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Fracture Risk in Dialysis and Kidney Transplanted Patients: A Systematic Review

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ABSTRACT

Chronic kidney disease is associated with an increased risk of fracture and cardiovascular mortality. The risk of fracture in hemodialysis (HD), peritoneal dialysis (PD) and kidney transplant (KT) patients is higher when compared with the general population. However, there exists a knowledge gap concerning which group has the highest risk of fracture. We aimed to compare the risk of fracture in HD, PD, and KT populations. We conducted a systematic review of observational studies evaluating the risk of fracture in HD, PD, or KT patients. Eligible studies were searched using MEDLINE, Embase, Web of Science, and Cochrane Library from their inception to January 2016, and in grey literature. Incidences (cumulative and rate) of fracture were described together using the median, according to fracture sites, the data source (administrative database or cohort and clinical registry), and fracture diagnosis method. Prevalence estimates were described separately. We included 47 studies evaluating the risk of fracture in HD, PD, and KT populations. In administrative database studies, incidence of hip fracture in HD (median 11.45 per 1000 person-years [p-y]), range: 9.3 to 13.6 was higher than in KT (median 2.6 per 1000 p-y; range 1.5 to 3.8) or in PD (median 5.2 per 1000 p-y; range 4.1 to 6.3). In dialysis (HD+PD), three studies reported a higher incidence of hip fracture than in KT. Prevalent vertebral fracture (assessed by X-rays or questionnaire) reported in HD was in a similar range as that reported in KT. Incidence of overall fracture was similar in HD and KT, from administrative databases studies, but lower in HD compared with KT, from cohorts or clinical registry studies. This systematic review suggests an important difference in fracture risk between HD, PD, and KT population, which vary according to the diagnosis method for fracture identification. © 2018 The Authors. *JBMR Plus* published by Wiley Periodicals, Inc. on behalf of American Society for Bone and Mineral Research.

KEY WORDS: CKD-MBD; FRACTURES; HEMODIALYSIS; PERITONEAL DIALYSIS; KIDNEY TRANSPLANTATION

Introduction

Chronic kidney disease (CKD) is a major public health issue worldwide. In 2011, more than 615,000 people suffered from end-stage renal disease (ESRD) in United States.[1,2] In 2012, the unadjusted prevalence of ESRD was 716.7 per million person (pmp) in Europe,[3] whereas 35,281 Canadians (excluding the province of Quebec) were suffering from ESRD in 2014.[4] Loss of kidney function leads to metabolic disorders that affect bone and vascular health known as CKD-mineral and bone disorder (CKD-MBD).[5–7] Clinically, CKD-MBD is associated with an increased risk of fracture and cardiovascular mortality.[8–12] Patients with ESRD will eventually require a renal replacement therapy (RRT) and will therefore be treated by hemodialysis (HD), peritoneal dialysis (PD), or kidney transplantation (KT).[13] The increased risk of fracture in HD, PD, and KT patients compared with the general population has been recognized.[8,14,15] Indeed, hip fracture has been shown to be the most common type of fracture in ESRD with a fracture rate 17.2 times greater than that observed in the general population.[8,15] This association was

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also reported in age, sex, and race subgroups.[8] The risk of vertebral fracture is also higher in older women with decreased kidney function.[16] However, there is currently a knowledge gap on whether the risk of fracture differs between the HD, PD, and KT population.

Whereas Beaubrun and colleagues[17] reported in the United States that the incidence rate of hip fracture in HD patients was 20.6 per 1000 persons-years in 2009, Nair and colleagues[18] reported a much lower incidence rate of 3.8 per 1000 person-years in KT patients. In contrast, another study reported that the risk of hip fracture in the first 3 years post-KT was 1.34-fold that of dialysis patients,[19] which is mainly explained by the use of high corticosteroids to prevent graft rejection. After the first 3 years post-KT, the risk of fracture declined and tended to be equal that of HD patients.[19] When comparing patients in dialysis, a recent study[2] showed that the risk of hip fracture in HD was 1.74-fold that in PD, whereas another study did not find any difference between HD, PD, and KT patients.[9] Given these disparities, we conducted a systematic review to identify the risk of fracture and cardiovascular mortality post-fracture in HD compared with PD or KT and in PD compared with KT populations.

Materials and Methods

Study design

Based on a protocol registered on Prospero (CRD42016037526) that was recently published,[20] we conducted a systematic review following the methodological recommendations of the Cochrane Handbook for Systematic Reviews of Interventions[21] and reported the results using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[22]

Eligibility criteria

We included observational studies (cohort studies, cross-sectional studies, case-control studies) conducted in CKD adults $\geq$18 years (at least 80% of participants) treated by either HD, KT, or PD and evaluating the risk of fracture (hip, vertebral, and/or overall fracture) without a comparator or compared with a renal replacement therapy (HD, KT, PD), non-dialyzed CKD, or general population. The primary outcome was the risk (incidence rate, incidence proportion, odds or prevalence) of fracture. Secondary outcomes were fracture sites (hip, vertebral, overall fracture), risk of cardiovascular mortality post fracture, all-cause mortality associated with fracture, length of hospitalization post fracture and number of hospitalizations post fracture (during the following years).

