Bone 130 (2020) 115075

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

Full length article

Bone mineral density at different sites and 5 years mortality in end-stage renal disease patients: A cohort study

Ken Iseri[a,e,*], Abdul Rashid Qureshi[a], Lu Dai[a], Jonaz Ripsweden[b,c], Olof Heimbürger[a], Peter Barany[a], Ingrid Bergström[d], Peter Stenvinkel[a], Torkel B. Brismar[b,c], Bengt Lindholm[a]

[a] Divisions of Renal Medicine and Baxter Novum, Department of Clinical Science, Intervention and Technology, Karolinska Institutet, Stockholm, Sweden
[b] Division of Medical Imaging and Technology, Department of Clinical Sciences, Intervention and Technology, Karolinska Institutet, Stockholm, Sweden
[c] Department of Radiology, Karolinska University Hospital, Huddinge, Sweden
[d] Division of Endocrinology, Metabolism and Diabetes, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden
[e] Division of Nephrology, Department of Medicine, Showa University School of Medicine, Tokyo, Japan

ARTICLE INFO

Keywords:
Osteoporosis
Bone mineral density
End-stage renal disease
Dialysis
Mortality

ABSTRACT

Background: Bone disease with osteoporosis and renal osteodystrophy is common in end stage renal disease (ESRD) patients and associates with cardiovascular disease (CVD) and increased morbimortality. We investigated associations of low bone mineral density (BMD) at various bone sites with five year all-cause and CVD mortality in ESRD patients.

Methods: In a post hoc analysis of 426 ESRD patients (median age 56 years, 62% men) starting dialysis, BMD (whole-body dual-energy X-ray absorptiometry, DXA), body composition, nutritional status (subjective global assessment, SGA), handgrip strength (%HGS), Framingham CVD risk score (FRS) and biochemical biomarkers of nutrition and inflammation were assessed. We used the Fine and Gray competing risk regression analysis to assess survival analysis.

Results: In multivariate logistic regression analysis, %HGS and intact parathyroid hormone associated with low tertile of: BMD_{total}, BMD_{head} and BMD_{pelvis}, after adjusting for FRS, SGA, %HGS, s-albumin, hsCRP, lean body mass index and year of recruitment. Patients with high FRS had low BMD_{head} ($p < 0.001$). Low tertile of BMD_{total} (sHR, 1.53), BMD_{head} (sHR 1.54) and BMD_{pelvis} (sHR 1.60) associated with increased all-cause mortality whereas no such associations were found for the trabecular bone rich sites BMD arm, leg, trunk, rib or spine. Low tertile of BMD_{total} (sHR 1.94), BMD_{head} (sHR 1.68), BMD_{leg} (sHR 2.25) and BMD_{pelvis} (sHR 2.45) associated with increased CVD mortality whereas BMD at other sites did not associate with CVD mortality.

Conclusion: Low head and pelvis BMD, and low total BMD, as assessed by whole-body DXA, were independent predictors of increased risk of all-cause and CVD mortality. Cortical BMD appeared to have stronger association to survival in ESRD than trabecular BMD.

1. Introduction

Patients with chronic kidney disease (CKD) suffer from CKD-mineral and bone disorders (CKD-MBD) including osteoporosis and renal osteodystrophy that associate with generalized vascular calcification, coronary artery calcification (CAC) and cardiovascular disease (CVD). These common interlinked features contribute to severe and not seldom fatal complications leading to markedly increased mortality especially in patients with end stage renal disease (ESRD). Bone disease in CKD is a "mixture" of *renal osteodystrophy* characterized by low bone quality due to turnover, mineralization, volume defects caused by renal disease, and *senile-menopausal osteoporosis*. Thus, the mechanical properties of bones are compromised by low bone quality as well as by low bone mass in ESRD. Impaired bone status associates with aortic calcification and vascular stiffening [1], and a high CAC score in hemodialysis patients associate with CVD events [2], the major cause of mortality in these patients.

Central dual-energy X-ray absorptiometry (DXA) yielding measures of bone mineral density (BMD) is a well-established tool for diagnosis of osteoporosis. In addition, whole-body DXA analyzing body composition including bone mineral content (BMC) may also be used to assess BMD. While BMD assessed by central DXA or whole-body DXA reflect similar

* Corresponding author at: Divisions of Renal Medicine and Baxter Novum, Karolinska Institutet, M99 Karolinska University Hospital Huddinge, 14186 Stockholm, Sweden.
E-mail address: iseriken@med.showa-u.ac.jp (K. Iseri).

https://doi.org/10.1016/j.bone.2019.115075
Received 9 June 2019; Received in revised form 23 August 2019; Accepted 20 September 2019
Available online 24 October 2019

bone properties, these methods are not equivalent, and therefore for the diagnosis of osteoporosis, the interpretation of BMD values yielded by the two methods may differ [3,4]. Nevertheless, in ESRD patients, a low BMD - as assessed by central DXA, whole-body DXA, and also by digital image processing (DIP) - associates not only with increased risk of future fractures but also with arteriosclerosis and coronary and vascular calcification [5–7] as well as with low muscle strength, low lean body mass and poor nutritional status. In a previous study, low BMD by whole-body DXA was found to be associated with body composition, especially total fat mass, poor nutritional status and increased mortality risk in ESRD patients [8].

