ORIGINAL ARTICLE

Association between bone mineral density at different anatomical sites and both mortality and fracture risk in patients receiving renal replacement therapy: a longitudinal study

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ABSTRACT

Background. The clinical utility of bone mineral density (BMD) measurement by dual-energy X-ray absorptiometry (DXA) is debated in end-stage kidney disease (ESKD). We assessed the ability of BMD measured at different anatomical sites to predict mortality and fracture risk in patients requiring renal replacement therapy (RRT).

Methods. We reviewed all-cause mortality as well as incident hip and overall fracture risk in RRT patients who had BMD measured at the femoral neck, lumbar spine, arm, head, pelvis and total body as part of their routine follow-up between January 2004 and June 2012 at a single university centre.
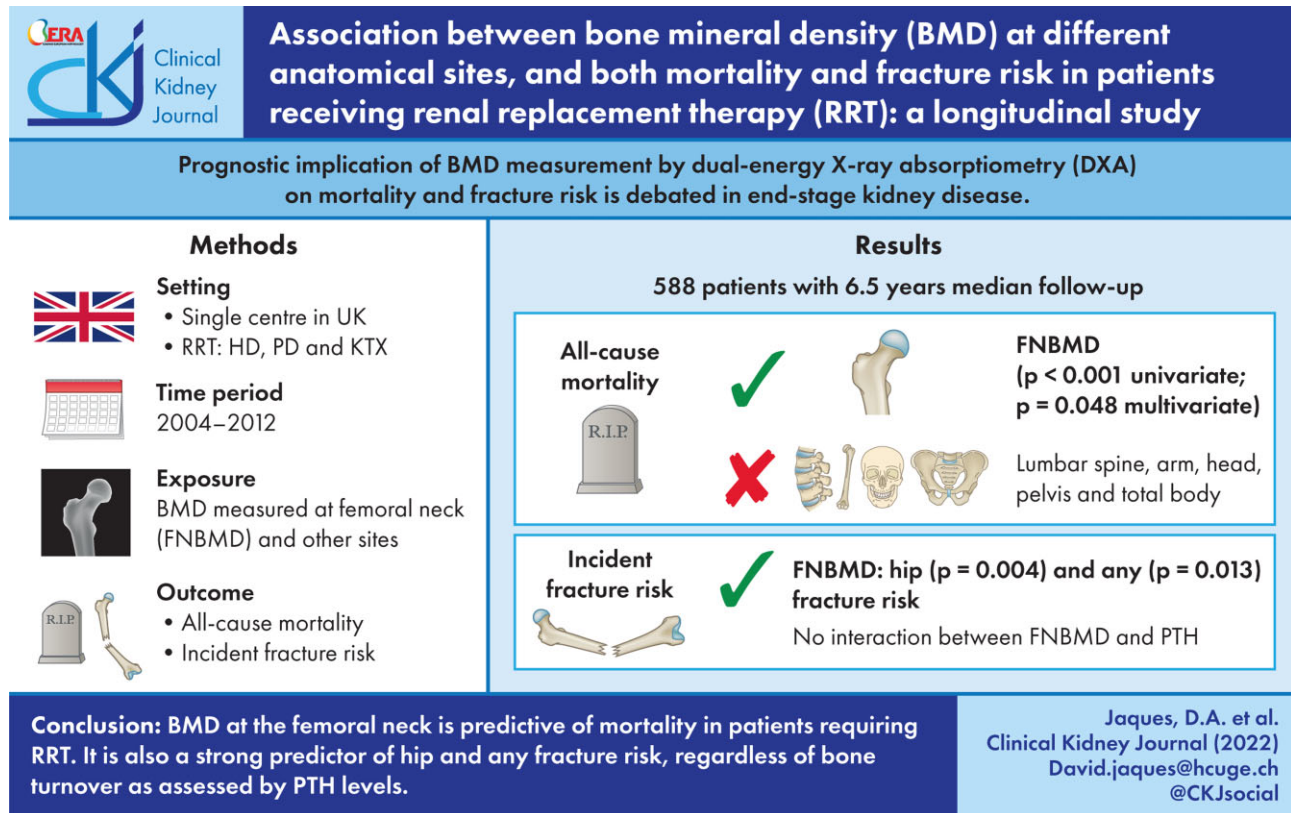
Results. A total of 588 patients were included. The median follow-up was 6.5 years, the mean age was 59.6 years and 57.9% were males. Femoral neck BMD (FNBMD) (normal/high versus low) was negatively associated with mortality in univariate and multivariate analyses ($P < .001$ and $P = .048$, respectively). Other sites of BMD measurements were not associated with mortality. In multivariate analysis, FNBMD was negatively associated with hip and any fracture risk ($P = .004$ and $P = .013$, respectively). No significant interaction was found between FNBMD and gender or parathyroid hormone (PTH) ($P = .112$ and $P = .794$, respectively).