Information sources and search strategy

We performed a search using electronic databases (Medline, Cochrane Library, Embase, and Web of Science), from their inception until January 2016. Our search strategy was based on key words related to the intervention (KT, HD, PD) and the outcome (fracture). A search strategy was first elaborated for Pubmed/Medline and Embase (Supplemental Table S1) then adapted to Cochrane Library and Web of Science with no restriction of language or year of publication. We then hand-searched reference lists of relevant articles and the Grey literature (Google Scholar, thesis repositories including Thesis portal Canada, EtHOS, DART-Europe E-Thesis Portal, the National Library of Australia's Trove, and ProQuest Dissertations & Theses Global).

Study selection and data management

After removing duplicates of identified records from our search strategies using EndNote (version X7.2.1, Thomson Reuters, New York, NY, USA, 1988–2014), two independent reviewers screened each study by title and abstract using standardized and pilot tested screening forms. Full texts were also screened when titles and abstract were insufficient to establish inclusion of a study in the review.

Data extraction and risk of bias assessment

Data of included studies were then independently extracted, using a standardized and piloted tested data extraction form. In each step, discrepancies between the two reviewers (AS and CF) were resolved through consensus or with the involvement of a third reviewer (FM), as required. Extracted data included information on the study, characteristics of the study population and intervention (HD, PD or KT), comparator, and outcomes. Primary investigators of included studies were contacted when needed. Risk of bias was assessed with a tool developed by the Cochrane Collaboration (ROBINS-I tool).[23] Risk of bias was

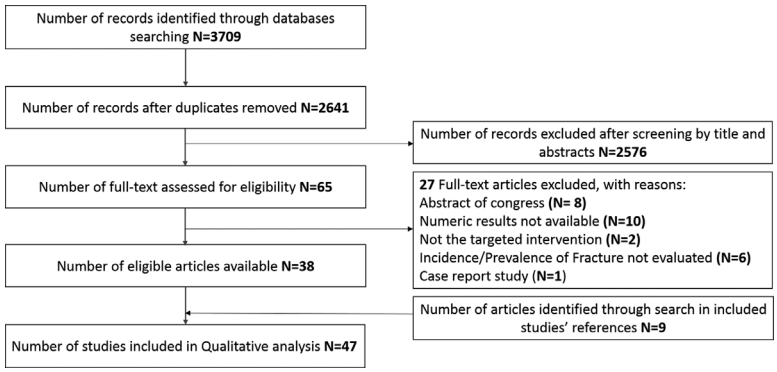

Fig. 1. Study selection's flow diagram. This figure describes the study selection process.

Table 1. Characteristics of Studies Evaluating the Risk of Fracture in Kidney Transplant According to the Design and Comparator Group

First author, year of publication, and study country	Sample size	White (%)	Age, years (mean)	Female (%)	Mean follow-up (years)	Mean follow-up post fracture (years)	Hip fracture	Vertebral fracture	Overall fracture	Risk of bias
Cross-sectional study, kidney transplant versus no comparator										
Braga 2006, Brazil[24]	191	NR	44.8	50.8	NR	NA		√	√	Critical
Durieux 2002, France[25]	59	71.0	49.6	45.8	8.5	NA		√	√	Critical
Patel 2001, United Kingdom[26]	165	90.0	47.0	42.4	NR	NA		√		Critical
Nam 2000, Korea[27]	166	NR	40.0	34.3	NR	NA		√		Critical
Nisbeth 1999, Sweden[28]	193	NR	50.9	39.9	NR	NA		√	√	Critical
Grotz 1994, Germany[29]	100	NR	44.0	46.0	NR	NA			√	Critical
Retrospective cohort study, kidney transplant versus no comparator										
Ferro 2015, United Kingdom[30]	21,769	71.1	NR	38.7	5.7	NR	√		√	Critical
Nair 2014, United States[18]	69,740	56.9	50.5	39.0	2.2	1[b]	√			Moderate
Nikkel 2012, United States[31]	77,430	65.8	48.8	39.7	3.9	NA			√	Critical
Opelz 2011, multinational[32]	20,509	86.9	47.9	38.4	5.0b	NA	√			Critical
Nikkel 2009, United States[33]	68,814	73.8	43.7	39.7	5.0b	NR			√	Critical
O'Shaughnessy 2002, United States[34]	1572	NR	NR	41.2	6.5	NR	√	√	√	Critical
Prospective cohort study, kidney transplant versus no comparator										
Ramsey-Goldman 1999, United States[35]	432	54.0	41.3	40.0	2.1	NA			√	Critical
Elmstedt 1981, Sweden[36]	204	NR	NR	42.7	6.2	NA			√	Critical
Retrospective cohort study, kidney transplant versus general population										
Naylor 2016,[a] Canada[37]	4821	NR	49.3	36.9	2.9	NR	√		√	Moderate
Vautour 2004, United States[38]	86	92.0	38.3	31.4	10.6	NR		√	√	Serious
Abbot 2001, United States[39]	33,479	75.6	42.9	39.8	1.7	NR			√	Moderate
Retrospective cohort study, kidney transplant versus dialysis										
Ball 2002, United States[19]	101,039	63.20	40.6	40.60	3.0	NR	√			Moderate