A meta-analysis based on prospective cohort studies in the general population demonstrated that lower BMD - at all investigated sites of BMD measurements – were associated with increased CVD-related and all-cause mortality [9]. In patients with ESRD, the bone-cardiovascular axis is perturbed due to the presence of CKD-MBD, vitamin D deficiency, secondary hyperparathyroidism, and numerous other metabolic and hormonal alterations [10,11] Bone status as assessed by BMD may therefore conceivably have an even greater impact on vascular calcification and cardiovascular events than in the general population. In ESRD patients, low *total BMD* by whole-body DXA associates with increased CVD-related and all-cause mortality [5,8], while there is much less information regarding the association between BMD at different bone sites and mortality. The aim of the present study was to evaluate the association of low BMD by whole-body DXA at various bone sites with all-cause and CVD mortality in ESRD patients.

2. Patients and methods

2.1. Patients

In a *post hoc* analysis of whole-body DXA data from an ongoing prospective cohort study of 426 adult ESRD patients, total BMD and BMD at different sites were assessed at baseline together with parameters reflecting nutritional status such as handgrip strength and biochemical biomarkers of nutrition and inflammation. Incident ESRD patients were enrolled at the Karolinska University Hospital at Huddinge between 1994 and 2016 in the malnutrition, inflammation and atherosclerosis (MIA) cohort study on determinants of clinical outcomes in ESRD [12]. Participants were investigated in conjunction with start of dialysis and were followed for survival analysis for 26 (7–60) months. The study exclusion criteria were age younger than 18 years, clinical signs of acute infection, active vasculitis or liver disease at the time of evaluation, or unwillingness to participate in the study. No patients were lost to follow-up during the study.

The Ethics Committee of the Karolinska Institutet at the Campus Flemingsberg (EPN) Stockholm, Sweden, approved the study protocol which adhered to the statutes of the Declaration of Helsinki, and written informed consent was obtained from each patient.

2.2. Clinical characterization

Demographics, etiology of CKD, presence of comorbidities (CVD, diabetes and malnutrition) were registered at baseline. Presence of CVD was defined as a clinical history or signs of ischemic cardiac disease, and/or presence of peripheral vascular disease and/or cerebrovascular disease. The risk of future CVD events was calculated using the Framingham's CVD risk score (FRS) according to sex and age stratified tables with specific scores assigned for systolic blood pressure, diabetes, anti-hypertensive medication, total cholesterol, HDL cholesterol and smoking status. The FRS provided an estimate of the 10-year risk of developing CVD for each patient [13].

Presence of protein-energy wasting (PEW) was assessed according to the subjective global assessment (SGA) score. Patients were classified as well-nourished (SGA = 1) or as having mild (SGA = 2), moderate (SGA = 3) or severe (SGA = 4) signs of malnutrition [14]. For simplicity, the patients were placed in two groups; well-nourished (SGA = 1) and malnourished (SGA > 1; defining patients with PEW).

Handgrip strength (HGS) was evaluated in the non-fistula arm using the Harpenden Dynamometer (Yamar, Jackson, MI, USA) and repeated three times, and the greatest value was recorded and expressed in kilograms. HGS was expressed in percent of values in healthy individuals, HGS%, considering the differences between the sexes, when included in the statistical analyses. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared.

2.3. Bone mineral density (BMD) and body composition

Whole-body dual-energy X-ray absorptiometry (DXA) was performed using the DPX-L device (Lunar Corp., Madison, WI, USA) to measure BMD, total fat mass and lean body mass. The 2-compartment model distinguishing fat and other compartments was used to obtain information about body composition. Lean (LBMI) and fat (FBMI) body mass index was expressed as kg/m^2. From the whole-body DXA scan, measurements of total BMD and of seven subregions were simultaneously obtained: head, arms, legs, trunk, hip, pelvis and spine. BMD was expressed in g/cm^2.

2.4. Biochemical assessments

After an overnight fast, venous blood samples were drawn and stored at −70 °C for biochemical analyses. White blood cell (WBC), hemoglobin, albumin, blood urea nitrogen, creatinine, calcium, phosphate, intact parathyroid hormone (i-PTH), triglyceride, cholesterol, HDL cholesterol and high-sensitivity C-reactive protein (hsCRP) were analyzed using routine methods at the Clinical Chemical Laboratory of Karolinska University Hospital, Stockholm, Sweden.

2.5. Statistical analyses

Data are expressed as median (10th–90th percentile) or percentage, as appropriate. Statistical significance was set at the level of $P < 0.05$. Comparisons between two groups were assessed with the non-parametric Wilcoxon test for continuous variables and Chi-square test for nominal variables. Comparisons between three groups were assessed with the non-parametric ANOVA Kruskal Wallis followed by Dunn's test for continuous variables. Non-parametric Spearman rank correlation analysis was used to determine associations between variables. Multivariate logistic regression models of continuous variables of low tertiles of total, head and pelvis BMD were analyzed and results shown as odds ratio (OR). The patients were followed from the inclusion date until renal transplantation or death or completing 60 months of follow-up. We selected the following confounders: Framingham CVD risk score, SGA, %HGS, albumin, hsCRP, and LBMI, which are well known to impact on all-cause and CVD mortality, and also year of recruitment. Causes of death were established by the death certificate issued by the attending physician. Crude mortality rate/1000 patient years (95% CI) was calculated according to tertiles of BMD. Fine and Gray competing risk regression analysis was used for all-cause and CVD mortality to obtain sub-distribution hazard ratio (sHR) for low tertile of BMD at various bone sites. Statistical analyses were performed using Statistical Software Stata 15.1 (Stata Corporation, College Station, TX, USA) and SAS Version 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Baseline characteristics and clinical parameters

Table 1 shows demographics and clinical characteristics of 426 ESRD patients. Their median age was 56 years, 62% of patients were male, 31% had diabetes and 36% clinical signs of CVD. The median Framingham CVD risk score was 18.3%. Patients with CVD had

Table 1
Baseline clinical and biochemical characteristics of 426 ESRD patients in relation to tertiles of total BMD.

