)
Australia–New Zealand	2.5	10.2 (8.1, 12.9)	30.6 (25.0, 37.6)
Belgium	3.7	15.7 (12.7, 19.3)	40.8 (33.8, 49.3)
Canada	3.8	8.6 (7.0, 10.7)	29.6 (24.5, 35.6)
France	3.9	11.4 (9.0, 14.4)	23.1 (18.7, 28.5)
Germany	1.4	7.2 (5.8, 9.1)	20.6 (16.8, 25.2)
Italy	3.1	8.1 (6.5, 10.1)	21.0 (17.2, 25.8)
Japan	2.2	4.9 (4.3, 5.7)	23.3 (20.6, 26.3)
Spain	1.6	6.7 (5.4, 8.2)	14.2 (11.6, 17.4)
Sweden	2.4	15.1 (12.3, 18.7)	42.3 (35.0, 51.1)
UK	2.3	5.1 (4.0, 6.5)	20.4 (16.5, 25.3)
US[c]	2.7	9.9 (8.9, 11.1)	24.8 (22.5, 27.5)
All DOPPS[d]	2.6	8.9 (8.4, 9.4)	25.6 (24.4, 27.0)

CI, confidence interval; DOPPS, Dialysis Outcomes and Practice Patterns Study.
[a]Among prevalent cross-section of patients (n=9089).
[b]Incidence=per 1000 patient years (patyrs) at risk, among all patients (n=12 782).
[c]US-DOPPS: 44 hip fractures (4328 patyrs at risk), 108 any fractures (4266 patyrs at risk).
[d]All DOPPS: 174 hip fractures (18 664 patyrs at risk), 489 any fractures (18 345 patyrs at risk).

Table 2 | Associations between history of hip fracture and baseline patient characteristics

Characteristic *(n/N pts)*	Adjusted odds ratio of history of hip fracture (95% CI)
Age, per 10 years older (*N*=9089)	1.17* (1.03, 1.32)
Female, versus male (3871/9089)	1.56** (1.18, 2.07)
Male, 18–54 (1575/9089)	1.00 (Ref.)
Male, 55–64 (1152/9089)	1.12 (0.59, 2.14)
Male, 65–74 (1381/9089)	1.34 (0.78, 2.37)
Male, ⩾75 (1110/9089)	0.87 (0.44, 1.72)
Female, 18–54 (1022/9089)	0.94 (0.53, 1.67)
Female, 55–64 (850/9089)	1.32 (0.70, 2.51)
Female, 65–74 (1082/9089)	1.89* (1.14, 3.15)
Female, ⩾75 (917/9089)	2.69** (1.52, 4.78)
Non-black race, versus black race (8238/9089)	1.96* (1.12, 3.45)
BMI, per 1 unit lower	1.05** (1.02, 1.09)
⩽21.6 (2823/8554)	1.39 (0.99, 1.96)
21.7–25.8 (2861/8554)	1.00 (Ref.)
>25.8 (2870/8554)	0.75 (0.52, 1.08)
Years on dialysis, per 1 year longer	1.07*** (1.04, 1.09)
⩽0.5 yrs (1052/9018)	1.00 (Ref.)
0.6–0.99 yrs (874/9018)	1.92 (0.78, 4.75)
1.0–1.99 yrs (1522/9018)	2.86* (1.44, 5.69)
2.0–2.99 yrs (1162/9018)	2.51* (1.17, 5.37)
3.0–3.99 yrs (917/9018)	3.20** (1.51, 6.76)
⩾4.0 yrs (3491/9018)	3.85*** (1.95, 7.59)
Prior transplant, yes versus no (626/9089)	1.52 (0.84, 2.75)
Prior parathyroidectomy, yes versus no (610/8978)	1.70* (1.06, 2.74)
Needs assistance to walk, yes versus no (2131/8798)	3.05*** (2.20, 4.24)
Resides in nursing home, yes versus no (459/8819)	1.75* (1.10, 2.77)
Phosphorus, per 1 mg/dl lower	1.06 (0.96, 1.17)
<3.5 (847/8580)	1.10 (0.72, 1.67)
3.50–4.49 (1613/8580)	1.00 (Ref.)
4.50–5.49 (2062/8580)	0.71 (0.48, 1.05)
⩾5.50 (4058/8580)	0.67* (0.47, 0.96)
Calcium, per 1 mg/dl higher	1.17 (0.99, 1.39)
<8.4 (636/7828)	1.02 (0.53, 1.96)
8.4–9.5 (3125/7828)	1.00 (Ref.)
9.6–10.1 (2275/7828)	1.10 (0.75, 1.60)
⩾10.2 (1792/7828)	1.57* (1.07, 2.31)
Albumin, per 1 g/dl lower	1.23 (0.94, 1.64)
⩽3.30 (1387/8206)	1.65* (>1.00, 2.72)
3.31–3.60 (1956/8206)	1.46 (0.91, 2.35)
3.61–3.80 (1317/8206)	1.22 (0.72, 2.07)
3.81–4.00 (1703/8206)	1.33 (0.79, 2.24)
>4.00 (1843/8206)	1.00 (Ref.)
PTH, per 200 pg/ml higher (*N*=6225)	1.00 (0.92, 1.09)
Bicarbonate, per 1 mEq/l higher (*N*=5757)	1.03 (0.99, 1.08)
Comorbid conditions, yes versus no	
Carpal tunnel syndrome or β2-microglobulin disorder (929/9005)	1.79** (1.17, 2.74)
Coronary artery disease (4127/9089)	0.89 (0.65, 1.22)
Cancer, other than skin (1055/8950)	1.16 (0.78, 1.74)
Other cardiovascular disease (3271/9023)	1.23 (0.91, 1.65)
Cerebrovascular disease (1544/9006)	1.08 (0.75, 1.57)
Congestive heart failure (2632/9002)	1.12 (0.83, 1.49)
Diabetes mellitus (3104/9012)	1.09 (0.79, 1.52)
Gastrointestinal bleeding (524/8985)	1.29 (0.79, 2.10)
Hypertension (7043/8993)	1.10 (0.77, 1.58)
Lung disease (969/9012)	1.23 (0.83, 1.83)
Dementia (266/8997)	1.08 (0.60, 1.94)
Other neurologic disorder (869/9010)	1.37 (0.93, 2.03)
Psychiatric disorder (1719/9013)	1.31 (0.97, 1.75)
Peripheral vascular disease (2362/9014)	1.19 (0.86, 1.64)
Recurrent cellulitis (726/8979)	0.90 (0.55, 1.46)

