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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Running title: Bone mineral density, mortality and fracture risk in RRT
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 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 center.

Results. 588 patients were included. Median follow-up was 6.5 years. Mean age was 59.6 with 57.9% males. Femoral neck BMD (FNBMD) (normal/high vs low) was negatively associated with mortality in univariate and multivariate analysis (p<0.001 and p=0.048, respectively). Other sites of BMD measurements were not associated with mortality. In multivariate analysis, FNBMD was negatively associated with hip and any fracture risk.
fracture risk (p=0.004 and p=0.013, respectively). No significant interaction was found between FNBMD and gender or PTH (p=0.112 and p=0.794, 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.

**Keywords:** bone mineral density, chronic kidney disease, dialysis, fracture, mortality, transplantation
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, evidences are limited. However, an association between BMD and mortality in dialysis patients has been previously described in observational studies(8–10). Regarding fracture risk, evidences are 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, KDIGO guidelines were revised to now suggest BMD evaluation to assess fracture risk in CKD patients including those on dialysis(16). Finally, limited data suggest that BMD also predicts fracture risk in kidney transplant recipients and KDIGO guidelines consequently suggest BMD evaluation also in this setting(16–18).

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

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

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 kidney transplant (KTX) who had DXA as part of their routine follow-up between January 2004 and June 2012 at a single university center (Royal Free Hospital, London, UK). Exclusion criteria were: 1) <18 years-old, 2) bilateral hip replacements, 3) unable to lie down on DXA table, 4) 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 attending physician’s discretion based on KDOQI 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 co-morbidities 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, Massachusetts, USA. BMD was expressed as g/cm² and measured at the following sites: femoral neck, lumbar spine (L1 to L4), arm, head, pelvis and total body. T and Z-score were obtained using the third National Health and Nutrition Examination Survey (NHANES III) reference population(22). Osteopenia and osteoporosis were defined as T-score below -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 multi-channel 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) according to distribution. Baseline characteristics were compared between three groups based on BMD tertiles at femoral neck. Patient’s characteristics were compared between groups using one-way ANOVA or Kruskal-Wallis and Chi-square 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 in tertiles and then dichotomized in two categories (normal/high vs low BMD). Cox proportional hazard 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 Cox proportional hazard 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 sensitivity analysis, interactions were tested amongst variables of interest. Models with and without interaction terms were compared using likelihood ratio (LR) test. Interaction was considered significant when p-value for LR test was <0.05. Variables were log-transformed according to distribution when appropriate. Results are presented as hazard ratios (HR) and associated 95% confidence intervals (95% CI). A two-sided p-value <0.05 was considered significant in every analysis. Statistical analyses were conducted using STATA version 15 (StataCorp, 4905 Lakeway Drive, College Station, Texas 77845 USA).

Ethics

This study was checked with, and complied with the United Kingdom (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. Median follow-up period was 6.5 (2.7 – 10.8 years). During follow-up, mean number of DXA measurement per patient was 1.7 +/- 1.2 with 1'027 DXA measurement in total. During the follow-up period, 399 deaths, 49 hip fractures, 48 spine fractures and 26 arm fractures were observed. Mean BMD at femoral neck (FNBMD) at baseline was 0.74 +/- 0.16 g/cm². Patients characteristics based on tertiles of FNBMD at baseline are described in table 1. Mean age was 59.6 with 57.9%
males. Overall, proportions of HD, DP and KTX patients were 62.2%, 34.8% and 2.9% respectively. Compared to patients with higher FNBMD, those with lower FNBMD were significantly older, more frequently female, had lower BMI, longer dialysis vintage, higher serum alkaline phosphatase, lower serum albumin and were less frequently on phosphate binders (p<0.05 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 table 1.