NR = Not Reported; NA = Not Applicable; √ = This type of fracture risk was assessed in the study.
[a]Also compared fracture risk in KT to non-dialysis CKD.
[b]Total follow-up time.

judged as low (the study is comparable to a well-performed randomized trial), moderate (the study provides sound evidence for a non-randomized study but cannot be considered comparable to a well-performed randomized trial), serious (the study has some important problems), critical (the study is too problematic to provide any useful evidence and should not be included in any synthesis), or no information (no information on which to base a judgment about risk of bias). Information on the source of funding was collected for each study to assess conflicts of interest.

Data analysis

Frequencies of fracture in included studies were first described separately as reported, then characterized using the median and interquartile range as summary measures for each RRT group (HD, PD, KT, or combined dialysis [HD + PD]) according to the fracture site (hip, vertebral, or overall fracture), the data source (administrative database or cohort and clinical registry), and the fracture diagnosis method. Prevalence of fracture is reported separately, while cumulative incidence was converted to incidence rate using the statistical approach recommended by Rothman.[24] For studies assessing the association between RRT and fracture and where a measure of association was available, we reported these measures by intervention group-comparator and fracture's site.

Results

We identified 2641 references from electronic and hand searches, and included 47 studies that evaluated the risk of fracture in HD, PD, and/or KT patients (Fig. 1), with sample sizes ranging from 29 to 935,621. Characteristics of the included studies are described in Tables 1, 2, and 3. Among the included studies, 22 were conducted in the United States, 13 in Europe, 10 in Asia, and 2 were multinational. The mean follow-up ranged from 1 to 10 years. We found 18 studies that evaluated the risk of fracture in KT group, without a comparator in 14 studies,[18,24–36] compared with the general population in 3 studies[37–39] and compared with dialysis population in 1 study[19] (Table 1). Concerning dialysis population (HD and PD), 5 studies reported the risk of fracture, without a comparator in 2 studies,[40,41] and compared with the general population in 3 studies.[8,14,42] Only one study evaluated the risk of fracture in PD patients without a comparator[43] (Table 2). In HD patients, 23 studies reported the risk of fracture, without a comparator in 15 studies,[44–58] compared with the general population in 4 studies,[11,59–61] with PD in 3 studies,[2,62,63] and with PD and KT in 1 study[9] (Table 3).

Hip fracture risk reported in HD, KT, PD, and dialysis (HD + PD) population

Incidence rate of hip fracture was reported by 10 studies[2,14,18,19,30,37,40–42,62] using administrative database and by 8 studies[9,32,34,57–60] conducted in a cohort or a clinical registry. In administrative database studies, incidences of hip fracture reported by 2 studies in HD group[2,62] (median 11.45 per 1000 person-years (p-y); range 9.3 to 13.6) were higher than those reported by 4 studies[18,19,30,37] in KT group (median 2.6 per 1000 p-y; range 1.5 to 3.8), or those reported by 2 studies[2,62][2] in PD group (median 5.2 per 1000 p-y; range 4.1 to 6.3) (Fig. 2*A*). In dialysis group (HD + PD), 3 of 5 studies[14,19,40–42] reported an incidence rate of hip fracture (median 14.2 per 1000 p-y; range 2.9 to 29.3) higher than that reported in the KT group (Fig. 2*A*). Only one study[28] reported a prevalence of hip fracture in a KT group (4.2%). The results were similar in studies conducted with cohorts or clinical registries. Indeed, incidences of hip fracture reported by 4 studies in HD group[9,57–59] were higher than those reported by 3 studies[9,32,34] in KT group (Fig. 2*B*). Only 1 study reported an incidence of hip fracture in a PD[9] or dialysis group,[8] estimated respectively at 3.5 and 13.9 per 1000 p-y.