CI, confidence interval; BMI, body mass index; PTH, parathyroid hormone; yrs, years. *$0.01 < P \leqslant 0.05$; **$0.0001 < P \leqslant 0.01$; *** $P \leqslant 0.0001$.
DOPPS II data (2002–2004) among prevalent cross-section of patients; n/N=number of patients with given characteristic/number of patients for whom data on that characteristic were available. Logistic models controlled for effects of facility clustering and adjusted for all factors listed in Table 2 – continuous and categorical variables run in separate models.

among females (Table 3). Patients with a prior kidney transplant also exhibited a higher RR of both new hip fractures (RR = 2.35, $P = 0.04$) and fractures of any type (RR = 1.76, $P = 0.007$). Lower serum albumin as a continuous measure correlated with higher RR of both new hip fractures (RR = 1.85 per 1 g/dl lower, $P < 0.0001$) and fractures of any type (RR = 1.45 per 1 g/dl lower, $P < 0.0001$). Confirmation of this trend for serum albumin was clearly demonstrated upon analyzing approximate quintiles of albumin levels, with the greatest risk occurring among patients with albumin ⩽3.3 g/dl ($RR_{HIP} = 3.59$, $RR_{ANY} = 1.91$, both $P \leqslant 0.00001$) versus albumin >4.0 g/dl (Table 3). Factors significantly associated with RR of a new hip fracture that were *not* predictive of fractures of any type included congestive heart failure (RR = 1.46, $P = 0.04$) and lung disease (RR = 0.59, $P = 0.04$). Conversely, factors associated with RR of a new fracture of any type, but not of a new hip fracture, included non-black (RR = 1.79, $P = 0.01$) versus black race, lower BMI (RR = 1.02 per 1 unit, $P = 0.03$), several categories of years on HD, PTH > 900 (RR = 1.72, $P = 0.03$) versus 150–300 pg/ml, and neurologic disorders other than dementia (RR = 0.67, $P = 0.02$) (Table 3, Figure 2).

In prospective Cox models that adjusted only for age, sex, country, and one medication at a time (univariate models), a significantly higher RR of both types of new fracture events was observed for several classes of medications, including adrenal cortical steroids (e.g., prednisone, hydrocortisone, and methylprednisolone), any type of antidepressant (AD) medication (including general AD medications, miscellaneous AD medications, selective serotonin reuptake inhibitors (SSRIs), tricyclics, and monoamine oxidase inhibitors), the SSRI class of AD medications in particular (e.g., sertraline, citalopram, paroxetine, and fluoxetine), combination narcotic medications (e.g., acetaminophen–codeine, acetaminophen–hydrocodone, and acetaminophen–oxycodone), and narcotic pain medications (e.g., oxycodone, morphine, and codeine). Furthermore, in these univariate models benzodiazepines (e.g., lorazepam, temazepam, and diazepam), the nonspecific class of miscellaneous anticonvulsants (e.g., gabapentin, carbamazepine, and lamotrigine), and multivitamins (nonspecific over-the-counter multivitamin preparations), but not statins or beta-blocking