**Mortality**

Results from Cox model using FNBMD (normal/high vs 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: age (HR 1.04, 95%CI 1.03 to 1.05, p<0.001), male gender (HR 1.30, 95%CI 1.02 to 1.66, p=0.029), smoking (HR 1.25, 95%CI 1.00 to 1.56, p=0.048), diabetes (HR 1.65, 95%CI 1.31 to 2.06, p<0.001) and CRP (HR 1.16, 95%CI 1.07 to 1.27, p<0.001). Other variables negatively associated with mortality were: PD compared to HD (HR 0.69, 95%CI 0.54 to 0.87, p=0.002), BMI (HR 0.97, 95%CI 0.94 to 0.99, p=0.018) and serum albumin (0.96, 95%CI 0.94 to 0.99, p=0.012). Variables not associated with mortality were: KTX compared to HD (p=0.181), CV disease (p=0.214), serum calcium (p=0.162) and serum phosphate (p=0.820).
Alternative results from Cox model using FNBMD expressed as T-score or presence of osteoporosis as a predictor of mortality are presented in supplementary table 2 and 3 respectively.

In univariate analysis, partially and fully adjusted models, BMD (normal/high vs low) measured at the following sites was not associated with mortality: lumbar spine, total body, head, pelvis and arm (supplementary table 4).

**Incident fractures risk**

Results from Cox model using FNBMD (normal/high vs 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, 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 2b). In the fully adjusted model, other variables positively associated with hip fracture risk were: age (HR 1.07, 95%CI 1.04 to 1.11, p<0.001), Afro-American compared to Caucasian (HR 3.02, 95%CI 1.03 to 8.83, p=0.044) and CRP (HR 1.36, 95%CI 1.02 to 1.80, p=0.030). Variables not associated with hip fracture risk were: PD compared to HD (p=0.470), KTX compared to HD (p=0.857), male gender (p=0.599), smoking (p=0.658), diabetes (p=0.338), BMI (p=0.448), Asian compared to Caucasian (p=0.438) and PTH (p=0.729). In the fully adjusted model, other variables positively associated with any fracture risk were: age (HR 1.05, 95%CI 1.03 to 1.08, p<0.001) and CRP (HR 1.29, 95%CI 1.05 to 1.58, p=0.014). Variables not associated with any fracture risk were: PD compared to HD (p=0.195), KTX compared to HD (p=0.061), male gender (p=0.447), smoking (p=0.861), diabetes (p=0.833), BMI (p=0.731), ethnicity (p=0.197) and PTH (p=0.534).
When considering hip fracture risk, no significant interaction was found between FNBMD and gender or PTH (p=0.112 and p=0.794 for LR test respectively). When considering any fracture risk, no significant interaction was found between FNBMD and gender or PTH (p=0.164 and p=0.842 for LR test respectively).

Alternative results from Cox model using FNBMD expressed as T-score or presence of osteoporosis as a predictor of incident fracture risk are presented in supplementary table 5 and 6 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, independently of potential confounders.

**BMD and mortality**

As compared to the general population where there is 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 paper, 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 BMD measured at femoral neck 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, p-value for FNBMD decreased to borderline values. A theoretical explanation for this equivocal result could be an insufficient statistical power. This is however unlikely 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 to previous studies translating into higher 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. On 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 predictor of mortality in our population. Of note, in line with prior observational studies, HD patients (compared to PD patients) as well as patients with low BMI and serum albumin had 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.

Amongst 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 are contrasting 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 to 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 five-year all-cause mortality in 426 starting dialysis (10). Hip BMD was not associated with mortality in this study. However, in contrast to 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 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., we could not find an association between mortality and BMD measured at total body or pelvis (10). Here again, the lack of cortical bone predominance could explain that 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). The association between BMD and fracture risk in this population is however 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 men only 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, limori et al. reported on 485 HD patients followed during 40 months with annual BMD measurement. They found BMD measured at the hip region to be predictive of any type of incident fracture, but only in females with a low PTH(15).

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. Similarly to limori et al., we found that FNBMD was predictive not only of hip fracture but also of overall fracture risk(15). 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 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 increased risk of any fracture in a third study(38). In contrast to these studies and results from limori et al., BMD predicted fracture risk regardless of gender and PTH levels in our study(15). 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.

Incidence of hip fracture has been shown to rise 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 increased fracture risk in our population, independently of BMD measurement.

**Limitations**

As with any observational study, association does not necessarily imply causation. Longitudinal design and multivariate adjustment however improved 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 center, such information could not be used. Information regarding treatment was also limited and the use of anti-resorptive medication could not be accounted for in this study, although center policy was not to use bisphosphonates in dialysis patients. Finally, although overall sufficient, the sample size did not allow for refined sub-group analyses. In particular, the very limited number of KTX patients did not allow definite conclusions to be drawn on this population.

