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ORIGINAL ARTICLE

Greater risk of hip fracture in hemodialysis than in peritoneal dialysis

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Abstract
Summary Several differences may have existed between patients treated with peritoneal dialysis and hemodialysis because of the difference in dialysis modality. This nationwide population-based cohort study demonstrated that patients on hemodialysis had an increased risk of hip fracture compared to patients on peritoneal dialysis; the hazard ratio was 1.52.
Introduction Numerous debates on which dialysis modality is "superior" have taken place in recent decades. However, no large-scale study has ever mentioned about the relationship between dialysis modality and risk of hip fracture.
Methods We identified 64,124 incident end-stage renal disease patients from the National Health Insurance Research Database in Taiwan between 1998 and 2008, including 59,457 (92.72 %) hemodialysis (HD) and 4,667 (7.28 %) peritoneal dialysis (PD) patients. After 8:1 propensity score matching, 31,554 patients, of whom 28,048 were HD and 3,506 were PD patients, were included in the study. We conducted the Cox proportional hazards model to examine the effects of dialysis modality and other variables on hip fracture risk.
Results A total of 2,587 hip fractures were identified in 64,124 dialysis patients. The incidence rate of hip fracture was 13.60 per 1000 patient-years in the HD group and 6.25 in the PD group. Dialysis modality, sex, age, presence of cardiovascular disease, diabetes, medication with antiepileptic drugs, diuretics, steroids, and vitamin D had statistically significant associations with hip fracture. Patients on HD had an increased risk of hip fracture compared to patients on PD; the hazard ratio (HR) was 1.52 (95 % CI: 1.09–2.12, P=0.02).
Conclusions In this population-based cohort study, HD had a greater hip fracture risk compared to PD; the HR was 1.52. We should focus more on reducing the risk of hip fractures in hemodialysis patients.

Keywords Dialysis modality · Hemodialysis · Hip fracture · Osteoporosis · Peritoneal dialysis

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Introduction

Among osteoporotic fractures, hip fractures are associated with the highest morbidity and mortality; over 50 % of patients are institutionalized within the first year after a fracture [1]. The prevalence of osteoporotic hip fractures among dialysis patients is higher than that of the general population [2]. A retrospective study reported that the incidence of hip fractures among hemodialysis (HD) patients was 17.4 times higher than that of the general population and occurred at a younger age [3].

Approximately 90 % of patients with end-stage renal disease (ESRD) worldwide are maintained on HD, and 10 % are

maintained on peritoneal dialysis (PD) [4]. Numerous debates on which dialysis modality is "superior" have taken place in recent decades. However, no large-scale study has ever mentioned about the relationship between dialysis modality and risk of hip fracture. In a study of 242 patients with ESRD, patients on PD had the highest risk of 25-hydroxyvitamin D deficiency. Abnormalities in vitamin D metabolism and parathyroid hormone (PTH) secretion result in a change of the trabecular microarchitecture, thinning, and increased porosity of the cortical bone [5, 6]; thus, whether patients treated with PD have an increased risk of hip fracture must be assessed.

We examine the incidence of hip fracture in dialysis patients in Taiwan and compare the incidence and hazard ratio (HR) between HD and PD patients.

Materials and methods

Database and study population

The data in this study were obtained from the National Health Insurance Research Database (NHIRD) of the Taiwanese National Health Insurance (NHI) program, which is an electronic medical claims database. This database includes the medical records of all patients insured by the NHI in Taiwan. Approximately 99.59 % of Taiwan's population was insured by the end of 2009 [7]. All dialysis patients in Taiwan were registered in this database. This study was approved by the Institutional Review Board (IRB) of China Medical University.

Incident ESRD patients who underwent dialysis for more than 3 months and who were older than 50 years were selected from January 1998 to December 2008. Patients with missing data (376 patients), a history of previous hip fractures before dialysis (2,361 patients), and medicated with antiosteoporotic drugs before dialysis or hip fracture (311 patients) were excluded.

A total of 64,124 incident ESRD patients comprised the unmatched cohort: 59,457 (92.72 %) HD and 4667 (7.28 %) PD patients (Table 1).

Ascertainment of dialysis modality

PD patients may initially receive temporary HD. Thus, dialysis modality was defined as the modality at day 90 after the first dialysis (intent-to-treat).