Table 3 | Associations between patient characteristics and RR of new hip fracture or new fracture of any type

Characteristic *(n/N pts)*	RR of hip fracture (95% CI)	RR of any fracture (95% CI)
Prior hip fracture (258/12,552)	4.52*** (2.57, 7.97)	3.17*** (2.13, 4.70)
Age, per 10 years older (*N*=12,782)	1.91*** (1.63, 2.25)	1.33*** (1.23, 1.45)
Female, versus male (5342/12,782)	1.41* (1.04, 1.89)	1.59*** (1.32, 1.92)
Male, 18–54 (2197/12,782)	1.00 (Ref.)	1.00 (Ref.)
Male, 55–64 (1622/12,782)	2.15* (1.01, 4.57)	1.25 (0.84, 1.85)
Male, 65–74 (1956/12,782)	2.38* (1.07, 5.26)	1.65* (1.10, 2.48)
Male, ⩾75 (1664/12,782)	5.05*** (2.36, 10.82)	1.86** (1.24, 2.77)
Female, 18–54 (1420/12,782)	0.85 (0.30, 2.35)	1.07 (0.67, 1.69)
Female, 55–64 (1133/12,782)	1.85 (0.75, 4.59)	2.36*** (1.56, 3.54)
Female, 65–74 (1488/12,782)	4.67*** (2.22, 9.83)	2.58*** (1.79, 3.63)
Female, ⩾75 (1301/12,782)	7.79*** (3.69, 16.43)	3.43*** (2.33, 5.06)
Non-black race, versus black race (11614/12,782)	2.02 (0.93, 4.34)	1.79* (1.14, 2.78)
BMI, per 1 unit lower	1.03 (0.99, 1.07)	1.02* (1.01, 1.04)
⩽21.6 (3634/11,747)	1.04 (0.72, 1.50)	1.18 (0.93, 1.49)
21.7–25.8 (3967/11,747)	1.00 (Ref.)	1.00 (Ref.)
>25.8 (4146/11,747)	0.78 (0.51, 1.18)	1.04 (0.83, 1.32)
Years on dialysis, per 1 year longer	1.02 (0.99, 1.06)	1.01 (0.99, 1.03)
⩽0.5 yrs (4625/12,709)	1.00 (Ref.)	1.00 (Ref.)
0.6–0.99 yrs (888/12,709)	1.04 (0.57, 1.90)	1.16 (0.79, 1.65)
1.0–1.99 yrs (1548/12,709)	1.27 (0.78, 2.07)	1.36* (1.00, 1.79)
2.0–2.99 yrs (1177/12,709)	1.18 (0.69, 2.03)	1.68** (1.21, 2.27)
3.0–3.99 yrs (931/12,709)	0.90 (0.48, 1.69)	1.54* (1.09, 2.14)
⩾4.0 yrs (3540/12,709)	1.14 (0.74, 1.73)	1.53** (1.16, 2.04)
Prior transplant, yes versus no (693/12,782)	2.35* (1.03, 5.36)	1.76** (1.16, 2.66)
Prior parathyroidectomy, yes versus no (654/12,528)	1.19 (0.58, 2.43)	1.24 (0.86, 1.78)
Needs assistance to walk, yes versus no (3083/12,342)	1.39 (0.97, 1.99)	1.18 (0.95, 1.46)
Phosphorus, per 1 mg/dl lower	0.99 (0.89, 1.10)	1.04 (0.98, 1.11)
<3.5 (1174/11,743)	1.62 (0.94, 2.81)	1.29 (0.93, 1.77)
3.50–4.49 (2228/11,743)	1.00 (Ref.)	1.00 (Ref.)
4.50–5.49 (2828/11,743)	1.26 (0.78, 2.04)	0.98 (0.76, 1.29)
⩾5.50 (5513/11,743)	1.29 (0.81, 2.06)	0.98 (0.77, 1.31)
Calcium, per 1 mg/dl higher	1.00 (0.82, 1.22)	1.10 (0.97, 1.25)
<8.4 (1135/10,503)	0.93 (0.46, 1.87)	0.86 (0.58, 1.34)
8.4–9.5 (4427/10,503)	1.00 (Ref.)	1.00 (Ref.)
9.6–10.1 (2845/10,503)	0.91 (0.60, 1.36)	0.96 (0.74, 1.23)
⩾10.2 (2096/10,503)	1.08 (0.69, 1.68)	1.20 (0.92, 1.59)
Albumin, per 1 g/dl lower	1.85*** (1.41, 2.44)	1.45*** (1.25, 1.72)
⩽3.30 (2582/11,043)	3.59*** (1.77, 7.25)	1.91*** (1.39, 2.66)
3.31–3.60 (2601/11,043)	2.81** (1.39, 5.69)	1.59** (1.16, 2.21)
3.61–3.80 (1636/11,043)	3.06** (1.44, 6.54)	1.55* (1.08, 2.24)
3.81–4.00 (2042/11,043)	2.51* (1.19, 5.27)	1.29 (0.90, 1.85)
>4.00 (2182/11,043)	1.00 (Ref.)	1.00 (Ref.)
PTH, per 200 pg/ml higher	0.95 (0.79, 1.14)	1.09* (1.01, 1.17)
<150 (3523/8162)	1.27 (0.78, 2.06)	1.05 (0.80, 1.38)
150–300 (2267/8162)	1.00 (Ref.)	1.00 (Ref.)
301–600 (1524/8162)	1.19 (0.63, 2.26)	1.24 (0.88, 1.76)
601–750 (295/8162)	0.33 (0.05, 2.37)	0.86 (0.41, 1.77)
751–900 (185/8162)	0.62 (0.08, 4.87)	1.03 (0.35, 3.08)
>900 (368/8162)	1.14 (0.34, 3.80)	1.72* (1.02, 2.90)

