Osteoporosis International (2019) 30:1015–1023
https://doi.org/10.1007/s00198-019-04864-4

ORIGINAL ARTICLE

Chronic kidney disease is associated with low BMD at the hip but not at the spine

K. S. Bezerra de Carvalho[1] · R.F.V. Vasco[1] · M.R. Custodio[1] · V. Jorgetti[1,2] · R.M.A. Moysés[1,3] · R.M. Elias[1,3]

Received: 26 July 2018 / Accepted: 20 January 2019 / Published online: 28 January 2019

Abstract

Summary Although chronic kidney disease is associated with other bone disorders, osteoporosis can be found in this context, and it is defined based on bone mineral density (BMD), measured by dual-energy X-ray absorptiometry. As CKD progresses, the percentage of normal BMD decreases, whereas that of osteopenia/osteoporosis increases, mostly due to hip involvement, particularly in patients with reduced renal function.

Introduction Osteoporosis is a highly prevalent disease in patients with chronic kidney disease (CKD). We investigated the features of bone mineral density (BMD) in patients with assorted kidney diseases and hypothesized that low BMD, as measured by dual-energy X-ray absorptiometry (DXA), would be more prevalent as kidney function decreased and would correlate with biomarkers of mineral and bone disease.

Methods DXA obtained from January 1, 2008, to December 31, 2017, clinical, demographic, and biochemical data at the time of image acquisition were recorded. Data from 1172 patients were included in this study (81.3% women, 79.9% white, and 8.1% diabetic).

Results Osteopenia and osteoporosis in at least one site (total hip or spine) were found in 32.7% and 20.0% of patients, respectively. As CKD progressed, the percentage of patients with normal BMD decreased, whereas the percentage of osteopenia and osteoporosis increased, which was mostly due to the total hip involvement, particularly in patients with estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2. Older age and hyperparathyroidism were independent risk factors for osteopenia/osteoporosis at the total hip; female gender, older age, and higher iCa were independently associated with the risk of osteopenia/osteoporosis at the spine. With eGFR > 90 ml/min as reference, the odds ratios for osteoporosis/osteopenia at the hip were 1.51 (95% CI 1.01–2.24) and 1.91 (95% CI 1.13–3.20) for patients with eGFR 30–60 and 15–30 ml/min/1.73 m^2, respectively. No CKD stage was significantly associated with the risk of osteoporosis/osteopenia at the spine.

Conclusion Our results highlighted that low BMD in patients with CKD is associated with age and hyperparathyroidism, and affects predominantly the hip.

Keywords Bone mineral density · Chronic kidney disease · DXA · Hip · Osteoporosis · Parathyroid hormone

Introduction

Osteoporosis is a disorder of low bone mass and impaired bone strength, causing an increased risk for fracture in the general population [1]. Chronic kidney disease (CKD) is a highly prevalent disease characterized by gradual loss of kidney function. According to Kidney Disease Improving Global Outcomes (KDIGO), it is defined as kidney damage (albuminuria) or glomerular filtration rate (GFR) < 60 ml/min/1.73 m^2 for 3 months or more, irrespective to cause [2]. Fractures are very common in patients with CKD, and their occurrence cannot be entirely explained by the aging population, since children with CKD have 3-fold increased fracture risk [3]. Known risk factors for fractures in the general

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00198-019-04864-4) contains supplementary material, which is available to authorized users.

✉ R.M. Elias
rosilenemotta@hotmail.com

[1] Nephrology Service, Hospital das Clinicas HCFMUSP, Universidade de Sao Paulo, Rua Dr. Enéas de Carvalho Aguiar 255, 7° andar, São Paulo, SP 05403-000, Brazil

[2] Hospital Samaritano, São Paulo, Brazil

[3] Universidade Nove de Julho, UNINOVE, São Paulo, Brazil

population can be exacerbated by CKD, such as hormonal deficiency [4], falls [5], and sarcopenia [6]. Fractures were reported to be greater than 2- to 100-fold more common in CKD than in age-matched individuals without CKD [7–9]. In patients with predialysis CKD, a history of osteoporosis was reported to be associated with a greater than 2-fold odds of hip fracture compared with the general population [8]. Most importantly, mortality rates after fracture were 3-fold greater in patients with CKD [10].

Data from the National Health and Nutrition Examination Survey (NHANES) suggest that CKD and osteoporosis are highly co-prevalent [8, 11], such that Moe and cols suggest the term CKD-induced osteoporosis [12], in the same way we use the expression steroid-induced osteoporosis. Among NHANES III participants, osteoporosis was twice as common in those with an estimated GFR (eGFR) < 60 ml/min when compared to those with an eGFR ≥ 60 ml/min [8].