**CONCLUSIONS**

In this longitudinal study, we report that BMD measured at the femoral neck is associated with increased risk of mortality in a CKD population of HD, PD and KTX patients. Although, low BMD at the femoral neck might be a marker of global patient frailty rather than a direct causal factor in this setting. In contrast to femoral neck, prognostic information based on BMD measured at lumbar spine, total body, head, pelvis and arm is not as valuable. In addition to mortality, BMD at femoral neck 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, BMD measured at the femoral neck 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.

FUNDING

This study required no specific source of funding.

CONFLICT OF INTEREST STATEMENT

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

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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/cm²)   | 0.74 +/- 0.16 | 0.57 +/- 0.07 | 0.73 +/- 0.04    | 0.92 +/- 0.11  | <0.001  |
| T-score         | -1.40 +/- 1.19 | -2.56 +/- 0.61 | -1.45 +/- 0.39  | -0.16 +/- 0.91 | <0.001  |
| Osteoporosis    | 88 (15.2%)    | 88 (44.9%)    | 0 (0%)           | 0 (0%)         | <0.001  |
| Z-score         | -0.32 +/- 1.18 | -1.30 +/- 0.79 | -0.39 +/- 0.64  | 0.74 +/- 1.00  | <0.001  |

Demographic characteristics

| Age (years)     | 59.6 +/- 16.2 | 64.8 +/- 15.9 | 59.5 +/- 16.1    | 54.5 +/- 15.2   | <0.001  |
| Gender (men)    | 341 (57.9%)   | 98 (50.0%)    | 120 (61.2%)      | 123 (62.7%)     | 0.020   |
| BMI (kg/m²)     | 26.3 +/- 5.5  | 24.3 +/- 4.6  | 26.3 +/- 5.1     | 28.3 +/- 6.0    | <0.001  |
| Ethnicity (Caucasian) | 294 (50.7%) | 101 (51.5%) | 105 (54.9%) | 88 (45.8%) | 0.195 |
| Smoker          | 223 (40.1%)   | 76 (41.3%)    | 78 (41.9%)       | 69 (37.1%)      | 0.586   |

Clinical characteristics

| Diabetic        | 209 (36.0%)   | 80 (41.0%)    | 66 (34.3%)       | 63 (32.6%)      | 0.192   |
| CV disease      | 150 (25.9%)   | 55 (28.0%)    | 55 (28.8%)       | 40 (20.8%)      | 0.144   |
| RRT             |               |               |                  |                |         |
| HD              | 362 (62.2%)   | 129 (65.8%)   | 113 (58.5%)      | 120 (62.1%)     | 0.283   |
| 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 | 21.9 (5.1 –) | 31.7 (7.5 –) | 18.4 (4.3 –)     | 17.4 (4.6 –)    | 0.020   |
| (months)   | 60.9 | 72.0 | 59.1 | 49.6 |        |
|------------|------|------|------|------|--------|
| Transplant vintage (months) | 93.2 (8.7 – 144.4) | 128.2 (28.3 – 174.8) | 53.6 (3.2 – 100.5) | 93.3 (2.6 – 128.8) | 0.475 |