BMI, body mass index; PTH, parathyroid hormone; RR, relative risk; yrs, years.
*$0.01 < P \leqslant 0.05$; **$0.0001 < P \leqslant 0.01$; ***$P \leqslant 0.0001$.
DOPPS II data (2002–2004); n/N=number of patients with given characteristic/number of patients for whom data on that characteristic were available. Cox models controlled for effects of facility clustering and adjusted for all factors listed in Table 3 – continuous and categorical variables run in separate models.

agents, were associated with a higher RR of new fractures of any type but not hip fracture events (Table 4).

In prospective Cox models that also adjusted for demographics, comorbidity, and laboratory measures (multivariable models), the significantly elevated association remained between RR of new hip fracture and both SSRI AD medications and combination narcotic medications (RR = 1.63 and RR = 1.74, respectively; both $P < 0.05$). Moreover, the following classes of medications remained significantly associated with RR of any type of fracture in the multivariable models: adrenal cortical steroids (RR = 1.40, $P < 0.05$), benzodiazepines (RR = 1.31, $P = 0.03$), multivitamins (RR = 1.22, $P = 0.02$), combination narcotic medications (RR = 1.72, $P = 0.001$), and narcotic pain medications (RR = 1.67, $P = 0.02$) (Table 4). Examination of the facility-level practice of prescribing multivitamins revealed no significant associations between new fractures and higher percentages of patients prescribed multivitamins within facilities.

DISCUSSION

This study has identified several new risk factors for hip and other bone fractures in HD patients. The extensive adjustment for comorbidity typical of DOPPS studies[5,6] and the consistency of the findings across 12 countries and four continents suggest promising opportunities for the prevention of bone fractures in HD patients.

A first new finding is the detection of an independent role of drugs in the onset of fractures. Previous evidence concerning this topic in end-stage renal disease (ESRD) patients was limited to the well-known deleterious impact of steroids on bone mass, probably accounting for the substantial risk of fractures in renal transplant recipients.[1] In addition to adrenal cortical steroids, our study further identified the use of SSRIs, benzodiazepines, narcotics, and multivitamins as independent risk factors for both hip and other bone fractures. Although the finding of a correlation with multivitamins very likely is a case of confounding by indication, the other findings, new in the ESRD population, are in line with numerous studies demonstrating a high risk of falling and attendant fracture in the elderly under benzodiazepines, ADs, or narcotics.[2,7–10]

While previous studies of the risk of fractures among HD patients focused almost exclusively on the determinants of bone disease (or osteopenia), our study broadens the perspective to potential risk factors for falling. Previous studies in the general population documented that risk factors for falling or a history of falling were strongly associated with the risk of subsequent fractures, even more strongly in some studies than the association between risk factors for osteoporosis or actual low-bone mineral density and the risk of subsequent fractures.[11–13] Our results are in line with a recent prospective study demonstrating a high incidence of falls among in-center Belgian HD patients.[14] Independent risk factors for falling included, among others, the intake of an AD, older age, diabetes, and the inability to successfully perform a simple walking test. While intake of any AD, frequently implicated in falls and fractures among the non-uremic elderly, was associated with a higher risk of falling in the earlier study, the risk of fractures in the present study was significantly associated with SSRI intake, and tended to be so with tricyclics, although not significantly. This difference may be due to residual confounding (despite the adjustment for many comorbid conditions in the DOPPS) with SSRIs being prescribed preferentially to frailer patients. Indeed, the published evidence from elderly non-uremics suggests that both classes of ADs (SSRIs and tricyclics) increase the risk of falls and fractures.[15,16] Alternatively, the much longer experience with tricyclics may reduce the associated risk (e.g., because lower dosages are prescribed). Overall, our findings do not contradict the importance of the effective treatment of depression, a poor prognostic marker in HD patients,[17] but underscore that drug treatment of depression should always carefully integrate the potential benefits and risks of such treatment.