Vertebral fracture risk in dialysis and kidney transplant population

Two studies[34,38] reported the incidence of vertebral fracture in KT group (7.2 and 15.4 per 1000 p-y), whereas only 1 study[41] reported this incidence in dialysis group (4.8 per 1000 p-y). Incident vertebral fracture was assessed by clinical history and X-rays,[38] using outside medical records and phone contact[34] and/or by inpatients claims.[41] Prevalent vertebral fracture was

Table 2. Characteristics of Studies Evaluating the Risk of Fracture in Dialysis and Peritoneal Dialysis According to the Design and Comparator Group

First author, year of publication, and study country	Sample size	White (%)	Age, years (mean)	Female (%)	Mean follow-up (years)	Mean follow-up post fracture (years)	Hip FX	Vertebral FX	Overall FX	Risk of bias
Retrospective cohort study, dialysis versus no comparator										
Nair 2013, United States[40]	409,040	76.5	76.0	48.1	NR	1[a]	√			Serious
Danese 2006, United States[41]	9007	53.8	61.7	42.5	NR	NR		√	√	Critical
Retrospective cohort study, dialysis versus general population										
Maravic 2014, France[42]	29,487	NR	NR	40.0	1a	NR			√	Critical
Alem 2000, United States[14]	326,464	100.0	NR	44.1	NR	NR	√			Moderate
Coco 2000, United States[8]	1272	17.5	58.0	52.2	3.2	1[a]	√			Moderate
Case-control study, peritoneal dialysis versus no comparator										
Ma 2013, China[43]	24	NR	73.3	40.0	1.3	NR			√	Critical

FX = fracture; NR = Not Reported; √ = This type of fracture risk was assessed in the study.
[a]Total follow-up time.

Table 3. Characteristics of Studies Evaluating the Risk of Fracture in Hemodialysis According to the Design and Comparator Group

First author, year of publication, and country	Sample size	White (%)	Age, years (mean)	Female (%)	Mean follow-up (years)	Mean follow-up post fracture (years)	Risk of bias	Hip fracture	Vertebral fracture	Overall fracture
Cross-sectional study, hemodialysis versus no comparator										
Simunovic 2015, Croatia[44]	767	NR	NR	NR	NR	NA	NI			√
Fusaro 2013, Italy[45]	387	NR	64.2	37.0	NR	NA	Serious		√	
Mares 2009, Japan[46]	72	100.0	65.0	44.0	NR	NA	Critical		√	
Kaneko 2007, United States[47]	7159	50.4	58.4	48.2	3.3	NA	Critical			√
Inaba 2005, Japan[48]	114	100.0	73.1	100.0	NR	NA	Critical			
Urena 2003, France[49]	70	100.0	60.5	37.1	NR	NA	Critical		√	√
Fontaine 2000, Belgium[50]	88	NR	58.0	42.1	NR	NA	Critical		√	√
Atsumi 1999, Japan[51]	187	0	54.2	0	NR	NA	Critical		√	√
Mohini 1991, United States[52]	66	NR	NR	NR	NR	NA	Critical		√	
Retrospective cohort study, hemodialysis versus no comparator										
Jamal 2006, Canada[53]	52	NR	66.0	28.85	NR	NR	Critical			√
Wagner 2014, United States[54]	935,221	NR	NR	NR	NR	NR	Critical			√
Chang 2013, Taiwan[55]	82,491	NR	NR	47.9	5.0[a]	NR	Critical			√
Wakasugi 2014, Japan[56]	128,141	NR	64.3	38.1	1.0[a]	NR	Serious	√		
Lavorato 2009, Brazil[57]	50	NR	NR	44.3	NR	NR	Serious	√		
Prospective cohort studies, hemodialysis versus no comparator										
Jadoul 2006, multinational[58]	12,782	NR	NR	418	NR	NR	Serious	√		√
Prospective cohort studies, hemodialysis versus general population										
Tentori 2014, multinational[59]	34,579	NR	65.0	41.1	1.6	0.6	Critical	√		√
Wakasugi 2013, Japan[60]	128,141	NR	64.3	38.1	1.0[a]	NR	Moderate	√		
Rodrıguez-Garcıa 2009, Spain[11]	193	NR	65.5	37.3	2.0[a]	NA	Critical		√	√
Rodríguez-García 2003, Spain[61]	99	NR	67.6	40.4	NR	NR	Serious		√	
Retrospective cohort study, HD versus peritoneal dialysis										
Zhe-Zhong 2014, Taiwan[62]	51,473	NR	60.4	52.1	4.1	NR	Moderate	√		
Mathew 2014, United States[63]	929,114	NR	NR	NR	NR	NR	Moderate	√		
Chen 2014, Taiwan[2]	64,124	NR	66.4	51.0	NR	NR	Moderate	√		
Stehman-Breen 2000, United States[b][9]	4952	52.1	59.7	48.3	2.9	NR	Moderate	√		

NR = Not Reported; NA = Not Applicable; NI = No Information; √ = This type of fracture risk was assessed in the study.
[a]Total follow-up time.
[b]Also compared with kidney transplant.