The dual-energy X-ray absorptiometry (DXA) is the gold standard method to measure bone mass and has been demonstrated to predict fracture risk in the general population. In contrast, the role of DXA in fracture risk assessment in CKD has been controversial. The 2009 KDIGO guidelines was recommended against routine bone mineral density (BMD) testing. However, more recent prospective trials in patients with predialysis CKD [13, 14] and in patients with end-stage renal disease on hemodialysis [15] indicate that low areal BMD measured by DXA at the forearm (one-third and ultra-distal radius), hip (total and femoral neck), and spine can, indeed, predict a future fracture. These studies support the clinical use of DXA as a fracture risk-screening tool in CKD, which was recognized by the update of KDIGO in 2016 [16], indicating that the same T-score cutoffs for osteopenia and osteoporosis can be used for CKD patients as for the general population.

The prevalence of osteopenia/osteoporosis is not well established among patients with CKD and, when available, is mostly obtained from patients not yet on dialysis [13]. Therefore, we ought to investigate the prevalence and pattern of BMD, as measured by DXA, in a cross section of patients with 1–5 CKD stages, in a decade of observation. We hypothesized that first, low BMD will be more prevalent as kidney function decreases and second, biomarkers of CKD-MBD will be associated with altered BMD.

Materials and methods

Source population

This was a retrospective study. CKD outpatients had been followed at the Nephrology Service of the Hospital das Clinicas, Universidade de Sao Paulo. Diabetes, nephrolithiasis, glomerulonephritis, and hypertension accounted for more than a half of kidney disease causes. Patients with eGFR > 60 ml/min/1.73 m^2 had been followed for a varied of reasons, including the above mentioned and others such as HIV-associated nephropathy, tubulopathy, polycystic kidney disease, and pyelonephritis. Electronic records from the Nephrology outpatient clinic at Hospital das Clinicas, Universidade de Sao Paulo, were assessed. All requisitions for DXA made between January 1, 2008, and December 31, 2017 were confronted and updated with the exam date. There was no standard protocol to investigate osteoporosis, and the criteria to screen patients by DXA were entirely up to their physicians. Clinical and demographic data were obtained by manual check for each included patient. All biochemistries were therefore selected within 3 months of the DXA acquisition. Inclusion criteria were as follows: having performed a DXA during the study observation period, age older than 18 years, and availability of key relevant variables including creatinine and parathyroid hormone.

Data collection

Data from the electronic records were obtained for the following clinical factors: body index mass (BMI) expressed as kilograms per square meter, age, sex, race, etiology of renal disease, and medication use. All charts were checked to ascertain the medications and clinical conditions through the physician prescription on line and medical notes. The eGFR was used as a measure of kidney function and to define the stage of CKD and was obtained using the CKD-EPI equation [17]. Laboratory measurements obtained were total serum calcium, ionized calcium, serum phosphate, and albumin, measured by automated colorimetry; serum 25 (OH)-vitamin D, quantified by chemiluminescence immunoassay (DiaSorin, StilWater, Minn., USA, reference range, RR, 30–100 ng/ml); plasma PTH (RR 11–62 pg/ml), measured by chemiluminescence immunoassay (Cobas, Roche Diagnostic GmbH, Mannheim, Germany); and alkaline phosphatase (RR range 32–122 U/l), measured by a kinetic automated method.

The local Research Ethics Committee (Cappesq #45163715.4.0000.0068) has approved the protocol. Since it was a retrospective study, no informed consent form was required.

X-ray absorptiometry (DXA)

Bone mineral density (BMD) was evaluated by DXA. All exams were performed using DXA Hologic QDR 4500 scanners (Hologic Inc., Bedford, MA, USA). We report the total hip BMD and the lumbar spine BMD, and the results were expressed in grams per square centimeter, as well as T-scores, i.e., the difference in standard deviation (SD) compared with the mean of healthy young sex-matched controls, and Z-scores, i.e., the difference in SD

compared with the mean value of healthy age-and sex matched controls. Certified technicians performed the DXA scans following a strict protocol. T-score was calculated using the National Health and Nutrition Examination Survey III reference database [18]. Subjects were considered to have normal BMD if their T-score was ≥ − 1 SD in at least one skeletal site, osteopenia if their score was between − 1 SD and − 2.4 SD in at least one skeletal site, and osteoporosis if their T-score was ≤ − 2.5 SD in at least one skeletal site [19]. The young Caucasian women were used as the reference population for both men and women as recommended by the International Society for Clinical Densitometry (ISCD) [20].