	All patients (n = 426)	Low tertile of tBMD (n = 138)	Middle + high tertile of tBMD (n = 288)	P value
Demography and clinical characteristics				
Age (years)	56 (34–69)	59 (33–70)	54 (35–68)	< 0.01
Males, n (%)	266 (62)	54 (39)	212 (74)	< 0.001
Diabetes mellitus, n (%) (n = 422)	132 (31)	44 (32)	88 (31)	0.82
Cardiovascular disease[a], n (%) (n = 422)	150 (36)	55 (40)	95 (33)	0.19
Current smoker, n (%) (n = 363)	76 (21)	34 (25)	42 (15)	< 0.05
Systolic blood pressure (mmHg) (n = 394)	147 (122-180)	147 (120–183)	147 (122–179)	0.88
Framingham CVD risk score (%) (n = 410)	18.3 (3.9–53.8)	17.6 (3.1–54.0)	19.0 (4.1–53.6)	0.54
Nutritional status				
PEW (SGA > 1), n (%) (n = 413)	141 (34)	67 (49)	74 (26)	< 0.001
Body mass index, (kg/m^2) (n = 425)	24.2 (19.8–30.8)	22.3 (18.1–29.0)	25.2 (21.0–31.1)	< 0.001
Lean body mass index, (kg/m^2) (n = 425)	16.5 (13.6–20.0)	15.1 (13.0–18.0)	17.1 (14.4–20.3)	< 0.001
Fat body mass index, (kg/m^2) (n = 425)	7.1 (3.6–11.9)	6.2 (3.0–11.8)	7.3 (3.7–12.0)	0.07
Handgrip strength[b] (%)(n = 392)	81 (51–118)	72 (44–91)	86 (56–121)	< 0.001
Circulating biomarkers				
White blood cell (10^9/L)	7.4 (5.0–11.6)	7.3 (4.6–11.6)	7.4 (5.1–11.7)	0.67
Hemoglobin (g/L)	104 (87–123)	105 (86–126)	104 (87–122)	0.59
Albumin (g/L)	34 (26–40)	33 (25–40)	34 (26–40)	0.40
Urea (mmol/L)	29 (21–43)	28 (19–39)	30 (21–43)	< 0.01
Creatinine (mg/dL)	8.0 (5.1–11.6)	6.9 (4.3–10.3)	8.7 (5.7–11.9)	< 0.001
Calcium (mmol/L)	2.5 (2.1–2.8)	2.4 (2.1–2.7)	2.5 (2.1–2.8)	0.28
Phosphate (mmol/L)	1.9 (1.4–2.7)	1.8 (1.3–2.6)	2.0 (1.4–2.7)	< 0.01
i-PTH (ng/L)	228 (49–557)	265 (69–690)	220 (47–527)	< 0.01
Triglyceride (mmol/L)	1.8 (0.9–3.5)	1.8 (0.9–3.5)	1.7 (0.9–3.5)	0.88
Cholesterol (mmol/L)	4.8 (3.3–7.2)	4.9 (3.3–7.6)	4.8 (3.3–6.9)	0.19
HDL cholesterol (mmol/L)	1.2 (0.8–1.9)	1.3 (0.8–2.4)	1.1 (0.7–1.9)	< 0.001
hsCRP (mg/L)	4.5 (0.7–28.7)	6.4 (0.7–41.2)	4.1 (0.7–24.1)	0.18
Medications				
β-blockers, n (%)(n = 412)	253 (61)	69 (50)	184 (64)	< 0.01
Ca-blocker, n (%) (n = 412)	200 (49)	57 (41)	143 (50)	0.07
ACEi/ARB, n (%)(n = 425)	259 (61)	77 (56)	182 (63)	0.17
Statins, n (%)(n = 425)	110 (26)	30 (22)	80 (28)	0.24

Continuous variables are presented as median (10–90 percentile). Categorical variables are presented as number (n)/percentage (%). [a]Defined as clinical history or signs of ischemic cardiac disease, and/or presence of peripheral vascular disease and/or cerebrovascular disease, [b]HGS, Handgrip strength as percentage of values for patients with eGFR= > 60. Abbreviations: tBMD, total bone mineral density; CVD, cardiovascular disease; PEW, Protein-energy wasting; SGA, Subjective global nutritional assessment; i-PTH, intact parathyroid hormone; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; ACEi, angiotensin-converting enzyme; ARB, angiotensin 2 receptor blocker.

significantly lower total BMD ($p < 0.05$), head BMD ($p < 0.001$) and pelvis BMD ($p < 0.05$). Self-reported physical activity was not statistically significantly associated with total BMD, head BMD or pelvis BMD.

Patients were divided into two groups according to tertiles of total BMD (low tertile vs. middle + high tertiles). Those with low tertile of total BMD (LtBMD) had higher age, higher percentage of females, higher frequency of current smokers and PEW, and higher i-PTH and HDL and lower serum urea, creatinine, and phosphate levels, and lower values of BMI, LBMI and HGS. Patients with LtBMD had lower BMD at all sites. Patients with middle + high tertiles of BMD were significantly more often prescribed β-blockers than the LtBMD group (64% vs. 50%, $p < 0.01$). Those with high FRS had lower head BMD (Fig. 1) while there was no significant difference in other sites of BMD.