**Laboratory characteristics**

|                          |       |       |       |       |       |
|--------------------------|-------|-------|-------|-------|-------|
| Serum calcium (mmol/L)   | 2.32 +/- 0.20 | 2.32 +/- 0.17 | 2.32 +/- 0.22 | 2.34 +/- 0.21 | 0.333 |
| Serum phosphate (mmol/L) | 1.54 +/- 0.48 | 1.46 +/- 0.43 | 1.55 +/- 0.47 | 1.60 +/- 0.54 | 0.07  |
| PTH (pmol/L)             | 19.8 (10.2 – 37.1) | 17.5 (10.2 – 33.7) | 21.3 (10.8 – 37.1) | 20.5 (10.3 – 39.3) | 0.571 |
| Vitamin D (nmol/L)       | 30.9 (15.8 – 57.7) | 29.9 (13.5 – 56.2) | 26.2 (15.0 – 48.0) | 44.4 (18.4 – 79.0) | 0.112 |
| Alkaline phosphatase (U/L)| 87.5 (66.5 – 121.0) | 98.0 (77.0 – 129.0) | 88.0 (64.0 – 117.0) | 80.5 (61.0 – 114.0) | 0.031 |
| Serum albumin (g/L)      | 38.8 +/- 4.9 | 37.8 +/- 4.9 | 39.2 +/- 5.0 | 39.5 +/- 4.7 | <0.001 |
| Haemoglobin (g/L)        | 114.7 +/- 16.0 | 115.5 +/- 15.5 | 113.3 +/- 16.1 | 115.3 +/- 16.4 | 0.320 |
| CRP (mg/L)               | 5.0 (2.0 – 14.0) | 5.0 (2.0 – 15.0) | 5.0 (2.0 – 16.0) | 5.0 (2.0 – 12.0) | 0.536 |

**Medications**

|                          |       |       |       |       |       |
|--------------------------|-------|-------|-------|-------|-------|
| Phosphate binder         | 468 (80.8%) | 145 (74.3%) | 159 (83.2%) | 164 (84.9%) | 0.017 |

Bold values correspond to p<0.05.
Abbreviations: FNBMD, femoral neck bone mineral density; BMI, body mass index; CV, cardiovascular; RRT, renal replacement therapy; HD, hemodialysis; PD, peritoneal dialysis; KTX, kidney transplant; PTH, parathormone; CRP, C reactive protein.
Table 2. Cox model using FNBMD (normal/high vs low) as a predictor of mortality

| Model                          | Hazard ratio     | p value |
|-------------------------------|------------------|---------|
| Univariate model              | 0.52 (0.42 to 0.64) | <0.001  |
| Partially adjusted model<sup>a</sup> | 0.63 (0.51 to 0.79) | <0.001  |
| Fully adjusted model<sup>b</sup> | 0.78 (0.61 to 0.99) | 0.048   |

<sup>a</sup>: Adjusted for RRT mode, age and gender.

<sup>b</sup>: Adjusted for variables considered above as well as smoking, diabetes, CV disease, BMI, serum calcium, serum phosphate, serum albumin and CRP.

Abbreviations: FNBMD, femoral neck bone mineral density; RRT, renal replacement therapy; CV, cardiovascular; BMI, body mass index; CRP, C reactive protein.
Table 3. Cox model using FNBMD (normal/high vs low) as a predictor of incident fracture risk

|                        | Hazard ratio         | p value     |
|------------------------|----------------------|-------------|
| **Hip fracture**       |                      |             |
| Univariate model       | 0.21 (0.10 to 0.45)  | <0.001      |
| Partially adjusted model\(^a\) | 0.33 (0.15 to 0.74)  | 0.007       |
| Fully adjusted model\(^b\) | 0.22 (0.08 to 0.62)  | 0.004       |
| **Any fracture**       |                      |             |
| Univariate model       | 0.30 (0.18 to 0.50)  | <0.001      |
| Partially adjusted model\(^a\) | 0.45 (0.26 to 0.77)  | 0.004       |
| Fully adjusted model\(^b\) | 0.42 (0.21 to 0.83)  | 0.013       |

\(^a\): Adjusted for RRT mode, age and gender.

\(^b\): Adjusted for variables considered above as well as smoking, diabetes, BMI, ethnicity, PTH and CRP.

**Abbreviations:** FNBMD, femoral neck bone mineral density; RRT, renal replacement therapy; BMI, body mass index; PTH, parathormone; CRP, C reactive protein.
Figure 1: Cox survival estimates for mortality according to FNBMD (normal/high vs 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.

Abbreviations: FNBMD, femoral neck bone mineral density; RRT, renal replacement therapy; CV, cardiovascular; BMI, body mass index; CRP, C reactive protein.
Figure 2: Cox survival estimates for incident fracture according to FNBMD (normal/high vs 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.

Abbreviations: FNBMD, femoral neck bone mineral density; RRT, renal replacement therapy; BMI, body mass index; PTH, parathormone; CRP, C reactive protein.