assessed by X-rays in 7 studies,[11,25–27,45,51,61] interview or medical records in 2 studies,[49,50] CT-scan in 1 study,[46] and interview alone in 2 studies.[24,28] In 6 HD group studies that used X-rays to assess vertebral fracture,[11,45,46,51,52,61] the prevalence was similar to that reported in 3 KT group studies[25–27] (Fig. 3*A*). No study reported vertebral fracture risk in PD patients. The results were also similar in studies that assessed vertebral fracture using interview, questionnaire, and/or medical

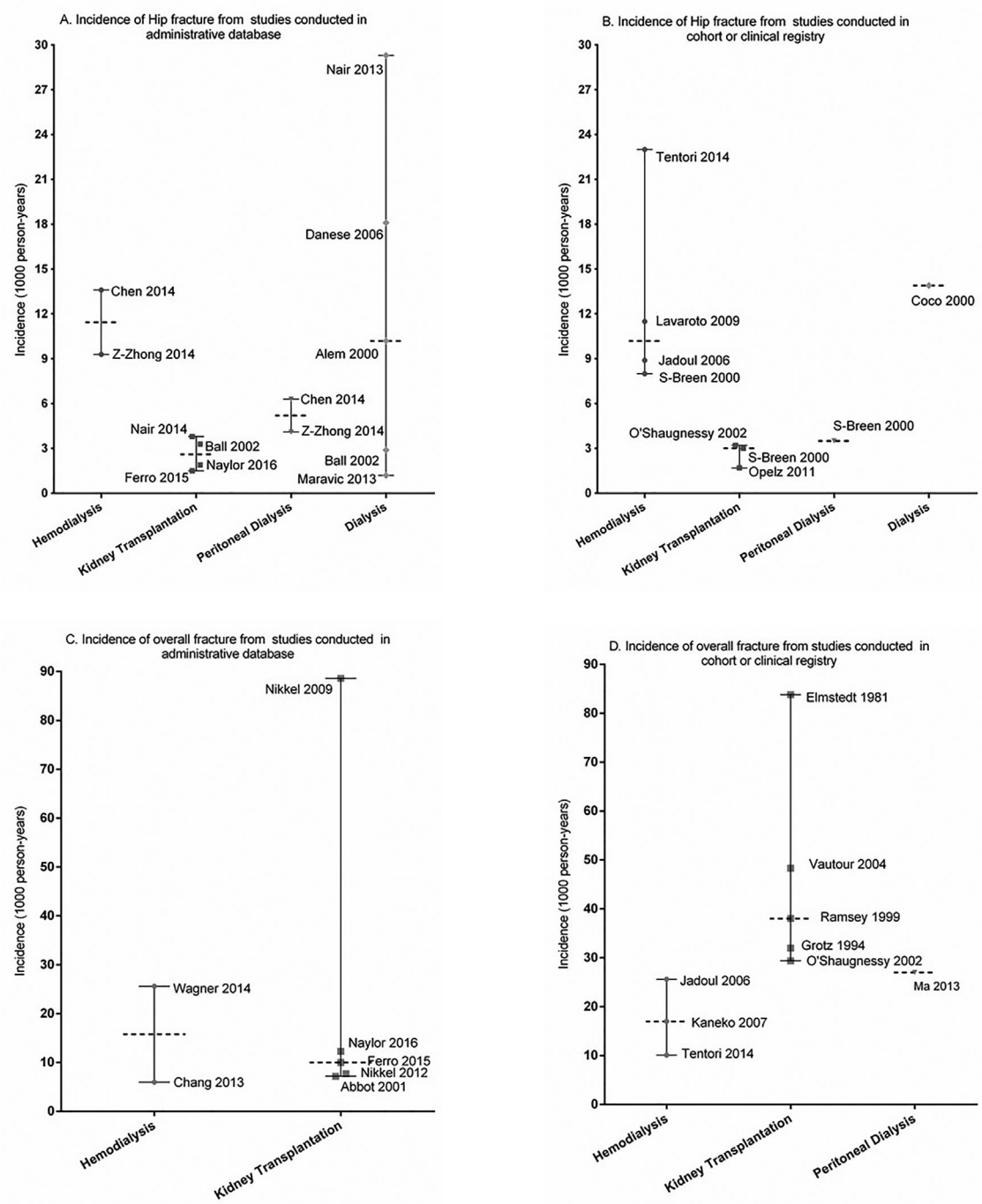

Fig. 2. Incidence rates of hip fracture and overall fracture in dialysis and kidney transplant patients. (*A*, *B*) The incidence rate of hip fracture reported in studies is identified with a bullet and the first author's name and publication year according to the therapy group. The median incidence rate and range of hip fracture according to the therapy group are also presented. (*C*, *D*) Results are presented here for the incidence rate of overall fracture.

records[24,28,49,50] (Fig. 3*B*). The prevalence of vertebral fracture reported in dialysis and KT populations are further detailed in Supplemental Table S2.