Conclusions. BMD measured at the femoral neck is predictive of mortality in patients requiring RRT, regardless of modality. Low BMD might be a marker of global patient frailty rather than a direct causal factor in this setting. FNBMD is also a strong predictor of hip and any fracture risk in this population, regardless of bone turnover as assessed by PTH levels. FNBMD is thus an overall prognostic marker in patients requiring RRT.

GRAPHICAL ABSTRACT

Association between bone mineral density (BMD) at different anatomical sites, and both mortality and fracture risk in patients receiving renal replacement therapy (RRT): a longitudinal study

Prognostic implication of BMD measurement by dual-energy X-ray absorptiometry (DXA) on mortality and fracture risk is debated in end-stage kidney disease.

Methods

Setting
• Single centre in UK
• RRT: HD, PD and KTX

Time period
2004–2012

Exposure
BMD measured at femoral neck (FNBMD) and other sites

Outcome
• All-cause mortality
• Incident fracture risk

Results

588 patients with 6.5 years median follow-up

All-cause mortality ✓ ✗ FNBMD ($p < 0.001$ univariate; $p = 0.048$ multivariate)

Lumbar spine, arm, head, pelvis and total body

Incident fracture risk ✓ FNBMD: hip ($p = 0.004$) and any ($p = 0.013$) fracture risk

No interaction between FNBMD and PTH

Conclusion: BMD at the femoral neck is predictive of mortality in patients requiring RRT. It is also a strong predictor of hip and any fracture risk, regardless of bone turnover as assessed by PTH levels.

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INTRODUCTION

The kidneys play a pivotal role in systemic mineral metabolism and chronic kidney disease (CKD) is associated with the syndrome of mineral and bone disorder (CKD-MBD) that comprises mineral, bone and cardiovascular (CV) abnormalities [1]. In addition to senile osteoporosis, CKD patients are thus subject to renal osteodystrophy characterized by alterations in bone turnover, mineralization and volume [2]. Taken together, features of CKD-MBD are associated with increased fracture risk, CV damage and mortality, particularly in patients with end-stage kidney disease (ESKD) [3–5].

In clinical practice, bone mineral density (BMD) is measured by dual-energy X-ray absorptiometry (DXA). In the general population, BMD measurement can predict fracture risk and associates with CV and all-cause mortality [6, 7]. In CKD, and even more so in ESKD, evidence is limited. However, an association between BMD and mortality in dialysis patients has been previously described in observational studies [8–10]. Regarding fracture risk, evidence is even scarcer and results from mainly cross-sectional studies are often contradictory on the significance of BMD in dialysis patients [11–14]. Nonetheless, one study reported BMD measured at the femoral neck to be useful in predicting any type of incident fracture in this population [15]. Based mainly on those results, the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines were revised to now suggest BMD evaluation to assess fracture risk in CKD patients, in-

cluding those on dialysis [16]. Finally, limited data suggest that BMD also predicts fracture risk in kidney transplant (KTX) recipients and KDIGO guidelines consequently suggest BMD evaluation in this setting [16–18].

However, several questions remain unanswered and the aim of the present study was to assess the ability of BMD to predict mortality and fracture risk in patients requiring renal replacement therapy (RRT) and to compare the clinical significance of different sites of BMD measurement in this setting.