Other drugs such as benzodiazepines, narcotics, and adrenal cortical steroids should also be prescribed for HD patients only after fully considering the potential risks and benefits associated with their intake.

Our study addressed for the first time the potential association of the use of statins with the risk of fracture in HD patients. A potential protective effect of statins was suggested by the recent finding of an association of a low-cholesterol serum level (potentially reflecting statin

Table 4 | RR of new fracture events, by patient baseline medication prescription

Medication	Patients, *N* (%)	Univariate[a] model		Multivariate[b] model	
		RR hip fracture	RR any fracture	RR hip fracture	RR any fracture
Adrenal cortical steroid	871 (6.9)	1.77*	1.65**	1.39	1.40*
Anticonvulsants, miscellaneous	490 (3.9)	1.37	1.54*	1.12	1.39
AD, any type	1,350 (10.7)	1.71*	1.43**	1.45	1.28
SSRI antidepressants	869 (6.9)	1.85*	1.48*	1.63*	1.31
Tricyclic antidepressants	334 (2.7)	1.54	0.95	1.20	0.85
Miscellaneous ADs	218 (1.7)	1.27	1.67	1.08	1.53
Benzodiazepines	2,171 (17.2)	1.28	1.41**	1.19	1.31*
Beta-blocking agents	3,793 (30.1)	0.92	0.94	0.85	0.90
Estrogen hormones – *females only*	171 (3.2)	1.84	1.64	1.72	1.47
Multivitamin preparations	6,024 (47.8)	1.04	1.25*	1.03	1.22*
Narcotic combinations	706 (5.6)	2.01**	1.94**	1.74*	1.72**
Narcotic pain medications	372 (3.0)	1.90*	1.98**	1.55	1.67*
(Anti-) Parkinson disease agents	134 (1.1)	0.90	0.75	1.03	0.89
Phenothiazine antipsychotics	151 (1.2)	1.13	1.79	1.15	1.81
Sedatives	303 (2.4)	1.53	1.40	1.32	1.25
Sedatives, miscellaneous	897 (7.1)	1.47	1.31	1.35	1.21
Statins	2,616 (20.8)	1.15	0.92	1.17	0.95

AD, antidepressants; RR, relative risk; SSRI, selective serotonin reuptake inhibitor.
*$0.01 < P \leq 0.05$; **$P \leq 0.01$.
DOPPS II data (2002–2004), among all patients (n=12 782); shown are results for medications prescribed to >1% of patients.
[a]Adjusted for one medication per model, plus age, sex, and country.
[b]Adjusted for one medication per model, plus age, sex, race, vintage, comorbidities, BMI, phosphorus, calcium, PTH, albumin, prior transplant, prior PTX, needing assistance to walk, and country.

treatment, not recorded in this study) with a lower risk of hospitalization for fracture,[18] as well as by the recent demonstration of a beneficial impact of pravastatin on bone turnover in uremic rats (Iwasaki-Ishizuka Y, Yamato H, and Fukagawa M. Pravastatin ameliorates suppressed bone formation in uremic rats with adynamic bone disease. *J Am Soc Nephrol* 2004; **15**: 8A). The evidence suggesting a protective effect of statins for fractures in the general population remains controversial. Indeed, whereas the results of case–control studies suggest a protective effect, the *post hoc* analysis of randomized controlled trials of statins prescribed for hypercholesterolemia do not suggest a protective role.[19] At any rate, our results indicating a modestly protective, yet statistically nonsignificant association do not suggest that statins should be prescribed to HD patients specifically with the hope of reducing their risk of fracture. Our study did not find any reduction of the risk of new hip or other fracture with the intake of beta-blocking agents, in contrast to recent data on non-uremics.[20] This discrepancy likely reflects the different pathophysiology of fractures and the variable adjustment for comorbidity in the respective studies. Finally, our study found a moderate but nonsignificant positive association of the risk of bone fracture with the intake of estrogens and significant direct association with multivitamins, both very likely explained by confounding by indication.