Overall fracture risk in dialysis and kidney transplant populations

Seven studies reported an incidence rate of overall fracture from an administrative database[30,31,33,37,39,54,55] compared with 9 studies[29,34–36,38,43,47,58,59] from a cohort or a clinical registry. From administrative databases, the incidences of overall fracture reported in 2 HD group studies[54,55] were similar to those reported in 5 KT group studies[30,31,37,39,64] (Fig. 2*C*). From cohorts or clinical registries, the incidences of overall fracture reported in 3 HD group studies[47,58,59] (median 17.0 per 1000 p-y; range 10.1 to 25.6) were lower than those reported by 5 KT group studies[29,34–36,38] (median 38.0 per 1000 p-y; range

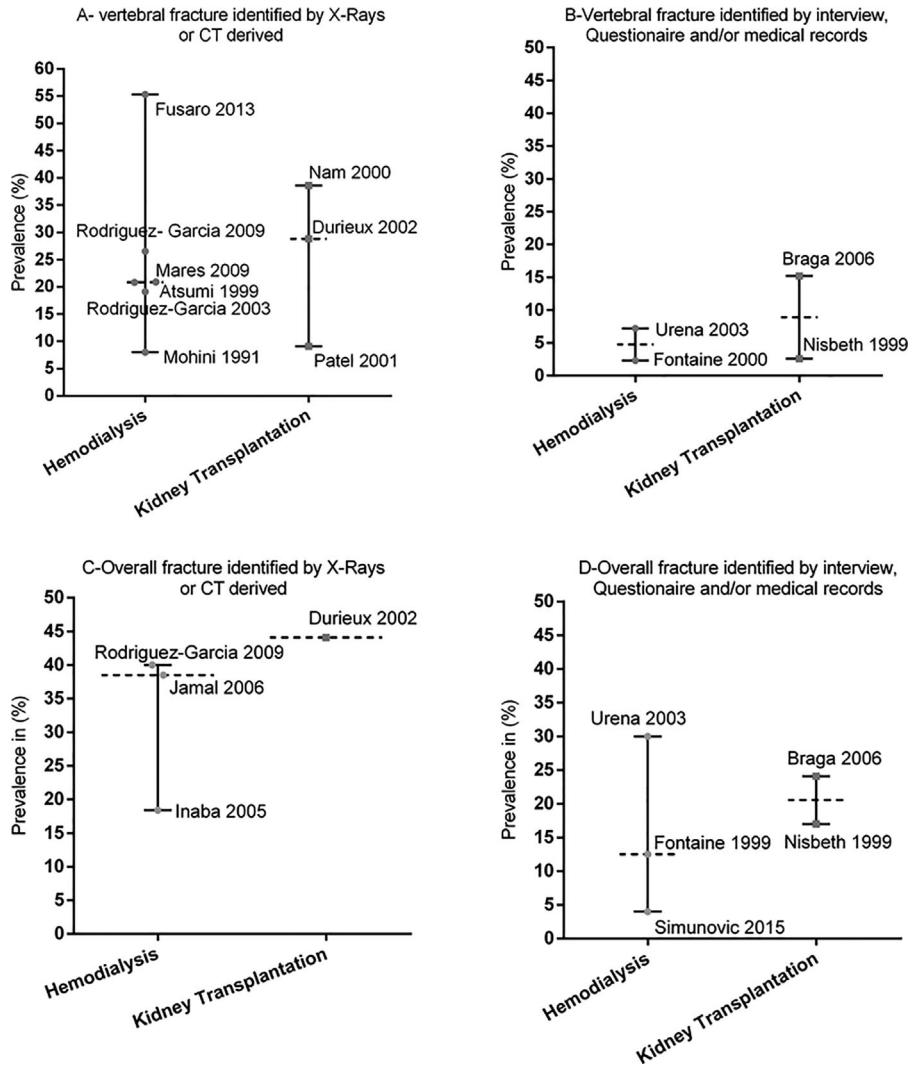

Fig. 3. Prevalence of vertebral and overall fracture in hemodialysis and kidney transplant patients. (*A*, *B*) The prevalence of vertebral fracture in studies is identified with a bullet and the first author's name and publication year according to the therapy group. The median prevalence and range of vertebral fracture according to the therapy group are also presented. (*C*, *D*) Results are presented here for the prevalence of overall fracture.

29.4 to 83.8). Only 1 study[43] reported an incidence of overall fracture using an administrative database in a PD group without any comparative study (Fig. 2*D*). In studies that used X-rays to diagnose fracture, 3[11,48,53] reported the prevalence of overall fracture (median 12.5 per 1000 p-y; range 4.0 to 30.0), whereas only 1 study[25] reported that prevalence in a KT group (Fig. 3*C*). In studies that used interview, questionnaire, and/or medical records to assess fracture, the prevalence of overall fracture reported in 3 HD group studies[44,49,50] was similar to that reported by 2 KT group studies[24,28] (Fig. 3*D*).