MATERIALS AND METHODS

Participants

We designed a retrospective observational study where we reviewed the computerized medical records of RRT outpatients treated with haemodialysis (HD), peritoneal dialysis (PD) or KTX who had DXA as part of their routine follow-up between January 2004 and June 2012 at a single university centre (Royal Free Hospital, London, UK). Exclusion criteria were as follows: <18 years old, bilateral hip replacement unable to lie down on a DXA table and declined to attend for scan. Incident hip, arm and spine fractures were considered. Fractures were documented based on verified radiology reports. CKD-MBD management was according to the attending physician's discretion based on Kidney

Disease Outcomes Quality Initiative 2003 guidelines or 2009 KDIGO guidelines [16, 19]. Centre policy was to follow UK Renal Association guidelines for dialysis prescriptions (HD and PD) [20, 21]. Patient comorbidities and relevant medical history were obtained from computerized medical records. Diabetes was defined based on the presence of related medication. CV disease was defined as myocardial infarction, stroke or peripheral vascular disease.

Variables

Whole-body DXA was performed using a Hologic Discovery A(S/N87402) (software version 13.5.2.1; Hologic, Marlborough, MA, USA). BMD was expressed as g/cm^2 and measured at the following sites: femoral neck, lumbar spine (L1–L4), arm, head, pelvis and total body. T- and Z-scores were obtained using the third National Health and Nutrition Examination Survey (NHANES III) reference population [22]. Osteopenia and osteoporosis were defined as a T-score <-1 and -2.5, respectively. BMD was assessed after starting dialysis and then according to the supervising clinician's discretion. Venous blood samples were measured using a standard multichannel biochemical analyzer (Roche Integra, Roche Diagnostics, Lewes, UK). Serum albumin was determined by the bromocresol green method. Intact parathyroid hormone (PTH) was measured using a two-site immunometric assay (Roche Diagnostics, Burgess Hill, Sussex, UK). Laboratory values were collected at the time of the initial DXA scan and then concomitantly with repeat BMD measurements.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD) or median [interquartile range (IQR)] according to distribution. Baseline characteristics were compared between three groups based on BMD tertiles at the femoral neck. Patient's characteristics were compared between groups using one-way analysis of variance or Kruskal–Wallis and chi-squared tests for continuous and categorical variables, respectively.

In a first set of analyses, all-cause mortality was considered as the outcome and BMD at various sites the main predictor. BMD was divided into tertiles and then dichotomized in two categories (normal/high versus low BMD). The Cox proportional hazards model was used with BMD as a two-level categorical variable. Multivariate analyses included the following variables as potential confounders based on prior scientific knowledge: RRT mode (HD, PD or KTX), age, gender, smoking, diabetes, CV disease, body mass index (BMI), serum calcium, serum phosphate, serum albumin and C-reactive protein (CRP) [3, 8, 23].

In a second set of analyses, incident fracture was considered as the outcome. BMD categorization and the Cox proportional hazards model were used as described above. Multivariate analyses included the following variables as potential confounders based on prior scientific knowledge: RRT mode (HD, PD or KTX), age, gender, smoking, diabetes, BMI, ethnicity, PTH and CRP [15, 18, 24].

In multivariate analyses including T-score, gender and ethnicity were omitted as covariates in order to avoid multicollinearity. As data could be collected on several occasions for every patient, multiple-records-per-subject was implemented for every model. In the sensitivity analysis, interactions were tested among variables of interest. Models with and without interaction terms were compared using the likelihood ratio (LR) test. Interaction was considered significant when the P-value for the LR test was <.05. Variables were log-transformed according to distribution when appropriate. Results are presented as hazard ratios (HRs) and associated 95% confidence intervals (CIs). A two-sided P-value <.05 was considered significant in every analysis. Statistical analyses were conducted using Stata version 15 (StataCorp, College Station, TX, USA).

Ethics

This study was checked with and complied with the UK National Health Service (NHS) Health Research Authority guidelines for clinical audit and service development (https://www.hra.nhs.uk). It was registered with the University College of London (UCL) Department of Nephrology Royal Free Hospital. This study was carried out in accordance with the Declaration of Helsinki (2013).