Statistical analyses

Data are presented as mean ± SD or median (25,75) to describe normal and non-normal distributed continuous variables, respectively. Categorical variables are expressed as proportions. We used the one-way ANOVA test or Kruskall-Wallis test, as appropriate, to compare continuous characteristics, and the chi-squared test or Fisher exact test to compare proportions among groups. Correlations between T-scores and independent variables were examined by the Spearman correlation coefficient. Multivariable logistic analyses were undertaken with osteopenia and/or osteoporosis at the total hip and at the spine as the dependent variable and with age, gender, hyperparathyroidism, iCa, and eGFR as the independent variables. Two models were built, one for the entire population and one for patients with an eGFR < 60 ml/min/1.73 m^2, for the risk of osteopenia/osteoporosis in each bone site (total hip and lumbar spine). Renal function measured by eGFR was tested as a continuous variable, and the probability risk derived from multivariable analysis was used to plot Fig. 2. The eGFR was categorized by CKD stages 1, 2, 3, 4, and 5, and odds ratio for osteopenia/osteoporosis was plotted in Fig. 3. CKD 1 (eGFR > 90 ml/min) was used as reference. A p value < 0.05 was considered significant. Analyses were performed using SPSS 21.0 (SPSS Inc., Chicago, IL, USA) and *GraphPad Prism® software* (GraphPad Software, Inc., CA, USA).

Results

Out of 1206 patients identified with DXA, 12 were excluded due to missing data on renal function and another 22 patients were excluded, as the image of DXA was missing. Therefore, a total of 1172 patients were enrolled into this study. Characteristics of patients are described in Table 1. The majority was female (81.3%), 79.9% were white, and 8.1% were diabetic. BMI was lower among patients with osteoporosis; BMI above 25 kg/m^2 was found in 52%, 32%, and 15% of patients with DXA showing normal, osteopenia, and osteoporosis results ($p = 0.0001$). A total of 31 patients were on dialysis. As shown in Table 1, patients with normal BMD were heavier and had better renal function, lower iCa, PTH, and AP. About 10.7% of patients were taking cholecalciferol, 3.2% were taking an active vitamin D (calcitriol), 0.9% were taking sevelamer, and 232 patients (19.8%) were taking glucocorticoids. Osteopenia or osteoporosis in at least one site (total hip or spine) was found in 32.7% and 20.0% of patients, respectively.

The analysis according to renal function (Table 2) showed that patients with eGFR > 90 ml/min/1.73 m^2 were younger; hyperparathyroidism (PTH > 65 pg/ml) was more frequent in late stages of CKD. As CKD progresses, the percentage of patients with normal BMD decreases, whereas the percentage of osteopenia and osteoporosis increases (Table 2). However, the difference between initial and late stages of CKD was more prominent at the total hip. Indeed, hip was more affected than spine, as assessed by DXA, in patients with and eGFR < 60 ml/min (Supplementary Table 1). Accordingly, osteopenia and/or osteoporosis was found only at the hip in 1.6%, only at the lumbar spine in 26.6%, in both sites in 9.5% and in none of sites in 62.3% of cases among patients with eGFR ≥ 60 ml/min/1.73 m^2, whether in patients with eGFR < 60 ml/min/1.73 m^2 was found only at the hip in 15.9%, only at the lumbar spine in 25.5%, in both sites in 15.6% and in none of the sites in 43.0%, difference that was statistically significant ($p < 0.0001$). Mean and 95% confidence intervals of T-scores at the total hip and spine, according to eGFR category, are illustrated in Fig. 1. T-scores at the total hip correlated with age ($r = -0.324$, $p = 0.007$), iCa ($r = -0.332$, $p = 0.009$), and 25 vitamin D ($r = 0.310$, $p = 0.027$); T-scores at the spine correlated with age ($r = -0.314$, $p = 0.008$), iCa ($r = -0.306$, $p = 0.016$), and phosphate ($r = 0.278$, $p = 0.026$).

Table 3 shows multivariate analyses on the risk of osteoporosis/osteopenia. For total hip, older age and hyperparathyroidism were independent risk factors in both, the entire population, and among patients with eGFR < 60 ml/min/1.73 m^2. Regarding spine, female gender, older age, and higher iCa were independently associated with the risk of osteopenia/osteoporosis in the entire population, whereas in patients with eGFR < 60 ml/min/1.73 m^2, only older age and hyperparathyroidism remained as independent risk factors. Figure 2 illustrates the probability risk of osteoporosis/osteopenia at the total hip in the entire population, in which age and hyperparathyroidism were modeled together. It should be noted that for the same age, the risk of having osteoporosis/osteopenia is much higher in the presence of hyperparathyroidism. We have modeled eGFR by category instead of a continuous variable, adjusted by age, gender, ionized calcium, and PTH, showing that the odds ratios for osteoporosis/osteopenia at the hip were 1.51 (95% CI 1.01–2.24) and 1.91 (95% CI 1.13–3.20) for patients with eGFR 30–60 and 15–30 ml/min/1.73 m^2,