Comparison of fracture risk in HD, PD, and KT groups versus non-dialyzed CKD or general population

Three studies[37–39] reported a higher risk of overall fracture in KT patients compared with the general population. Three other studies[8,14,42] observed a higher risk of hip fracture in dialysis compared with the general population (Supplemental Table S3). In HD, 2 studies[59,60] reported a higher incidence of hip fracture compared with general population, whereas Rodriguez-Garcia and colleagues[11,61] did not observe a significant difference between the prevalence of vertebral fracture in HD and the general population, but no measure of association was provided (Supplemental Table S3).

Comparison of fracture risk in HD versus PD versus KT or non-dialyzed CKD

One study[19] reported a higher risk of hip fracture in KT patients compared with dialysis patients, whereas another study[9] did not observe a difference in hip fracture risk when comparing HD with PD and KT patients. Three studies[2,62,63] reported a significantly higher risk of hip fracture in HD versus PD patients. Finally, Naylor and colleagues[37] recently observed a higher risk of overall fracture in KT patients compared with non-dialyzed CKD (Supplemental Fig. S1).

Mortality post fracture

Five studies[8,40–42,62] evaluated the risk of overall mortality post fracture in dialysis population. Three of these studies reported a

higher mortality rate in fractured dialysis patients compared with the general population,[8] non-dialysis,[42] or non-fractured dialysis population randomly selected.[41] Mortality within 30 days post hip fracture in dialysis patients ≥67 years was 17.40% (95% confidence interval [CI] 16.9% to 18.0%) in the study from Nair and colleagues.[40] Likewise, Zhe-Zhong and colleagues[62] reported a mortality rate of 3.2% in dialysis patients after hip fracture. When considering only patients in HD, Rodriguez-Garcia and colleagues,[11] Kaneko and colleagues,[47] and Tentori and colleagues[59] reported a higher mortality rate post fracture in HD compared with the general population, which exceeded 500 per 1000 p-y in the later study. In KT population, the 30-day mortality rate post-fracture was 2.2 per 100 events as reported by Nair and colleagues[18] and 20.7 per 100 events as reported by Ferro and colleagues[30] (Supplemental Table S4).

Hospitalization stays and cost post-fracture

Only 1 study[42] evaluated this outcome and reported a longer length of hospitalization stays and higher hospitalization costs due to fracture in dialysis versus non-dialysis population (Supplemental Table S4).

Risk of bias

In studies evaluating the incidence or prevalence of hip, vertebral, or overall fracture in HD, PD, KT, or dialysis, the majority were at critical risk of bias when evaluating fracture.[18,24–36,40,41,43–55,57,58,60] Five studies[40,45,56–58] were at serious risk of bias, 1 study had no information,[44] and another study[18] was at moderate risk. All studies that performed direct comparison between HD, PD, KT, and dialysis were at moderate risk of bias for fracture.[2,9,19,62,63] The risk of bias in studies comparing the risk of fracture in HD versus general population was moderate in 1 study,[60] serious in 1 study,[61] and critical in 2 studies.[11,59] The risk of bias in studies comparing the risk of fracture in dialysis to that in the general population was moderate in 2 studies[8,14] and critical in the other study.[42] The risk of bias in studies comparing the risk of fracture in KT population with that in the general population was moderate in 2 studies[37,39] and serious in 1 study.[38]

Discussion

In this systematic review, we identified 47 studies reporting the risk of fracture in dialysis and KT populations. The incidence of hip fracture in HD group was consistently higher than that reported in PD or KT groups. For overall fracture risk, the incidence seems to be higher in KT compared with HD when considering only studies conducted in cohorts or clinical registries, whereas the incidence is similar in both groups using administrative database studies. Most of these studies have focused on hip or overall fracture, whereas vertebral fracture was rarely addressed. In contrast to fracture incidence, the prevalence of vertebral or overall fracture seems to be similar between HD and KT population. Globally, the risk of bias in these studies was considered critical. The results reinforce the importance of bone fragility as a major health issue in CKD population. Because no direct comparison has been performed due to heterogeneity between studies, the risk of fracture between dialysis and KT population should be further studied.