RESULTS

During the study period, 588 patients had at least one DXA measurement and were thus included in the present analysis. The median follow-up period was 6.5 years (IQR 2.7–10.8). During follow-up, the mean number of DXA measurements per patient was 1.7 ± 1.2 with 1027 DXA measurements in total. During the follow-up period, 399 deaths, 49 hip fractures, 48 spine fractures and 26 arm fractures were observed. The mean femoral neck BMD (FNBMD) at baseline was 0.74 ± 0.16 g/cm^2. Patients' characteristics based on tertiles of FNBMD at baseline are described in Table 1. The mean age was 59.6 years with 57.9% males. Overall, proportions of HD, DP and KTX patients were 62.2%, 34.8% and 2.9%, respectively. Compared with patients with higher FNBMD, those with lower FNBMD were significantly older; more frequently female; had lower BMI, longer dialysis vintage, higher serum alkaline phosphatase, and lower serum albumin and were less frequently on phosphate binders (P < .05 for all). Other demographic, clinical and laboratory characteristics were similar across tertiles of FNBMD. An alternative description of patients characteristics based on FNBMD categories (normal, osteopenia and osteoporosis) is presented in Supplementary data, Table S1.

Mortality

Results from the Cox model using FNBMD (normal/high versus low) as a predictor of mortality are presented in Table 2. In univariate analysis, FNBMD was negatively associated with mortality. When adjusting for RRT mode, age and gender, FNBMD was negatively associated with mortality (partially adjusted model). When adjusting for smoking, diabetes, CV disease, BMI, serum calcium, phosphate, albumin and CRP, in addition to the above-mentioned variables, FNBMD was negatively associated with mortality (fully adjusted model) (Figure 1). In the fully adjusted model, other variables positively associated with mortality were as follows: age [HR 1.04 (95% CI 1.03–1.05), P < .001], male gender [HR 1.30 (95% CI 1.02–1.66), P = .029], smoking [HR 1.25 (95% CI 1.00–1.56), P = .048], diabetes [HR 1.65 (95% CI 1.31–2.06), P < 0.001] and CRP [HR 1.16 (95% CI 1.07–1.27), P < .001]. Other variables negatively associated with mortality were as follows: PD compared with HD [HR 0.69 (95% CI 0.54–0.87), P = .002], BMI [HR 0.97 (95% CI 0.94–0.99), P = .018) and serum albumin [0.96 (95% CI 0.94–0.99), P = .012]. Variables not associated with mortality were as follows: KTX compared with HD (P = .181), CV disease (P = .214), serum calcium (P = .162) and serum phosphate (P = .820).

Alternative results from the Cox model using FNBMD expressed as the T-score or the presence of osteoporosis as a predictor of mortality are presented in Supplementary data, Tables S2 and S3, respectively.