In gender-specific analyses, head BMD was significantly higher in female ESRD patients, whereas other BMD sites were lower compared to male patients. Moreover, female patients had a higher FBMI and lower LBMI compared to male patients (Table S1).

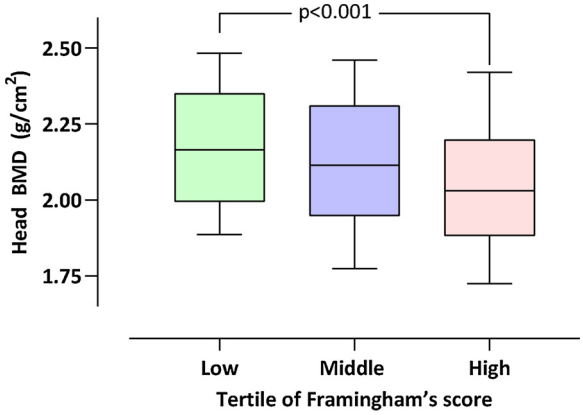

Fig. 1. Association between tertiles of Framingham's score and head BMD.

3.2. Univariate correlations between various sites of BMD and other variables

Table S2 shows Spearman rank correlation analysis between different sites of BMD and other variables. %HGS (range of rho = 0.17 to rho = 0.32) and BMI (range of rho = 0.12 to rho = 0.54) were significantly associated with BMD at all sites, whereas the presence of diabetes was not associated with BMD at any site. On the other hand, SGA (rho = -0.17 to rho = -0.28) and LBMI (rho = 0.33 to rho = 0.52) were significantly associated with BMD at all bone sites except the head site.

3.3. Multivariable predictors of low total, head and pelvis BMD

Predictors of low tertile of total BMD, head BMD and pelvis BMD from multivariate logistic regression analysis (Table 2) included for:

Low total BMD: female gender ($p < 0.001$), 1-SD of LBMI ($p < 0.001$), 1-SD of %HGS ($p < 0.001$), and 1-SD of i-PTH ($p < 0.001$), but not 1-SD of age ($p = 0.81$), 1-SD of hsCRP ($p = 0.28$), DM ($p = 0.28$), CVD ($p = 0.60$) and PEW ($p = 0.47$).

Table 2
Predictors of low tertile of total BMD, head BMD and pelvis BMD from multivariate logistic regression analysis in all 426 patients.

	Total BMD(pseudo r = 0.26)		Head BMD(pseudo r = 0.14)		Pelvis BMD (pseudo r = 0.18)	
	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value
Age (+1SD increase)	1.04 (0.75-1.44)	0.81	1.44 (1.05-1.97)	< 0.05	1.00 (0.73-1.35)	0.97
Gender (male vs. female)	0.33 (0.17-0.61)	< 0.001	2.32 (1.23-4.36)	< 0.01	0.63 (0.34-1.15)	0.13
Diabetes (yes vs. no)	0.71 (0.38-1.32)	0.28	0.93 (0.53-1.63)	0.79	1.03 (0.58-1.82)	0.93
CVD (yes vs. no)	1.20 (0.61-2.33)	0.60	1.06 (0.57-1.97)	0.85	1.39 (0.74-2.62)	0.31
PEW (SGA > 1)	1.25 (0.68-2.32)	0.47	0.62 (0.34-1.14)	0.13	1.58 (0.89-2.81)	0.12
LBMI (+1SD increase)	0.48 (0.33-0.70)	< 0.001	0.59 (0.41-0.83)	< 0.01	0.53 (0.37-0.76)	< 0.001
%HGS (+1SD increase)	0.57 (0.40-0.79)	< 0.001	0.67 (0.49-0.92)	< 0.05	0.64 (0.47-0.88)	< 0.01
i-PTH (+1SD increase)	1.97 (1.38-2.80)	< 0.001	1.68 (1.27-2.23)	< 0.001	1.42 (1.06-1.91)	< 0.05
hsCRP (+1SD increase)	0.86 (0.66-1.13)	0.28	0.82 (0.62-1.08)	0.16	0.87 (0.67-1.13)	0.31

Abbreviations: OR, odds ratio; CVD, cardiovascular disease; PEW, protein energy wasting; SGA, Subjective global nutritional assessment; LBMI, lean body mass index; FBMI, fat body mass index; %HGS, handgrip strength as percentage of values for patients with eGFR = > 60; i-PTH, intact parathyroid hormone; hsCRP, high sensitive C-reactive protein.

Low head BMD: female gender ($p < 0.01$), 1-SD of LBMI ($p < 0.01$), 1-SD of %HGS ($p < 0.05$), 1-SD of i-PTH ($p < 0.001$), 1-SD of age ($p < 0.05$), but not 1-SD of hsCRP ($p = 0.16$), DM ($p = 0.79$), CVD ($p = 0.85$) and PEW ($p = 0.13$).

Low pelvis BMD: 1-SD of LBMI ($p < 0.001$), 1-SD of %HGS ($p < 0.01$), and 1-SD of i-PTH ($p < 0.05$), but not female gender ($p = 0.13$), 1-SD of age ($p = 0.97$), 1-SD of hsCRP ($p = 0.31$), DM ($p = 0.93$), CVD ($p = 0.31$) and PEW ($p = 0.12$).

3.4. Crude mortality rate /1000 person-years for all-cause death

Crude all-cause mortality rates were higher in low BMD tertile than in middle + high BMD tertiles for total BMD (203 vs. 95 per 1000 person-years), and - as shown in Fig. 2 (inserts in figure) - at head (191 vs. 99 per 1000 person-years) and pelvis (203 vs. 93 per 1000 person-years) sites.

