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Full Length Article

Vertebral bone density associates with coronary artery calcification and is an independent predictor of poor outcome in end-stage renal disease patients

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ABSTRACT

Objective: Chronic kidney disease-mineral bone disorder (CKD-MBD) is a major complication of end-stage renal disease (ESRD). Reduced bone mineral density (BMD) is associated with vascular calcification. Here we investigated associations between vertebral bone density (VBD) and coronary artery calcification (CAC), quantified by cardiac computed tomography (CT), and BMD quantified by dual-energy X-ray absorptiometry (DXA), and their relations with mortality.

Methods: In 231 ESRD patients (median age 56 years, 63% males) comprising incident dialysis patients, prevalent peritoneal dialysis patients and recipients of living donor kidney transplant, VBD (Hounsfield units, HUs) and CAC scores (Agatston units, AUs) were quantified by cardiac CT, and, in 143 of the patients, BMD was measured by DXA of total body. Metabolic and inflammation biomarkers potentially linked to CKD-MBD were also analysed.

Results: Patients with low tertile of VBD were older and had more often cardiovascular disease (CVD), and higher HbA1c (non-diabetics), interleukin-6 and CAC score. Low VBD was independently associated with higher CAC score (>100 AUs) after adjustment for age, gender, diabetes, CVD, inflammation and cohorts. In Cox proportional hazards analysis, low VBD was independently associated with all-cause mortality after adjustment for age, gender, diabetes, CVD, inflammation and subjective global assessment (SGA). The root mean-squared error of prediction (RMSE) showed a good degree of association between VBD and BMD evaluated from DXA. In receiver-operator characteristics curve (ROC) analysis, lower VBD was more strongly associated with higher CAC score and all-cause mortality than BMD evaluated from DXA.

Conclusions: While assessments of BMD by DXA and CT showed good degree of agreement, associations of high CAC, and mortality, with low VBD were stronger than those based on low BMD by DXA. The strong independent associations of low VBD with high CAC score and increased mortality risk suggest that VBD may serve as an important prognosticator in ESRD patients.

1. Introduction

Chronic kidney disease-mineral bone disorder (CKD-MBD) is a common major complication of end-stage renal disease (ESRD) [1]. Reduced bone mineral density (BMD) is associated with an increased risk of cardiovascular disease (CVD) [2–4], which is a main cause of morbidity and mortality of ESRD patients [5]. Low BMD is associated with increased cardiovascular events and mortality in the general population as well as in ESRD [4,6,7].

The risk of CVD in ESRD patients is independently predicted by coronary artery calcification (CAC) [8,9]. High CAC score can be treated as an independent risk factor for cardiovascular risk beyond that provided by Framingham risk factors [10,11]. High CAC score is a strong predictor of worse clinical outcome in ESRD [12,13]. It is well established that vascular calcification (VC) and bone mineralization share several common pathways [14,15] and molecular mechanisms [16]. An association of decreased BMD with VC has been reported in both the general population

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[17–20] and in ESRD [21–23]. In addition, osteoporosis has been implicated in the progression of CAC over time [24–26]. In contrast, other studies both in the general population [27–30], and in ESRD [31], did not confirm an association between bone density and VC.

Although diagnosis of osteoporosis currently is based on BMD values gained from dual-energy X-ray absorptiometry (DXA) [32], computed tomography (CT) has been widely used as a non-invasive quantitative bone mineral determination [33] and volumetric vertebral bone density (VBD) by CT correlates well with planar VBD, determined by DXA [34]. Furthermore, CT might be superior to DXA for the detection of fractures [35] and the evaluation of osteoporosis treatment [36]. There are few studies using CT that have reported an association of VBD with CAC in ESRD [21,37,38]. However, it is unclear whether VBD measured using CT could be a potential complementary measurement for DXA scanning, or an alternative, and whether use of VBD may help to classify the degree of CAC and be of value to predict clinical outcome.

In the present study, we investigated associations between VBD and CAC score, both determined by cardiac CT scan, and associations between VBD and all-cause mortality, in 231 ESRD patients. In addition, we assessed the association, and validated the degree of agreement, between BMD measured from cardiac CT and BMD evaluated from DXA, in a subset of 143 ESRD patients.

2. Methods

2.1. Patients

A total 231 adult ESRD patients (63% males; median age 56 (10th–90th percentiles 28–75) years) were included from three ESRD cohorts: *incident dialysis cohort* comprising 95 (41%) patients with CKD stage 5 from an ongoing prospective cohort study described in detail previously [39] (this study started in 1994, and from April 2008 cardiac CT scans were included in the protocol), *prevalent peritoneal dialysis* (*PD*) *cohort* [40] comprising 55 (24%) PD patients, and *living donor kidney transplant* (*LD-Rtx*) *cohort* [41] comprising 81 (35%) patients. The patients who all agreed to undergo cardiac CT scans were recruited between March 2008 and June 2015 at the Department of Renal Medicine at Karolinska University Hospital, Stockholm. The Ethics Committee of Karolinska University Hospital Huddinge approved the study protocols. Informed consent was obtained from all patients before their inclusion in the study.