Table 1. Patients' characteristics at baseline according to tertiles of FNBMD

Characteristics	Overall (N = 588)	Low BMD (n = 196)	Medium BMD (n = 196)	High BMD (n = 196)	P-value
FNBMD (g/cm^2), mean ± SD	0.74 ± 0.16	0.57 ± 0.07	0.73 ± 0.04	0.92 ± 0.11	**<.001**
T-score, mean ± SD	−1.40 ± 1.19	−2.56 ± 0.61	−1.45 ±0.39	−0.16 ± 0.91	**<.001**
Osteoporosis, n (%)	88 (15.2)	88 (44.9)	0 (0)	0 (0)	**<.001**
Z-score, mean ± SD	−0.32 ± 1.18	−1.30 ± 0.79	−0.39 ± 0.64	0.74 ± 1.00	**<.001**
Demographic characteristics					
Age (years), mean ± SD	59.6 ± 16.2	64.8 ± 15.9	59.5 ± 16.1	54.5 ± 15.2	**<.001**
Gender (men), n (%)	341 (57.9)	98 (50.0)	120 (61.2)	123 (62.7)	**.020**
BMI (kg/m^2), mean ± SD	26.3 ± 5.5	24.3 ± 4.6	26.3 ± 5.1	28.3 ± 6.0	**<.001**
Ethnicity (Caucasian), n (%)	294 (50.7)	101 (51.5)	105 (54.9)	88 (45.8)	.195
Smoker, n (%)	223 (40.1)	76 (41.3)	78 (41.9)	69 (37.1)	.586
Clinical characteristics					
Diabetic, n (%)	209 (36.0)	80 (41.0)	66 (34.3)	63 (32.6)	.192
CV disease, n (%)	150 (25.9)	55 (28.0)	55 (28.8)	40 (20.8)	.144
RRT, n (%)					
HD	362 (62.2)	129 (65.8)	113 (58.5)	120 (62.1)	.283
PD	203 (34.8)	59 (30.1)	74 (38.3)	70 (36.2)	
KT	17 (2.9)	8 (4.0)	6 (3.1)	3 (1.5)	
Dialysis vintage (months), median (IQR)	21.9 (5.1–60.9)	31.7 (7.5–72.0)	18.4 (4.3–59.1)	17.4 (4.6–49.6)	**.020**
Transplant vintage (months), median (IQR)	93.2 (8.7–144.4)	128.2 (28.3–174.8)	53.6 (3.2–100.5)	93.3 (2.6–128.8)	.475
Laboratory characteristics					
Serum calcium (mmol/L), mean ± SD	2.32 ± 0.20	2.32 ± 0.17	2.32 ± 0.22	2.34 ± 0.21	.333
Serum phosphate (mmol/L), mean ± SD	1.54 ± 0.48	1.46 ± 0.43	1.55 ± 0.47	1.60 ± 0.54	.07
PTH (pmol/L), median (IQR)	19.8 (10.2–37.1)	17.5 (10.2–33.7)	21.3 (10.8–37.1)	20.5 (10.3–39.3)	.571
Vitamin D (nmol/L), median (IQR)	30.9 (15.8–57.7)	29.9 (13.5–56.2)	26.2 (15.0–48.0)	44.4 (18.4–79.0)	.112
Alkaline phosphatase (U/L), median (IQR)	87.5 (66.5–121.0)	98.0 (77.0–129.0)	88.0 (64.0–117.0)	80.5 (61.0–114.0)	**.031**
Serum albumin (g/L), mean ± SD	38.8 ± 4.9	37.8 ± 4.9	39.2 ± 5.0	39.5 ± 4.7	**<.001**
Haemoglobin (g/L), mean ± SD	114.7 ± 16.0	115.5 ± 15.5	113.3 ± 16.1	115.3 ± 16.4	.320
CRP (mg/L), median (IQR)	5.0 (2.0–14.0)	5.0 (2.0–15.0)	5.0 (2.0–16.0)	5.0 (2.0–12.0)	.536
Medications					
Phosphate binder, n (%)	468 (80.8)	145 (74.3)	159 (83.2)	164 (84.9)	**.017**

Bold values are significant at P < .05.

Table 2. Cox model using FNBMD (normal/high versus low) as a predictor of mortality

Model	HR (95% CI)	P-value
Univariate model	0.52 (0.42–0.64)	**<.001**
Partially adjusted model[a]	0.63 (0.51–0.79)	**<.001**
Fully adjusted model[b]	0.78 (0.61–0.99)	**.048**

[a]Adjusted for RRT mode, age and gender.
[b]Adjusted for variables considered above as well as smoking, diabetes, CV disease, BMI, serum calcium, serum phosphate, serum albumin and CRP.
Bold values are significant at P < .05.

In univariate analysis, partially and fully adjusted models, BMD (normal/high versus low) measured at the following sites was not associated with mortality: lumbar spine, total body, head, pelvis and arm (Supplementary data, Table S4).

Incident fractures risk

Results from the Cox model using FNBMD (normal/high versus low) as a predictor of incident hip fracture and any fracture risk are presented in Table 3. In univariate analysis, FNBMD was negatively associated with hip fracture and any fracture risk. When adjusting for RRT mode, age and gender, FNBMD was negatively associated with hip and any fracture risk (partially adjusted model). When adjusting for smoking, diabetes, BMI,

Table 3. Cox model using FNBMD (normal/high versus low) as a predictor of incident fracture risk

Model	HR (95% CI)	P-value
Hip fracture		
Univariate model	0.21 (0.10–0.45)	**<.001**
Partially adjusted model[a]	0.33 (0.15–0.74)	**.007**
Fully adjusted model[b]	0.22 (0.08–0.62)	**.004**
Any fracture		
Univariate model	0.30 (0.18–0.50)	**<.001**
Partially adjusted model[a]	0.45 (0.26–0.77)	**.004**
Fully adjusted model[b]	0.42 (0.21–0.83)	**.013**

[a]Adjusted for RRT mode, age and gender.
[b]Adjusted for variables considered above as well as smoking, diabetes, BMI, ethnicity, PTH and CRP.
Bold values are significant at P < .05. FNBMD, femoral neck bone mineral density; RRT, renal replacement therapy; BMI, body mass index; PTH, parathromone; CRP, C-reactive protein.