Likewise, crude CVD mortality rates were higher in low BMD tertile than in middle + high BMD tertiles for total BMD (120 vs. 53 per 1000 person-years), and - as shown in Fig. 2 (inserts) - at head (117 vs. 54 per 1000 person-years) and pelvis (128 vs. 48 per 1000 person-years) sites.

3.5. Multivariate competing risk analysis for all-cause and CVD mortality

During 60 months of follow-up, 133 patients (31%) died, due to CVD (n = 76) or other causes (n = 57) and 168 patients (39%) underwent renal transplantation. Multivariate competing risk analysis for *all-cause mortality* showed increased risk in patients with low total BMD (sHR = 1.53, $p < 0.05$), low head BMD (sHR = 1.54, $p < 0.05$) and low pelvis BMD (sHR = 1.60, $p < 0.05$) (Fig. 2 and Table S3).

Multivariate competing risk analysis for *CVD mortality* showed

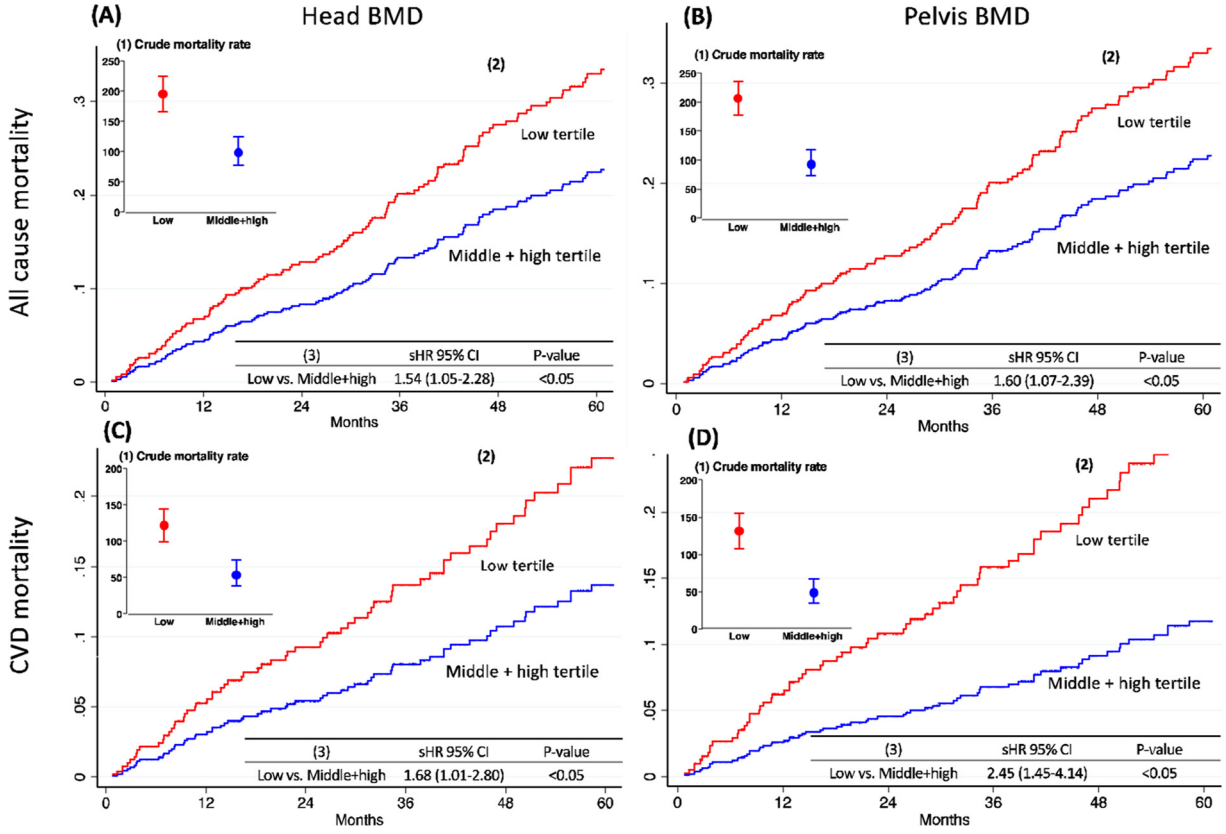

Fig. 2. Multivariate adjusted survival curve for all-cause and CVD mortality and crude mortality rate/1000 patient years (95% CI) according to tertiles of head BMD (**A**, **C**) and pelvis BMD (**B**, **D**).

increased risk in patients with low total BMD (sHR = 1.94, $p < 0.05$), low head BMD (sHR = 1.68, $p < 0.05$) and low pelvis BMD (sHR = 2.45, $p < 0.001$) (Fig. 2 and Table S3). In addition, low leg BMD associated with higher risk of CVD mortality (sHR: 2.25, $p < 0.05$), Table S3. The multivariate competing risk analyses were adjusted for 1-SD of Framingham CVD risk score, SGA, 1-SD of %HGS, 1-SD of albumin, 1-SD of hsCRP, 1-SD of LBMI, and year of recruitment of patients.

4. Discussion

In the present study, low tertiles of total BMD, head BMD and pelvis BMD by whole-body DXA associated with increased *all-cause* and *CVD mortality* after adjusting for 1-SD of Framingham CVD risk score, SGA, 1-SD of %HGS, 1-SD of albumin, 1-SD of hsCRP, 1-SD of LBMI and year of recruitment of patients. Leg BMD was significantly associated with *CVD mortality* after similar adjustments.