Another interesting finding is evidence suggesting that a high PTH level may be an independent risk factor for bone fractures. Stehman-Breen *et al.*[21] did not detect such an association in ESRD patients from the US in the Dialysis Morbidity and Mortality Study Wave 1. Coco *et al.*[3] observed that a low PTH level was associated with a higher risk of hip fracture in a cohort of some 1200 HD patients in the US. These discrepancies may result from the smaller size or limited adjustment for comorbidity in the previous studies, or alternatively from the availability of only a single PTH measurement for most patients, a limitation potentially obscuring an association of the burden of hyperparathyroidism over time with subsequent fractures. In addition, the results of Danese *et al.*[22] suggest that the relationship of PTH level to fracture may be U-shaped, a suggestion that we were unable to confirm. Our findings suggest that control of excessive hyperparathyroidism may contribute to reducing the incidence of bone fractures in HD patients. This suggestion is in line with the recent *post hoc* analysis demonstrating a reduction of the risk of fractures in patients randomized to cinacalcet versus placebo[4] and with a recent analysis of data from the Dialysis Morbidity and Mortality Study Waves 1, 3, and 4.[22]

Our study further confirms several risk factors for bone fractures already identified both in the general population and in the few prior studies on fractures in HD patients: low BMI, female sex, older age, non-black versus black race, a history of transplantation, length of time on HD, and a history of previous hip fracture.[1,3,21] Our study did not identify diabetes as an independent risk factor for hip or any fractures in HD patients. This is in agreement, for hip fractures, with the paper of Stehman-Breen *et al.*[21] on Dialysis Morbidity and Mortality Study Wave 1 HD patients, but not with that of Ball *et al.*,[1] from the same group, on wait-listed HD patients and transplant recipients. Similarly, in the general population, some[23,24] but not all[11] studies have identified diabetes as an independent risk factor for hip fractures. Clearly this area requires further investigation.

In addition to identifying new risk factors and confirming existing factors for bone fractures in HD patients, this study introduces several descriptive correlations between patient characteristics and prior hip fractures (Table 2). Direct interpretation of these results admittedly is limited, yet such retrospective associational analyses are informative as hypothesis-generating explorations. Although testing these hypotheses may be beyond the scope and ability of the present investigation, we present the information to the larger community, which may have additional supportive data or the means to effectively test the hypotheses these data suggest.

Finally, our results extend the available data on the incidence of hip fractures in HD patients. Previous studies reported a yearly incidence of about 1% among white ESRD patients in the US and 0.3% among wait-listed dialysis patients in the US.[1,25] The results of these studies were not generalizable as a result of the inclusion of only white patients in one and only wait-listed patients in the other, with patients drawn exclusively from the US in both cases. In our study, the yearly incidence of hip and any fracture was 0.89 and 2.6%, respectively, without significant differences between most DOPPS countries, after adjustment for comorbidity and demographics. The yearly incidence of hip fractures is markedly higher in HD patients than in the general population across all 12 DOPPS countries. Indeed, in the general population it ranges from 0.07 to 0.22% at a similar mean age (around 60–65 years).[26–28] Thus, our results extend to the worldwide community of HD patients the observation of a much higher risk of hip fracture in HD versus non-uremic patients. In fact, as illustrated for the US DOPPS and general populations (Figures 1 and 2), the hip fracture incidence for HD patients of both sexes is similar to the incidence observed among non-uremic subjects older by 10–20 years. This finding is not trivial in view of the more than doubling of the RR of death associated with a hip fracture in HD patients.[3,29]

The higher risk of hip fracture seen among HD patients than among the general population has many possible explanations. Our results demonstrating that an elevated PTH level, independent of serum calcium and phosphorus, increases the risk of fractures suggests that uremic osteodystrophy may be one of the explanations. The higher risk with longer time on dialysis may be related to both β2-microglobulin amyloidosis and chronic uremic osteodystrophy. However, the higher risk of hip fracture associated with HD likely reflects the higher risk of falling among HD patients than among non-uremics, in line with a recent study

on falls in HD patients.[14] Both polymedication (among other regimens with central nervous system active agents) and comorbid conditions that reduce muscle mass and lessen the ability to walk without assistance may be contributing factors.

Another possible explanation is that hyperhomocysteinemia plays a role in the onset of fractures. Two recent large prospective observational studies indeed found that a high homocysteine level was an independent risk factor for hip or osteoporotic (mainly hip/wrist) fractures in the US and the Netherlands.[12,30] That this relationship may be causal was recently supported by a trial demonstrating a much lower risk of hip fracture in hemiplegic patients randomized to folate and vitamin B12 than in those taking a placebo.[31] *Post hoc* analyses of ongoing randomized, controlled trials of folic acid supplementation in chronic kidney disease patients may shed additional light on this topic.