ethnicity, PTH and CRP, in addition to the above-mentioned variables, FNBMD was negatively associated with hip and any fracture risk (fully adjusted model) (Figure 2A and B). In the fully adjusted model, other variables positively associated with hip fracture risk were as follows: age [HR 1.07 (95% CI 1.04–1.11), P < .001], African-American compared with Caucasian [HR 3.02 (95% CI 1.03–8.83), P = .044] and CRP [HR 1.36 (95% CI 1.02–1.80), P = .030]. Variables not associated with hip
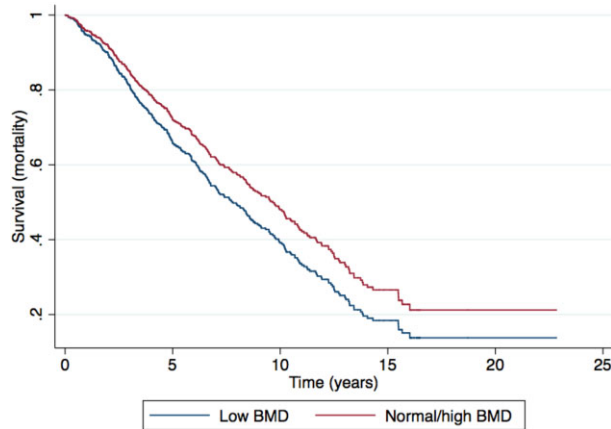
FIGURE 1: Cox survival estimates for mortality according to FNBMD (normal/high versus low). Estimates are based on the fully adjusted model and are thus adjusted for RRT mode, age, gender, smoking, diabetes, CV disease, BMI, serum calcium, serum phosphate, serum albumin and CRP.
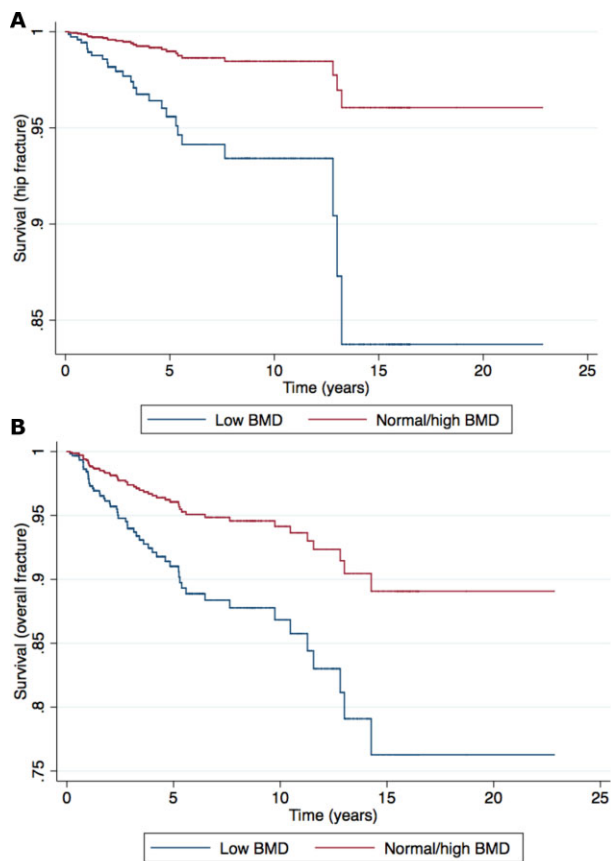

FIGURE 2: Cox survival estimates for incident fracture according to FNBMD (normal/high versus low). **(A)** Hip fracture. **(B)** Any fracture. Estimates are based on the fully adjusted model and are thus adjusted for RRT mode, age, gender, smoking, diabetes, BMI, ethnicity, PTH and CRP.

fracture risk were as follows: PD compared with HD (P = .470), KTX compared with HD (P = .857), male gender (P = .599), smoking (P = .658), diabetes (P = .338), BMI (P = .448), Asian compared with Caucasian (P = .438) and PTH (P = .729). In the fully adjusted model, other variables positively associated with any fracture risk were as follows: age [HR 1.05 (95%

CI 1.03–1.08), P < .001] and CRP [HR 1.29 (95% CI 1.05–1.58), P = .014]. Variables not associated with any fracture risk were as follows: PD compared with HD (P = .195), KTX compared with HD (P = .061), male gender (P = .447), smoking (P = .861), diabetes (P = .833), BMI (P = .731), ethnicity (P = .197) and PTH (P = .534).