Whole-body DXA is widely used, because it is safe, easy to use and shows good precision and reproducibility [15]. However, DXA is known to be influenced by artifacts and local structural changes [16], which could lead to overestimation of BMD. Extensive osteophyte formation and degenerative changes are often seen in elderly patients. Abdominal aortic calcification is highly prevalent in ESRD. Therefore, under these situations, BMD measurements especially at the site of spine can be misleading [17]. BMD at hip and radius sites are generally lower in patients with ESRD than in the general population; however, at lumbar spine BMD is often similar to that in the general population [17]. In our previous study, low vertebral bone density measured by computed tomography (CT), which is not hampered by the presence of aortic calcification, was associated with increased mortality [18].

In the present study, whole-body DXA spine BMD was not associated with all-cause and CVD mortality, which is in agreement with a previous study that investigated the association between bone mass by central DXA and all-cause mortality in 88 hemodialysis patients [19]. Thus, although spine measurement is a common site to measure BMD, lumbar spine might be not suitable site to predict mortality in ESRD due to the above mentioned technical aspects of DXA. A previous study showed that female hemodialysis patients had lower BMD by central DXA at all sites (spine, hip and forearm) compared to males [20]. We report similar findings, i.e., that BMD yielded by whole-body DXA at all sites - except head BMD - was significantly lower in women compared to men.

Perhaps somewhat surprisingly, low head BMD was quite strongly associated with CVD and all-cause mortality. The head appears to be a unique site for BMD measurements compared to other sites due to its relatively higher proportion of cortical bone [21,22]. In humans, 80% of the skeleton is composed by cortical bone and the rest is trabecular bone; however, the proportion of cortical to trabecular varies among different skeletal sites [23]. The mandible, which is a part of bone constituting the skull, has a high proportion of cortical bone, close to that of the femoral neck 22]. In CKD, high-resolution peripheral quantitative computed tomography (HRpQCT) shows rapid loss of cortical bone whereas trabecular bone loss was not found [24], suggesting that cortical bone-rich sites may be more important to reflect disease status than trabecular bone-rich sites.

It has been shown that BMD of the head decreases with age and increases with higher BMI to a different extent than that of the rest of the body in normal women [25]. In our study, total BMD and BMD at all bone sites -except head BMD - was lower in women than in men. The finding that women had higher head BMD than men may be related to the high incidence of hyperostosis cranii among women [26].

In a study on 704 amateur sportsmen, physical activity associated with higher total body BMD and regional BMD by whole-body DXA but did not associate with head BMD [27]; this may be related to the fact that the head is not weight bearing and not notably involved in physically strenuous exercises. Another study reported that the head BMD was not influenced by activity or disease [28]. Accordingly, we find no association between physical activity and head BMD; however, patients with high Framingham's score had low head BMD (ANOVA, $p < 0.001$). In addition, our multivariate logistic regression analysis also showed that lower LBMI, %HGS and i-PTH were strongly associated with low head BMD.

We found no significant association between arm site BMD (assessed by whole-body DXA) and all-cause and CVD mortality. In contrast, a recent report showed that forearm BMD was associated with 2-years (univariate Kaplan Meier) survival in 102 chronic hemodialysis patients [29]. This discrepancy may be due to the fact that we performed a multivariate competing risk analysis, adjusting for various confounders, while the other study performed univariate analysis.

As regarding other sites of BMD in ESRD, some studies revealed that low hip BMD by central DXA correlated with all-cause mortality [19,30]. However, we found an association of leg region BMD with CVD mortality but not with all-cause mortality while BMD at trunk site was not significantly associated with CVD mortality. Low BMD of trabecular bone, which is present to a higher proportion in hip and lumbar spine, appear to have less association with increased mortality observed in ESRD patients than BMD of cortical bone. This might be due to differences between cortical and trabecular bone reflecting alterations in bone metabolism caused by disease.

Some limitations should be considered when interpreting these results. First, we performed whole-body BMD, which may differ from the central DXA measurements. However, whole-body DXA measurements is widely used in the clinical practice. Second, although we evaluated CVD-related and all-cause death events, we did not follow fracture events after inclusion in the present study. Thus, we could not evaluate the complications after new fractures. Third, we did not analyze serum vitamin D (25-hydroxyvitamin D and 1,25-dihydroxy vitamin D) and several other key factors in CKD-MBD. Fourth, bone strength, which is determined by bone mass and bone quality, was not assessed. Fifth, detailed information about bone status is lacking as we did not analyze bone turnover markers, and bone biopsies were not performed. However, the intention of the study was to investigate which sites of BMD that were associated with outcomes in ESRD, using whole-body DXA, which is an easy to perform technique as compared to other methods, such as HRpQCT. The present study also has some strengths worth mentioning. Phenotyping was detailed and included both traditional and several non-traditional risk factors, and BMD was measured at several sites. As compared to the general population [9], the association of low total BMD and low BMD at head and pelvis sites with all-cause and CVD mortality appeared to be stronger with higher sHR. One possible cause for the discrepancy of results from general population is the presence of CKD-MBD induced by kidney dysfunction [31–33]. For example, secondary hyperparathyroidism in ESRD aggravates renal bone disease by inducing osteitis fibrosa. Even though DXA cannot distinguish this form of renal osteodystrophy, low BMD reflecting low bone mass associated with poor clinical outcomes in ESRD patients.