Ascertainment of hip fracture

The number of hip fractures that occurred during follow-up was determined using information in the NHIRD hospitalization files, which include data on inpatient hospital stays. Hospitalization data were considered from 1 January 1998 to 31 December 2008. Hip fractures were identified using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes indicating cervical, intertrochanteric, or subtrochanteric hip fractures.

Table 1 Total numbers of dialysis patients from 1998 to 2008

	N (%)	HD *N* (%)	PD *N* (%)
Total	64,124 (100)	59,457 (92.72)	4667 (7.28)
Year			
1998	4,543 (7.08)	4,387 (96.57)	156 (3.43)
1999	4,533 (7.07)	4,302 (94.90)	231 (5.10)
2000	4,738 (7.39)	4,460 (94.13)	278 (5.87)
2001	5,091 (7.94)	4,794 (94.17)	297 (5.83)
2002	5,776 (9.01)	5,418 (93.80)	358 (6.20)
2003	5,866 (9.15)	5,477 (93.37)	389 (6.63)
2004	5,997 (9.35)	5,587 (93.16)	410 (6.84)
2005	6,834 (10.66)	6,371 (93.23)	463 (6.77)
2006	6,486 (10.11)	5,932 (91.46)	554 (8.54)
2007	6,890 (10.74)	6,135 (89.04)	755 (10.96)
2008	7,370 (11.49)	6,594 (89.47)	776 (10.53)
Fracture			
No	61,537 (95.97)	56,909 (92.48)	4,628 (7.52)
Yes	2,587 (4.03)	2,548 (98.49)	39 (1.51)
Incidence[a]	13.36	13.60	6.25

PD peritoneal dialysis, *HD* hemodialysis

[a] Fracture incidence is expressed as the number of fractures per 1000 person-years

Propensity score (PS) matching

The proportion of PD patients is only 7.28 % (4,667/64,124), and patients treated with PD were different compared to patients treated with HD, for age, health status, and especially comorbidities, which are important covariates associated with hip fracture risk. Therefore, we established study cohorts who were matched with propensity scores; eight HD patients were randomly matched for each identified PD patient. The propensity score was estimated using a logistic regression model including covariates that are generally considered important factors associated with hip fractures. These covariates included demographic variables and baseline comorbidities. The demographic variables used in this study included gender and age. The baseline comorbidity history included hypertension, cardiovascular disease (CVD), diabetes, dementia, chronic pulmonary disease, neurological disease, and rheumatic disease. All illnesses were identified using the ICD-9-CM. Thereafter, 31,554 patients, of whom 28,048 were HD and 3,506 were PD patients, were included in the study.

Study endpoint

All study patient cases were followed to ascertain whether they had subsequent admissions for hip fracture. The follow-up period started from the first dialysis until the first of the following: date of hip fracture diagnosis, date of death, date of withdrawal from the NHI program, date of renal transplantation, or date of follow-up termination (31 December 2008).

Statistical analysis

We used the chi-square test to verify the matching efficiency of the sample distributions and differences between PD and HD patients. The incidence density of hip fractures was calculated for the two groups.

We conducted the Cox proportional hazards model, estimating the HR and 95 % confidence interval (CI) to examine the effects of dialysis modality and other variables on hip fracture risk. Variables were included in the multivariate model either in an attempt to control for confounding factors or as independent risk factors of fracture after adjustment for other covariates. Models were adjusted for demographic variables, baseline comorbidities, and oral medications. The oral medications included in this study were antiepileptic drugs, calcium, diuretics, steroids, and vitamin D.

All analyses were performed using SAS 9.1 statistical software (SAS Institute Inc., Cary, NC, USA). The results were considered statistically significant when two-tailed *P* values were less than .05.

Results

The characteristics of the study population before PS matching are shown on Table 1. Over half the patients (50.98 %) were women, and 49.02 % were men. The incident number of ESRD patients increased yearly, from 4,533 patients in 1999 to 7,370 patients in 2008. The percentage of patients who underwent PD increased steadily from 3.43 % (156/4,543) in 1998 to 10.53 % (776/7,370) in 2008. The peak age group in HD patients was 65–69 years (17.66 %), followed by 70–74 years (16.61 %) and 60–64 years (15.80 %). The peak age group in PD patients was 50–54 years and decreased gradually with increasing age (Table 2).