When considering hip fracture risk, no significant interaction was found between FNBMD and gender or PTH (P = .112 and P = .794 for the LR test, respectively). When considering any fracture risk, no significant interaction was found between FNBMD and gender or PTH (P = .164 and P = .842 for the LR test, respectively).

Alternative results from the Cox model using FNBMD expressed as the T-score or presence of osteoporosis as a predictor of incident fracture risk are presented in Supplementary data, Tables S5 and S6, respectively.

DISCUSSION

In this longitudinal study, BMD measured at the femoral neck was predictive of mortality in a population of HD, PD and KTX patients after a median follow-up of 6.5 years, while BMD measured at other sites was not. Moreover, FNBMD was strongly associated with increased hip as well as any fracture risk in this population, independent of potential confounders.

BMD and mortality

As compared with the general population where there is an abundance of data, the association between BMD and mortality is less evident in ESKD patients requiring RRT. Two earlier studies reported an association between hip BMD and mortality in HD patients [8, 25]. In a more recent article, forearm, but not hip or spine, BMD was associated with mortality [9]. A Swedish group reported that total body BMD was an independent predictor of mortality in a series of studies including both HD and PD patients [3, 10, 26]. Finally, in a report by the same group, low vertebral BMD measured by computed tomography (CT) was more strongly associated with mortality than total body BMD measured by DXA [23].

Our results differ from those of previous studies in several aspects. Most importantly, while FNBMD measured was an independent predictor of mortality in our population, the significance of this association was markedly altered when adjusting for potential clinical and biological confounders. Specifically, when markers of CV burden were included in the model, the P-value for FNBMD decreased to borderline values. A theoretical explanation for this equivocal result could be insufficient statistical power. This is unlikely, however, as our sample size was larger than that of prior comparable studies. Moreover, our median follow-up period of 6.5 years was also significantly longer compared with previous studies, translating into a greater number of events and increased statistical power [3, 8, 10, 26]. A more plausible explanation for this borderline finding is the confounding effect of considered covariates. From a pathophysiological point of view, the assumed relationship between low BMD and increased mortality involves the bone–vascular axis, whereby defective bone status may reflect vascular alterations [27]. As such, it could be postulated that the direct causal factor for increased mortality in this setting is in fact the impaired vascular status, while bone alteration could merely represent an indirect marker of CV burden. In line with this hypothesis, age, male gender, smoking, diabetes and CRP were all significant predictors of mortality in our population. Of note, in line with prior

observational studies, HD patients (compared with PD patients) as well as patients with low BMI and serum albumin had a higher mortality risk [28–30]. According to those results, low FNBMD could thus be perceived as a global marker of patient frailty rather than a direct causal factor in the overall prognosis of ESKD patients.

Among various BMD measurement sites, the femoral neck was the only predictor of mortality in our study, while lumbar spine, total body, head, pelvis and arm were not. Our results contrast with those of prior studies [10]. Vascular calcification is highly prevalent in ESKD and may alter BMD evaluation, as structural tissue alterations influence DXA measurements [31]. As such, abdominal aortic calcifications could explain why spinal BMD assessment was not correlated to mortality in our report as well as in several prior studies [8–10, 25]. It is globally still debated which BMD measurement site is most appropriate to evaluate patients' overall prognosis. DXA and high-resolution CT demonstrated preferential cortical bone alterations in CKD patients as compared with trabecular-rich regions [32]. Cortical-rich sites, such as the skull and the femoral neck, could thus represent preferred markers of underlying pathology in CKD patients. FNBMD has also been highly negatively correlated with cortical porosity as assessed by bone biopsy [33]. Those elements could explain the preferential prognosis value of FNBMD in our study. A previous study reported on BMD measured at different anatomical sites and 5-year all-cause mortality in 426 patients starting dialysis [10]. Hip BMD was not associated with mortality in this study. However, in contrast to the femoral neck, the global hip region is richer in trabecular bone, potentially explaining this negative result. Authors also found low head BMD to be associated with increased mortality in this report. However, while BMD at all body sites was lower in women than in men, women had higher head BMD than men in this study. This finding could potentially be related to the significant prevalence of hyperostosis cranii in postmenopausal women [34]. As multivariate adjustment did not account for the gender effect in this report, this result could merely represent a confounding effect of gender on mortality risk. The fact that our analyses were adjusted for gender could explain that we did not reproduce this finding in the present study. Finally, in contrast to Iseri et al. [10], we could not find an association between mortality and BMD measured at the total body or pelvis. Here again, the lack of cortical bone predominance could explain why those areas were not significant in predicting mortality in our study.