Dialysis patients (HD and PD) are mostly aged population who suffer from hypogonadism and multiple comorbidities such as diabetes, inactivity, frailty, and cardiovascular disease that predispose them to increased risk of fall and fracture. In addition, some specific factors related to mineral abnormalities in dialysis may further explain the increased risk of fracture in these patients. These include low vitamin D levels, secondary hyperparathyroidism, abnormal calcium metabolism, chronic acidosis state, and higher exposition to heparin due to chronic HD that contribute to low bone mass and worsening of bone microarchitecture and quality.[6,65–68] As a matter of fact, bone microarchitecture defects seem to be different between dialysis population as Pelletier and colleagues[69] have recently shown that trabecular volumetric bone mineral density at the tibia was significantly lower in HD patients compared with PD patients. Nickolas and colleagues[70] also reported that patients on HD had more severe decreases in cortical bone mineral density and greater increases in cortical porosity at the radius comparatively to PD patients. These higher cortical deteriorations could be explained by a higher level of parathyroid hormone in HD patients. Indeed, it has been suggested that PD patients had lower levels of bone markers, which may protect them from secondary hyperparathyroidism-induced high bone turnover disease.[71–73] Recognizing the increased fracture risk in CKD population and its determinants especially in subgroups of dialysis patients are therefore of utmost importance as this condition is currently not correctly addressed by the nephrology community.

In KT patients, the increased risk of fracture is mostly explained by the high steroid doses that are used to reduce graft rejection risk in addition to the standard immunosuppressive regimens that are known to affect bone metabolism.[19,74–77] After transplantation, a high proportion of patients will continue to have abnormalities in parathyroid hormone levels that will affect bone structure.[78,79] Indeed, it has been reported that loss of trabecular bone that contributes to reduced bone strength was most severe in patients with both low and high parathyroid hormone levels.[78,79] Furthermore, KT patients have already a preexistent bone disease that predisposes them to an increased fracture risk post-transplant. The optimal treatment of bone fragility in KT population remains currently unclear. As the steroid doses given to those patients are progressively lowered after KT, it has been suggested that the risk of hip fracture may be higher in dialysis versus KT patients' years after KT.[19] The use of early corticosteroid withdrawal protocol[31] seems to have a role in preservation of bone mineral density at the central skeleton.[78] However, it has also been associated with progressive declines in cortical and trabecular bone density at the peripheral skeleton.[78] At this time, the exact mechanisms leading to bone loss after KT is still not well understood as well as the optimal therapy that should be proposed to these patients in order to reduce fracture risk.

In this systematic review, we have found 5 studies that compared fracture risk between subgroups of dialysis and KT patients. Three studies that compared the risk of hip fracture between HD and PD patients reported a higher risk in HD versus PD, whereas 1 study[19] observed a higher risk of hip fracture for KT versus combined dialysis patients.[9] Only 1 study has compared the risk of hip fracture between HD, PD, and KT, which did not reveal a statistical difference. However, the later results should be interpreted with caution, as only 1 subject experienced an episode of fracture in the PD group. Until now, because of lack of adequate studies, the comparative risk of fracture between dialysis and KT population remains therefore poorly understood. Comparative studies on fracture risk and its

consequences in advanced CKD population are needed to guide prognostication, to clarify the fracture burden on the health cost, and to help define the design of future prevention trials. Recognizing the subgroups of dialysis or KT patients with the higher risk of fracture will guide the evaluation, planning, and implementation of specific strategies to prevent or treat bone fragility, as well as the organization of care of these aging and already vulnerable patients. In line with the recent KDIGO guidelines in CKD-MBD,[80] we believe that it is now time to better target fracture prevention in advanced CKD population to improve the global patients' quality of life and reduce health cost associated with these severe complications.

Our review has several strengths. We have already registered and published our protocol. We used robust methodology according to the highest standards suggested by Cochrane handbook. We included in our review both dialysis and kidney transplant populations, which have commonly been evaluated separately in previous studies. Our review gives an update on comparative risk of fracture in subgroups of dialysis and kidney transplant patients, who are a highly morbid and vulnerable population not yet adequately addressed in osteoporosis studies. Because the diagnosis of fracture may differ from a study to another, we have reported in this systematic review the results according to the methods used for fracture assessment (administrative data, X-rays, questionnaire, clinical registry). We believe that this constitutes a strength of our study. Our review has also limitations. It was not possible to calculate pooled data estimates because of lack of adequate studies assessing the same outcome and to heterogeneity among included studies. Therefore, we could not take into account the effect of age on fracture incidence because a meta-analysis was not performed. Moreover, the context of the fracture was frequently unknown (traumatic or not).[33] Finally, the assessment of mortality, length of stay, and cost post fracture was limited because we are likely to miss studies conceived specifically to evaluate the association between HD, PD, or KT and these outcomes. However, we believe that studies conducted for these outcomes are poorly available in the literature.

In conclusion, from this review, the comparison of fracture risk in dialysis and kidney transplant population suggests clinically important differences across these groups. Unfortunately, these comparisons were rarely performed and heterogeneity prevented us from conducting a quantitative evaluation of differences. Characterization of fracture risk as well as the societal implications of this complication in dialysis and KT population should clearly be the focus of future studies.

Disclosures

All authors state that they have no conflicts of interest.

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