In conclusion, in incident dialysis patients, low total BMD, head BMD and pelvis BMD as assessed by whole-body DXA were significantly associated with increased all-cause and CVD mortality after adjusting for various confounders. Low BMD in leg region was significantly associated with CVD mortality. These results showing that total BMD - and BMD at the sites of head, pelvis and leg region - have strong associations with clinical outcomes in ESRD, suggest that BMD measured at these sites using whole-body DXA may be suitable for assessment of mortality. This observation may be of value for clinical practice. Another observation linked to these findings is that cortical bone seems to be more strongly associated with survival in ESRD than trabecular bone. The sites containing rich cortical bone component appear to be especially valuable for monitoring the prognosis of ESRD patients because these sites may reflect patients´ health condition and bone pathology linked to the metabolic alterations of CKD-MBD.

Declaration of Competing Interest

BL is employed by Baxter Healthcare Corporation. None of the other authors declare any conflict of interest.

Authors' contributions

OH, PB and PS designed the MIA cohort study and recruited patients included in the present study. KI and ARQ designed the present study, performed statistical analyses, interpreted the results, prepared figures and tables, and drafted the manuscript. All authors contributed to data collection, revised the manuscript, and approved the final version of the manuscript.

Funding

This study was supported by a grant from Baxter Healthcare to Baxter Novum, Department of Clinical Science, Intervention and Technology, Karolinska Institutet. The study also benefited from generous support from Strategic Research Programme in Diabetes at Karolinska Institutet (Swedish Research Council grant No 2009-1068. (PS), Heart and Lung Foundation (PS), Njurfonden (PS), and Westmans Foundation (PS). This study also received funding from the European Union's Horizon 2020 research and innovation program under the Marie Sklodowska-Curie grant agreement No 722609.

Acknowledgments

We thank all patients who participated in the study and those who carried out the extensive clinical and laboratory work in the clinical investigational unit and the renal laboratory at Dept. of Renal Medicine, Karolinska University Hospital. Showa University Research Fund, Japan funded KI. Baxter Novum is the result of a grant from Baxter Healthcare to Karolinska Institutet.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.bone.2019.115075.

References

[1] G.M. London, S.J. Marchais, A.P. Guérin, P. Boutouyrie, F. Métivier, M.-C. de Vernejoul, Association of bone activity, calcium load, aortic stiffness, and calcifications in ESRD, J. Am. Soc. Nephrol. 19 (9) (2008) 1827–1835, https://doi.org/10.1681/ASN.2007050622.

[2] M. Matsuoka, K. Iseki, M. Tamashiro, et al., Impact of high coronary artery calcification score (CACS) on survival in patients on chronic hemodialysis, Clin. Exp. Nephrol. 8 (1) (2004) 54–58, https://doi.org/10.1007/s10157-003-0260-0.

[3] M. Boyanov, Estimation of lumbar spine bone mineral density by dual-energy X-ray absorptiometry: standard anteroposterior scans vs sub-regional analyses of whole-body scans, Br. J. Radiol. 81 (968) (2008) 637–642, https://doi.org/10.1259/bjr/22307093.

[4] L.J. Melton, A.C. Looker, J.A. Shepherd, et al., Osteoporosis assessment by whole body region vs. site-specific DXA, Osteoporos. Int. 16 (12) (2005) 1558–1564, https://doi.org/10.1007/s00198-005-1871-y.

[5] K. Matsubara, M.E. Suliman, A.R. Qureshi, et al., Bone mineral density in end-stage renal disease patients: association with wasting, cardiovascular disease and mortality, Blood Purif. 26 (3) (2008) 284–290, https://doi.org/10.1159/000126925.

[6] A. Aoki, F. Kojima, K. Uchida, Y. Tanaka, K. Nitta, Associations between vascular calcification, arterial stiffness and bone mineral density in chronic hemodialysis patients, Geriatr. Gerontol. Int. 9 (3) (2009) 246–252, https://doi.org/10.1111/j.1447-0594.2009.00528.x.

[7] P. Raggi, A. Bellasi, E. Ferramosca, G.A. Block, P. Muntner, Pulse wave velocity is inversely related to vertebral bone density in hemodialysis patients, Hypertens (Dallas, Tex 1979) 49 (6) (2007) 1278–1284, https://doi.org/10.1161/HYPERTENSIONAHA.107.086942.

[8] S.-H. Park, T. Jia, A.R. Qureshi, et al., Determinants and survival implications of low bone mineral density in end-stage renal disease patients, J. Nephrol. 26 (3) (2013) 485–494, https://doi.org/10.5301/jn.5000185.

[9] X. Qu, X. Huang, F. Jin, et al., Bone mineral density and all-cause, cardiovascular and stroke mortality: a meta-analysis of prospective cohort studies, Int. J. Cardiol. 166 (2) (2013) 385–393, https://doi.org/10.1016/j.ijcard.2011.10.114.

[10] M.G. Vervloet, Z.A. Massy, V.M. Brandenburg, et al., Bone: a new endocrine organ at the heart of chronic kidney disease and mineral and bone disorders, Lancet Diabetes Endocrinol. 2 (5) (2014) 427–436, https://doi.org/10.1016/S2213-8587(14)70059-2.

[11] A. Covic, M. Vervloet, Z.A. Massy, et al., Bone and mineral disorders in chronic kidney disease: implications for cardiovascular health and ageing in the general population, Lancet Diabetes Endocrinol. 6 (4) (2018) 319–331, https://doi.org/10.1016/S2213-8587(17)30310-8.

[12] P. Stenvinkel, O. Heimbürger, F. Paultre, et al., Strong association between malnutrition, inflammation, and atherosclerosis in chronic renal failure, Kidney Int. 55 (5) (1999) 1899–1911, https://doi.org/10.1046/j.1523-1755.1999.00422.x.