BMD and fracture risk

The increased risk of fracture in ESKD patients as compared with the general population is well established [35]. However, the association between BMD and fracture risk in this population is still debated, as prior studies have yielded contradictory results. In an early study, lumbar spine BMD was associated with vertebral fracture risk in HD patients, but only men were included and results were not adjusted for potential confounders [11]. Several later reports could not confirm an association between BMD measured at different sites and fracture risk in HD patients [12–14]. Importantly, Iimori et al. [15] reported on 485 HD patients followed during 40 months with annual BMD measurements. They found BMD measured at the hip region to be predictive of any type of incident fracture, but only in females with low PTH.

In our population of HD, PD and KTX patients, BMD measured at the femoral neck was a strong predictor of incident fracture risk. This is in marked contrast with previous negative studies [12–14]. Insufficient statistical power is, however, a likely limitation of these studies, as they generally included 100 patients at most. Similar to Iimori et al. [15], we found that FNBMD was predictive not only of hip fracture, but also of overall fracture risk. Previous studies reporting on fracture risk and PTH levels in dialysis patients are notably discordant. A first study described a higher risk of hip fracture with low PTH [36]. A second study reported a weakly significant U-shaped association between PTH and the risk of vertebral and hip fracture [37]. Finally, at the other end of the spectrum, elevated PTH was associated with an increased risk of any fracture in a third study [38]. In contrast to these studies and results from Iimori et al. [15], BMD predicted fracture risk regardless of gender and PTH levels in our study. Moreover, as interaction testing was negative, gender and PTH level did not significantly modulate the relationship between BMD and fracture risk in our population. This would suggest that low BMD predisposes to fracture regardless of the underlying osteodystrophic physiopathology and bone turnover as assessed by standard biochemical markers might not have a significant role in determining fracture risk in this population.

The incidence of hip fracture has been shown to increase with age regardless of CKD severity [39]. However, previous reports focusing on BMD evaluation did not find a significant association between age and fracture risk in dialysis [13, 15]. In our study, aging was very significantly associated with increased fracture risk. Interestingly, this relationship was independent of other predictors as well as BMD itself, suggesting a susceptibility to fracture in aging patients beyond what could be inferred from reduced BMD only. In that regard, inflammation as measured by CRP was also associated with an increased fracture risk in our population, independent of BMD measurement.

Limitations

As with any observational study, association does not necessarily imply causation. Longitudinal design and multivariate adjustment, however, improved the reliability of our findings. While several laboratory values were measured, specific biomarkers of bone turnover were not available in this cohort. Moreover, as bone biopsy is not routinely performed in our centre, such information was not available. Information regarding treatment was also limited and the use of anti-resorptive medication could not be accounted for in this study, although centre policy was not to use bisphosphonates in dialysis patients. Finally, although overall sufficient, the sample size did not allow for refined subgroup analyses. In particular, the very limited number of KTX patients did not allow definite conclusions to be drawn for this population.

CONCLUSIONS

In this longitudinal study, we report that bFNBMD is associated with an increased risk of mortality in a CKD population of HD, PD and KTX patients. However, low FNBMD might be a marker of global patient frailty rather than a direct causal factor in this setting. In contrast to the femoral neck, prognostic information based on BMD measured at the lumbar spine, total body, head, pelvis and arm is not as valuable. In addition to mortality, FNBMD is also a strong predictor of hip as well as overall fracture risk in this population, regardless of bone turnover as assessed by PTH levels. Thus FNBMD is a reliable prognostic marker in patients requiring RRT and could thus potentially serve as a target to guide interventions. Whether treatments aimed at increasing

BMD could improve patients' prognosis has to be tested in interventional studies.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

FUNDING

None.

CONFLICT OF INTEREST STATEMENT

All authors declare no conflicts of interest. This manuscript has not been published and is not being considered for publication elsewhere, in whole or in part, in any language.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

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