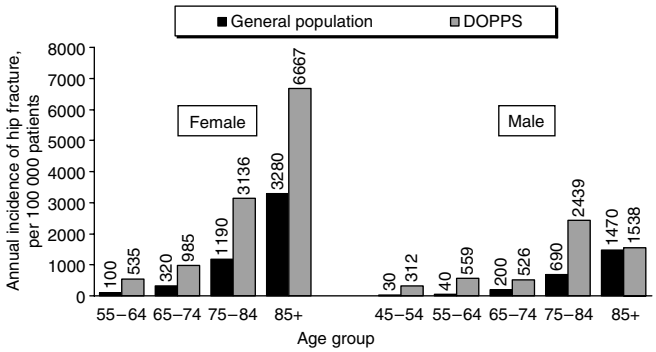

Figure 1 | Annual incidence of hip fracture, by age and sex. General population incidence estimates from US Department of Health and Human Services, Centers for Disease Control, National Center for Health Statistics, National Hospital Discharge Survey, year 2000; DOPPS incidence estimates based on a period-prevalent sample of patients and hospital admissions for hip fractures, 2002–2003.

Some limitations of the present study should be discussed. First, the validity of the diagnoses of fractures was not (and could not be) checked in this study. Fortunately, the diagnosis of bone fracture is usually quite easy with widely available skeletal *X*-rays, thus making a significant bias less likely. Second, whereas hip fractures were distinguishable from among all reported fracture-related events, other fracture types were less well defined and consequently analyzed collectively. Recognizably, the collective grouping of 'any type of fracture' includes those having differential degrees of structural and functional impairment. Should, however, the pathophysiology of fractures be markedly dependent on their location, the heterogeneity of 'any fractures' would have reduced, rather than increased, the power to detect risk factors. Finally, the medications taken by each patient were recorded only at inclusion in the study and

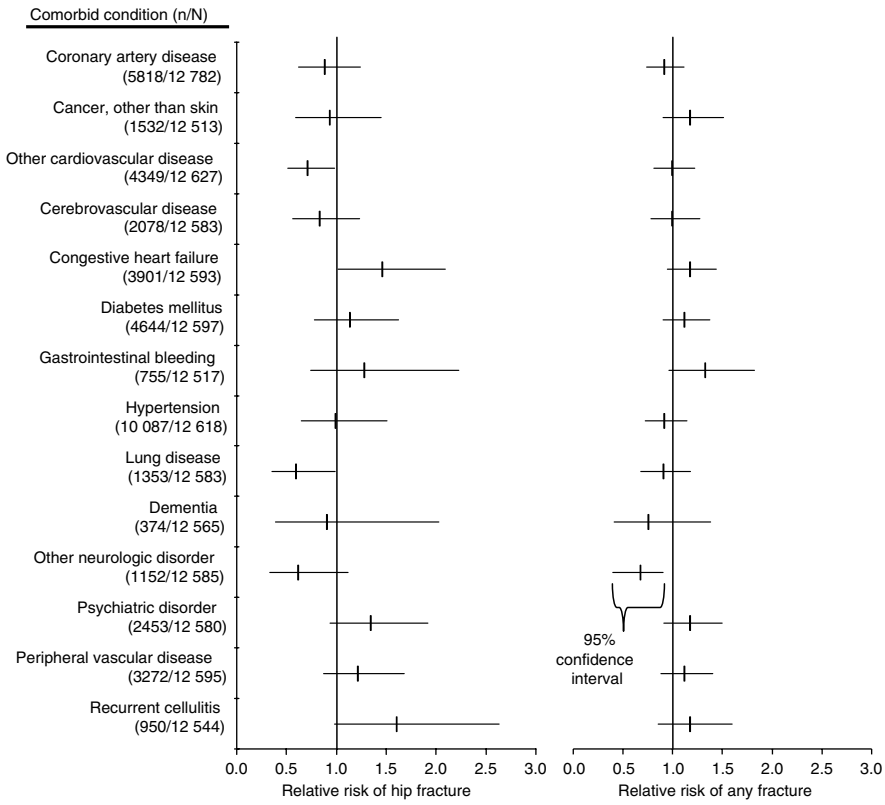

Figure 2 | Associations between RR of new fracture and comorbid conditions. DOPPS II data (2002–2004), among all patients. Cox models controlled for effects of facility clustering and all factors listed in Table 3 except the categorical counterparts of continuous measures (e.g., categories of age/sex, years on ESRD, BMI, laboratory values).

patient compliance with prescribed medication could not be verified. This limitation should, however, have tended to reduce (or blur) rather than increase the observed association between some drugs and the prospective risk of fracture, whereby an observed association is potentially understated relative to the 'true' association if patients precisely adhered to prescribed therapies. Thus, significant observations are especially supported despite any bias introduced by non-compliance, and weaker correlations might be demonstrably significant in the presence of a perfectly compliant study population.