A total of 2,587 hip fractures were identified in 64,124 dialysis patients. The overall incidence of hip fractures in dialysis patients was 4.03 % (2,587/64,124), and 98.49 % (2,548/2,587) of hip fractures were among the patients treated with HD. The incidence of hip fracture was 13.60 per 1,000 patient-years in the HD group and 6.25 in the PD group.

Patients treated with PD were different compared to patients treated with HD, for age, health status, and especially comorbidities. Before PS matching, PD and HD patients were significantly different ($P<.001$) in gender, age, and presence of hypertension, cardiovascular disease, diabetes, dementia, chronic pulmonary disease, and neurological disease. After PS matching, all variables between PD and HD patients were statistically nonsignificant except the variable of hypertension (Table 2). Thus, the bias between PD and HD patients could be reduced.

The results of the multivariate Cox proportional hazards model analysis are shown in Table 3. Dialysis modality, sex, age, presence of CVD, diabetes, medication with antiepileptic drugs, diuretics, steroids, and vitamin D had a statistically significant association with hip fracture after adjustment for gender, age, comorbidities, and medication. However, the presence of hypertension, dementia, neurological disease, chronic pulmonary disease, rheumatic disease, and medication with calcium had no statistically significant association with hip fracture. Factors that were independently associated with an increased risk of hip fracture included HD, increasing age, female sex, presence of diabetes, and medication with diuretics. Conversely, patients with CVD, medication with antiepileptic drugs, steroids, and vitamin D were independently associated with a decreased risk of hip fracture. Patients on HD had an increased risk of hip fracture compared to patients on PD; HR was 1.52 (95 % CI: 1.09–2.12, $P=0.02$).

More patients switched from PD to HD than from HD to PD. Therefore, several biases may exist in the group of PD patients. Three models (intent-to-treat, as-treated, and PD + HD vs PD or HD only) were analyzed to solve this issue. HD patients had an increased risk of hip fracture in all the three models (Table 4).

Discussion

The causes of renal osteodystrophy among ESRD patients are multiple, including secondary hyperparathyroidism, abnormal vitamin D metabolism, relative immobility, hypogonadism, β2- microglobulin-associated amyloidosis, chronic acidosis, aluminum deposition, osteomalacia, steroid therapy, and other disorders [8]. Age-associated osteoporosis should also be considered. As renal failure progresses, ensuing abnormalities in vitamin D metabolism and PTH secretion result in a change of the trabecular microarchitecture, thinning, and an increased porosity of the cortical bone [6]; thus, hip fracture rates are significantly increased in dialysis patients and transplant recipients [5].

The data from the US Renal Data System (USRDS) demonstrated a fourfold increase of hip fracture risk among ESRD patients [9], and the mortality rate of dialysis patients after hip fracture was 2.7 times higher than that of patients without a hip fracture [10]. In this study, the incidence of hip fracture was 13.36 per 1,000 person-years in 64,124 dialysis patients,

Table 2 Patient characteristics before and after propensity score matching

	Before matching				After 1:8 matching			
Characteristics	(%)	HD (%)	PD (%)	*P*	(%)	HD (%)	PD (%)	*P*
N	64,124	59,457	4,667		31,554	28,048	3,506	
Gender				<0.001				0.10
Female	50.98	50.79	53.46		51.28	51.12	52.60	
Male	49.02	49.21	46.54		48.72	48.88	47.40	
Age (years)				<0.001				0.43
50~54	13.97	13.24	23.31		15.73	15.87	14.63	
55~59	14.52	14.08	20.12		17.36	17.36	17.37	
60~64	15.83	15.80	16.18		17.20	17.08	18.17	
65~69	17.45	17.66	14.78		17.21	17.20	17.26	
70~74	16.21	16.61	11.11		13.69	13.66	13.95	
75~79	12.38	12.69	8.31		10.52	10.50	10.64	
≥80	9.64	9.91	6.19		8.30	8.34	7.99	
Hypertension	86.00	86.15	84.10	<0.001	86.65	86.88	84.80	<0.001
Cardiovascular disease	71.38	71.98	63.64	<0.001	70.63	70.74	69.74	0.23
Diabetes	58.62	59.32	49.69	<0.001	57.93	58.10	56.62	0.10
Dementia	2.74	2.81	1.82	<0.001	2.43	2.45	2.28	0.58
Chronic pulmonary disease	35.19	35.68	28.91	<0.001	33.66	33.85	32.17	0.05
Neurological diseases	29.62	30.19	22.41	<0.001	26.43	26.37	26.93	0.49
Rheumatic diseases	3.31	3.29	3.56	0.34	3.34	3.32	3.48	0.65