2.2. Measurement of coronary artery calcification (CAC)

CAC was assessed by using CT, an accurate non-invasive approach, performed on a 64-channel detector scanner (LightSpeed VCT; General Electric (GE) Healthcare, Milwaukee, WI, USA) in cine mode. Scans were ECG-gated and a standard non-contrast protocol was used with a tube voltage of 100 kV, tube current of 200 mA, 350 ms rotation time, 2.5 mm slice thickness and display field of view (DFOV) 25 cm. CAC data were processed and analysed using Advantage Workstation (GE Healthcare). Smartscore 4.0 (GE Healthcare) was used to assess CAC score. CAC was quantified as a lesion with an area >1 mm^2 and a peak intensity >130 Hounsfield Units (HUs) based on the Agatston method previously described in detail and expressed in Agatston units (AUs) [42]. Total CAC score was calculated as the sum of the CAC score in the left main artery, the left anterior descending artery, the left circumflex artery and the right coronary artery. According to previous data, a CAC score >100 AUs is associated with an increased risk of myocardial ischaemia and coronary heart disease-related events [43,44]. In the present study, this threshold was used to identify patients with definite to extensive plaque burden.

2.3. Measurement of thoracic vertebral bone density (VBD)

VBD was measured from images of the thoracic spine captured during the cardiac CT scan for measurement of CAC, as described previously [45]. The cardiac CT scan captured thoracic vertebrae T5–T12 from the patients; however, the current analysis was limited to T8 to T10 vertebrae, since data from the other thoracic vertebrae were incomplete. The analysis of VBD was based on the mean attenuation within a region of interest (ROI) placed at the mid-vertebral body and in the anterior one-half to one-third of the vertebral body (Fig. 1) where it (1) encompassed a large area exclusively of trabecular bone; (2) excluded cortical bone; and (3) excluded the basivertebral plexus. Since VBD was measured at multiple vertebrae locations per subject, the mean density obtained from T8 to T10 (mVBD) was considered as a surrogate measure of VBD and was expressed in HUs for statistical analysis.

All VBD images were captured and one trained independent observer blind to the clinical data placed ROIs fulfilling the criteria for inclusion. A radiologist (TB) with 17 years of experience examined each ROI and adjusted its placement when necessary to exclude vertebral abnormalities such as main vessels, bone islands or to exclude an entire vertebra from measurement when the following abnormalities were noted: fractures, metastatic lesions, benign focal lesions within the vertebra, or any other vertebral pathology.

2.4. Measurement of dual-energy X-ray absorptiometry (DXA)

DXA was performed in 143 ESRD patients out of the 231 patients using a DPX-L device (GE Lunar iDXA with software enCore 2008 version 12, 30, 008, GE Medical systems, Chalfont St. Giles, UK). In 88 patients DXA was not performed, mainly due to limited access to the scanner. BMD of total body (tBMD) was simultaneously measured also at its different skeletal sub-regions: head, arms, legs, trunk, ribs and pelvis. BMD was expressed in g/cm^2 and as a T-score, indicating the number of standard deviations (SD) from the mean scores for 30-year-old normal men and women separately, and as a Z-score, indicating the T-score adjusted by age.

2.5. Laboratory analyses and other measurements

All blood samples were obtained in the morning after an overnight fast. Serum samples were immediately analysed for standard serum analyses and the samples were kept frozen at −70 °C if not analysed immediately. Plasma interleukin-6 (IL-6) and tumor necrosis factor (TNF) were analysed by commercial kits available for an Immulite Automatic Analyzer (Siemens Medical Solutions, Los Angeles, CA, USA) according to the instructions of the manufacturer. Serum insulin growth factor-1 (IGF-1) was measured on an Immulite automatic analyzer (Diagnostic Products Corporation Corp., Los Angeles, CA, USA). Other analyses, including high sensitivity C-reactive protein (hsCRP), intact parathyroid hormone (iPTH), 25-OH vitamin D, 1,25-OH vitamin D, serum lipids and lipoproteins, mineral and electrolytes, and others were analysed at the accredited Chemical Laboratory of Karolinska University Hospital, Sweden.

Height and body weight were obtained at the baseline and body mass index (BMI) was recorded. Subjective global assessment (SGA) was used to evaluate overall protein energy wasting (PEW) as previously described [46]. PEW was defined as SGA score >1. Arterial systolic and diastolic blood pressures (BP) were measured three times in the morning after a 15-min resting period, and the mean blood pressure (MBP) used. Signs of CVD based on earlier or present occurrence of documented cerebrovascular, cardiovascular, or peripheral vascular disease were recorded, as previously described [41].

2.6. Statistical analysis

Data are expressed as median (range of 10th to 90th percentile) or percentage or relative risk ratio (95% CI, confidence intervals), 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 Fischer's exact test for