In conclusion, our results suggest that more selective prescription of psychoactive medications such as benzodiazepines, SSRI ADs, and narcotic medications, as well as more effective treatment of severe hyperparathyroidism, are promising strategies to reduce the burden of hip and other bone fractures in HD patients.

MATERIALS AND METHODS

This study includes data gathered from 2002 to 2004 as part of DOPPS II, an international, prospective, observational study of HD practice patterns and their associated outcomes in 12 countries: Australia, Belgium, Canada, France, Germany, Italy, Japan, New Zealand, Spain, Sweden, the United Kingdom, and the US. Nationally representative samples of dialysis facilities ($n = 320$) were recruited in each country. Within each participating facility, a prevalent cross-sectional patient sample was obtained by randomly selecting 20–40 patients at the time the dialysis unit initiated data collection, and totaled 9089 across the 320 facilities in DOPPS II. Eligible patients were those aged 18 years or older and receiving chronic, maintenance HD therapy within each selected dialysis unit. Additionally, during the course of study participation, each facility sequentially enrolled (up to) the first 15 patients aged 18 years or older who had initiated chronic HD within the past 30 days ($n = 3693$). Institutional review boards in each country approved the study, and informed patient consent was obtained in accordance with local requirements. Further details regarding DOPPS study design, facility sampling, patient sampling, data collection, sample size determinations, and data management have been reported previously and are incorporated herein by reference.[5,32]

Medical record abstraction performed by facility staff was used to obtain baseline data regarding demographic factors, comorbid conditions, laboratory values, years since ESRD onset, and currently prescribed medications upon patient entry into the study, and similarly each patient's medical record was also assessed for occurrence of hip fracture, diagnosis of calciphylaxis, kidney transplant, and parathyroidectomy at or before entry into the study.

Hospitalizations and outpatient visits (including fracture-related visits) occurring during the study, along with diagnoses and procedures relevant to the hospitalization or outpatient visit, were reported chronologically for each patient. Such information was generally made available prospectively by way of in-center patient treatment records. Capturing both hospitalization events and outpatient visits provided a reasonable expectation that the vast majority of fracture-related events were recorded in this study. In the DOPPS data, hip fractures were distinguishable from among all reported fracture-related events, whereas fracture types other than hip fracture were less well defined and consequently analyzed collectively.

Primary analyses involving baseline patient characteristics associated with a history of hip fracture were restricted to the initial prevalent cross-sectional sample of 9089 patients. Statistical modeling of time to new occurrence of hip fracture and any fracture used the entire sample of 12 782 patients.

Statistical methods

Logistic regression was used to estimate associations between baseline patient characteristics and history of hip fracture, as indicated in the patients' medical records. For these associations multivariable models were used; these models accounted for facility clustering effects using robust standard error estimates and were adjusted for age, sex, race, BMI, years since ESRD onset, prior renal transplant, prior parathyroidectomy, inability to walk without assistance, residency in a nursing home, serum phosphorus, albumin-corrected serum calcium, serum albumin, intact PTH, serum bicarbonate, history of carpal tunnel syndrome or $\beta 2$ microglobulin disorder, 13 summary comorbid conditions (coronary artery disease, cerebrovascular disease, congestive heart failure, other cardiovascular disease, cancer other than of the skin, diabetes mellitus, gastrointestinal bleeding, hypertension, lung disease, psychiatric disorder, neurologic disorder other than dementia, peripheral vascular disease, and recurrent cellulitis or gangrene), dementia, and country. Serum calcium was corrected for serum levels of albumin by the following formula: Corrected calcium (mg/dl) = total calcium (mg/dl) + 0.8 × (4–serum albumin (g/dl)). The analyzed PTH data were based only on measurements from facilities reporting use of the intact molecule PTH assay type (approximately 90% of dialysis units). PTH values from facilities reporting use of an assay type other than intact molecule assay were not included in these analyses.

Cox proportional hazards regression models were used to assess relationships between patient characteristics and time to first reported occurrence of a new fracture event resulting in an inpatient hospitalization or an outpatient visit for fracture care. All Cox models accounted for facility clustering effects (using robust standard estimates based on the sandwich estimator) and were adjusted for having a history of hip fracture in addition to the factors included in the logistic regression analyses described above. Prospective associations between fracture events and a variety of medication classes also were investigated. For these analyses, time from enrollment to first reported occurrence of a new fracture event initially was evaluated using Cox models adjusted only for age, sex, country, and one medication class at a time. Additional covariates for demographics, comorbidities, and laboratory measures subsequently were added to adjust for case mix differences in these models, but still controlling for only one medication per model.

All statistical analyses were performed with SAS software, version 9.1 (SAS Institute; Cary, NC, USA).

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