PD peritoneal dialysis, *HD* hemodialysis

which is significantly higher than the incidence (5.75 per 1,000 person-years) in the general population of Taiwan [11].

Patients treated with PD were different compared to patients treated with HD, for age, health status, and especially comorbidities, which are important covariates associated with hip fracture risk. By including correlated covariates in the PS matching model, the bias between groups can be reduced. Gayat et al. demonstrated that the PS matching could lead to an unbiased estimate of the treatment effect [12]. Therefore, we established study cohorts who were matched with PS.

The Cox proportional hazards model demonstrated that increasing age, female sex, presence of diabetes, and medication with diuretics were independently associated with increased hip fracture risk; medication with vitamin D was associated with decreased hip fracture risk. These findings were consistent with those of previous studies [13–18].

Risk factors that were inconsistent with previous studies included the presence of CVD, dementia, neurological disease, chronic pulmonary disease, and medications with steroids and antiepileptic drugs. However, several differences may exist because the populations targeted by previous studies were osteoporotic patients and not ESRD patients. This study was focused on the relationship between dialysis modality and hip fracture; other risk factors of hip fracture were used to control confounding factors in the multivariate model. Further studies are required to improve the understanding of risk factors associated with hip fractures of dialysis patients.

Numerous debates on which dialysis modality is superior have taken place in recent decades. However, most debates focused on which modality was associated with a better survival rate or better quality of life for patients with ESRD. No large-scale study has ever mentioned about the relationship between dialysis modality and risk of hip fracture. Only one study has compared the risk of hip fracture between PD and HD patients. Stehman-Breen et al. used the data from USRDS DMMS-1 to analyze the risk factors of hip fracture among ESRD patients and found that the incidence rate of hip fracture was 7.91 per 1,000 patient-years in the HD group and 3.47 in the PD group (P=0.52) [10]. They concluded that dialysis modality was not an important predictor of hip fracture. Because their study population included 4,952 patients, the mean follow-up time was 2.86 years, and only 1 patient in the PD group had a hip fracture; thus, the statistical nonsignificance may have been caused by the small sample.

Several differences may have existed between patients treated with PD and HD because of the difference in dialysis modality. HD patients showed a higher incidence of delayed graft function and primary allograft failure, had elevated erythrocyte superoxide dismutase, lower glutathione peroxidase and catalase activities, decreased levels of Se, Zn, and Fe,

Table 3 Analysis of hazard ratios of hip fracture in dialysis patients with multivariable model

Variables	Unadjusted		Adjusted	
	HR	*P*	HR (95 % CI)	*P*
Dialysis modality (intent-to-treat)				
PD (reference)				
HD	1.69	0.002	1.52 (1.09–2.12)	0.02
Gender				
Female (reference)				
Male	0.68	<0.001	0.68 (0.60–0.77)	<0.001
Age (years)				
50~54 (reference)				
55~59	1.50	0.004	1.46 (1.11–1.92)	0.008
60~64	2.08	<0.001	2.05 (1.58–2.67)	<0.001
65~69	3.08	<0.001	2.90 (2.25–3.73)	<0.001
70~74	4.19	<0.001	3.97 (3.07–5.15)	<0.001
75~79	5.58	<0.001	5.29 (4.04–6.92)	<0.001
≥80	7.42	<0.001	6.99 (5.29–9.23)	<0.001
Diseases[a]				
Hypertension	1.10	0.47	0.96 (0.74–1.25)	0.75
Cardiovascular disease	1.03	0.78	0.75 (0.61–0.91)	0.005
Diabetes	1.37	<0.001	1.43 (1.26–1.64)	<0.001
Dementia	1.35	0.009	0.86 (0.67–1.09)	0.21
Chronic pulmonary disease	1.07	0.30	0.94 (0.83–1.06)	0.30
Neurological disease	1.28	<0.001	1.13 (0.99–1.30)	0.07
Rheumatic disease	1.04	0.79	1.08 (0.83–1.42)	0.56
Medication[b]				
Antiepileptic drugs	0.71	<0.001	0.73 (0.65–0.83)	<0.001
Calcium	0.79	0.049	0.95 (0.74–1.21)	0.67
Diuretics	1.70	0.001	1.41 (1.01–1.97)	0.05
Steroids	0.80	0.02	0.81 (0.66–0.98)	0.03
Vitamin D	0.42	<0.001	0.49 (0.42–0.56)	<0.001