[13] R.B. D'Agostino, R.S. Vasan, M.J. Pencina, et al., General cardiovascular risk profile for use in primary care, Circulation 117 (6) (2008) 743–753, https://doi.org/10.1161/CIRCULATIONAHA.107.699579.

[14] A.R. Qureshi, A. Alvestrand, A. Danielsson, et al., Factors predicting malnutrition in hemodialysis patients: a cross-sectional study, Kidney Int. 53 (3) (1998) 773–782, https://doi.org/10.1046/j.1523-1755.1998.00812.x.

[15] A. Bazzocchi, F. Ponti, U. Albisinni, G. Battista, G. Guglielmi, DXA: technical aspects and application, Eur. J. Radiol. 85 (8) (2016) 1481–1492, https://doi.org/10.1016/j.ejrad.2016.04.004.

[16] A. El Maghraoui, C. Roux, DXA scanning in clinical practice, QJM 101 (8) (2008) 605–617, https://doi.org/10.1093/qjmed/hcn022.

[17] Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group, KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD), Kidney Int. Suppl. 76 (113) (2009) S1–130, https://doi.org/10.1038/ki.2009.188.

[18] Z. Chen, A.R. Qureshi, J. Ripsweden, et al., Vertebral bone density associates with coronary artery calcification and is an independent predictor of poor outcome in end-stage renal disease patients, Bone 92 (2016) 50–57, https://doi.org/10.1016/j.bone.2016.08.007.

[19] M.W. Taal, S. Roe, T. Masud, D. Green, C. Porter, M.J.D. Cassidy, Total hip bone mass predicts survival in chronic hemodialysis patients, Kidney Int. 63 (3) (2003) 1116–1120, https://doi.org/10.1046/j.1523-1755.2003.00837.x.

[20] L. Orlic, Z. Crncevic, D. Pavlovic, L. Zaputovic, Bone mineral densitometry in patients on hemodialysis: difference between genders and what to measure, Ren. Fail. 32 (3) (2010) 300–308, https://doi.org/10.3109/08860221003611661.

[21] E. Klemetti, P. Vainio, V. Lassila, Mineral density in the mandibles of partially and totally edentate postmenopausal women, Scand. J. Dent. Res. 102 (1) (1994) 64–67, https://doi.org/10.1111/j.1600-0722.1994.tb01155.x.

[22] E. Klemetti, P. Vainio, V. Lassila, E. Alhava, Cortical bone mineral density in the mandible and osteoporosis status in postmenopausal women, Scand. J. Dent. Res. 101 (4) (1993) 219–223 http://www.ncbi.nlm.nih.gov/pubmed/8362200.

[23] B. Clarke, Normal bone anatomy and physiology, Clin. J. Am. Soc. Nephrol. 3 (Suppl 3) (2008) S131–9, https://doi.org/10.2215/CJN.04151206.

[24] T.L. Nickolas, E.M. Stein, E. Dworakowski, et al., Rapid cortical bone loss in patients with chronic kidney disease, J. Bone Miner. Res. 28 (8) (2013) 1811–1820, https://doi.org/10.1002/jbmr.1916.

[25] T.B. Brismar, J. Ringertz, Effect of bone density of the head on total body DEXA measurements in 100 healthy Swedish women, Acta Radiol. 37 (1) (1996) 101–106, https://doi.org/10.1080/02841859609174368.

[26] A. SALMI, A. VOUTILAINEN, I.R. HOLSTI, C.E. UNNERUS, Hyperostosis cranii in a normal population, Am. J. Roentgenol. Radium Ther. Nucl. Med. 87 (1) (1962) 1032–1040, https://doi.org/10.3109/02841859609174368.

[27] J. Morel, B. Combe, J. Francisco, J. Bernard, Bone mineral density of 704 amateur sportsmen involved in different physical activities, Osteoporos. Int. 12 (2) (2001) 152–157, https://doi.org/10.1007/s001980170148.

[28] L.K. Bachrach, C.M. Gordon, SECTION ON ENDOCRINOLOGY, Bone densitometry in children and adolescents, Pediatrics 138 (4) (2016) 339–346, https://doi.org/10.1542/peds.2016-2398.

[29] L. Orlic, I. Mikolasevic, Z. Crncevic-Orlic, I. Jakopcic, J. Josipovic, D. Pavlovic, Forearm bone mass predicts mortality in chronic hemodialysis patients, J. Bone Miner. Metab. 35 (4) (2017) 396–404, https://doi.org/10.1007/s00774-016-0766-7.

[30] S. Disthabanchong, S. Jongjirasiri, S. Adirekkiat, et al., Low hip bone mineral density predicts mortality in maintenance hemodialysis patients: a five-year follow-up study, Blood Purif. 37 (1) (2014) 33–38, https://doi.org/10.1159/000357639.

[31] C.P. Kovesdy, K. Kalantar-Zadeh, Bone and mineral disorders in pre-dialysis CKD, Int. Urol. Nephrol. 40 (2) (2008) 427–440, https://doi.org/10.1007/s11255-008-9346-7.

[32] M. Cozzolino, M. Mangano, A. Stucchi, P. Ciceri, F. Conte, A. Galassi, Cardiovascular disease in dialysis patients, Nephrol. Dial. Transplant. 33 (suppl_3) (2018) iii28–iii34, https://doi.org/10.1093/ndt/gfy174.

[33] A.B. Reiss, N. Miyawaki, J. Moon, et al., CKD, arterial calcification, atherosclerosis and bone health: inter-relationships and controversies, Atherosclerosis 278 (August) (2018) 49–59, https://doi.org/10.1016/j.atherosclerosis.2018.08.046.