N=31,554

PD peritoneal dialysis, *HD* hemodialysis, *CI* confidence interval, *HR* hazard ratio

[a] No disease group was used as reference group

[b] No medication group was used as reference group

Table 4 Multivariant analysis for dialysis and hip fractures in different models

Analysis model	Adjusted Cox model[a]		Age (years), mean (SD)
	HR (95 % CI)	*P*	
Intent-to-treat			
PD (reference)			65.13 (9.46)
HD	1.52 (1.09–2.12)	0.02	65.14 (9.61)
As treated			
PD (reference)			65.54 (9.61)
HD	1.71 (1.15–2.55)	0.008	65.09 (9.58)
Dialysis			
PD only (reference)			65.78 (9.65)
HD only	1.65 (1.10–2.47)	0.02	65.16 (9.61)
HD + PD	1.31 (0.68–2.49)	0.42	62.81 (8.48)

PD peritoneal dialysis, *HD* hemodialysis, *CI* confidence interval, *HR* hazard ratio, *SD* standard deviation

[a] Adjusted for gender, age, diseases, and medication

and attenuation of serum antioxidant capacity [19–21]. However, the most important difference of PD and HD that may influence the risk of hip fracture is vitamin D. Elder et al. examined 242 patients with renal failure and found that patients on PD had lower levels of 25-hydroxyvitamin D than those on HD [22]. Furthermore, they identified positive associations between 25-hydroxyvitamin D levels and the Z score of bone mineral density (BMD) and an association between femoral neck BMDs with a fracture at any site. According to the study of Elder et al. [22], patients on PD had lower vitamin D levels and potentially have a higher risk of hip fracture than patients on HD. Conversely, our study demonstrated that patients on HD had a higher risk of hip fracture; the HR was 1.52. This result cannot be explained with the theory of vitamin D and BMD.

Pelletier et al. studied the microarchitecture of the bone in dialysis patients by using high-resolution quantitative computed tomography and demonstrated that trabecular volumetric BMD and microarchitecture at the tibia were significantly lower in HD patients [23]. The trabecular volumetric BMD is an important factor of bone strength and may result in different bone fragility between PD and HD patients. This theory can explain our finding that patients on HD had a higher risk of hip fracture. Further prospective studies are required to elucidate the pathophysiological mechanism of dialysis and hip fracture.

The 1-year mortality rate after hip fracture was higher than that without hip fracture in dialysis patients; thus, we should focus more on patients treated with HD, by improving health education, medication for osteoporosis, and fall prevention, to reduce the risk of hip fractures.

This study has several limitations. First, a retrospective study was used to ascertain the information regarding causes and effects from existing claims data. Second, although we try to correct for the significant demographic differences between the groups, there may have been some significant biochemical factors associated with bone and mineral metabolism that have not been addressed. Third, information that may influence the risk of hip fracture, such as laboratory data (PTH, serum calcium, and phosphorus), BMD, health behavior, and patient lifestyles, was unavailable in the claims data. However, this study represented the experience of the entire incident dialysis population spanning an 11-year period in Taiwan, and the

available sample size was large enough to permit propensity matching. The results of this study may have clinically relevant indications and may assist in dialysis modality choices for ESRD patients.

In conclusion, in this population-based cohort study, HD patients had a higher risk of hip fracture compared to PD patients, and the HR was 1.52 (95 % CI: 1.09–2.12, P= 0.02). We should focus more on patients treated with HD, by improving health education, medication for osteoporosis, and fall prevention, to reduce the risk of hip fractures.

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Conflicts of interest None

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