Table 1 Characteristic of patients according to bone density

	All $N = 1172$	Normal $N = 554$	Osteopenia $N = 383$	Osteoporosis $N = 235$	P
Age (years)	51 ± 16	45 ± 16	58 ± 13*	55 ± 17*	*0.0001*
Female gender (%)	81.3	50.7	71.2	78.1	0.374
Ethnicity (%)					
White	79.9	45.3	33.4	21.3*	*0.011*
Asian	1.2	55.0	30.7	14.2*	
Other	18.9	28.6	28.6	42.9*	
Weight (kg)	68.9 ± 14.6	73.1 ± 14.9	66.7 ± 13.3*	62.1 ± 12.4*	*0.0001*
Body Mass Index (kg/m^2)	27.4 ± 5.5	28.4 ± 5.7	27.1 ± 5.1*	25.7 ± 5.0*	*0.0001*
Etiology of CKD (*n* (%))					
Diabetes	8.1	8.3	6.5	10.2	0.702
Nephrosclerosis	16.3	15.7	16.2	17.9	
Glomerulonephritis	36.2	36.1	38.4	32.8	
Nephrolithiasis	28.9	28.3	29.5	29.4	
Other/unknown/none	10.5	11.6	9.4	9.8	
Prednisone use (%)	19.8	22.5	18.5	16.2	0.114
Creatinine (mg/dl)	0.9 (0.7, 1.3)	0.9 (0.7, 1.2)	1.0 (0.7, 1.5)*	1.0 (0.8, 1.5)*	*0.0001*
eGFR (ml/min/1.73 m^2)	73 ± 35	80 ± 34	67 ± 32*	67 ± 40*	*0.0001*
Total calcium (mg/dl)	9.4 ± 0.7	9.4 ± 0.7	9.5 ± 0.6	9.5 ± 0.7	0.067
Ionized calcium (mg/dl)	5.03 ± 0.36	4.99 ± 0.33	5.07 ± 0.31*	5.07 ± 0.47*	*0.001*
Phosphate (mg/dl)	3.5 ± 0.8	3.5 ± 0.8	3.5 ± 0.7	3.6 ± 1.0	0.528
PTH (pg/ml)	50 (35, 81)	43 (32, 66)	55 (38, 89)*	55 (39, 105)*	*0.0001*
Alkaline phosphatase (UI/l)	74 (58, 102)	69 (56, 89)	75 (57, 104)	81 (62, 112)*	*0.007*
25 (OH) vitamin D	27.0 ± 9.9	26.9 ± 9.7	26.9 ± 9.7	26.1 ± 9.8	0.246
Albumin (g/dl)	4.3 ± 0.5	4.3 ± 0.5	4.3 ± 0.5	4.3 ± 0.5	0.863
Magnesium (mEq/l)	2.0 ± 0.3	1.9 ± 0.2	2.0 ± 0.3	2.0 ± 0.2	0.101
Bicarbonate (mmol/l)	25.3 ± 3.4	25.4 ± 3.3	25.3 ± 3.2	24.9 ± 3.8	0.276

Values are expressed as mean ± SD, median (25,75), or percentage. AP was obtained only in 480 patients. Ionized calcium was available in 76.5% of patients. Normal was defined if T-score was ≥ − 1 SD at one or more skeletal sites, osteopenia if T-scores was between − 1 SD and − 2.4 SD at one or more skeletal sites, and osteoporosis if T-score was ≤ − 2.5 SD at least one skeletal sites

Values lower than 0.05 is considered significant

CKD chronic kidney disease, *PTH* parathyroid hormone, *eGFR* estimated glomerular filtration rate, *PTH* parathyroid hormone

*$p < 0.005$ vs. normal

respectively. No eGFR category was significantly associated with the risk of osteoporosis/osteopenia at the spine. Figure 3 depicts the odds ratio and 95% CI for the risk of osteopenia/osteoporosis at the total hip and the lumbar spine.

About 132 patients had repeated DXA during the study period, 80 with initial eGFR ≥ 60 ml/min/1.73 m^2 and 52 already with initial eGFR < 60 ml/min/1.73 m^2. In this latter subgroup of patients with CKD, T-scores worsened at spine in 17 (32.7%) and at hip in 16 (30.8%) patients, with 6 (11.5%) patients getting worse in both sites. These percentages were similar to that observed in patients with eGFR ≥ 60 ml/min/1.73 m^2 (31.2 and 36.2% had decreased bone mineral density at hip and spine, respectively). Annual decrease of T-scores at total hip was − 0.09 (− 0.26, 0.07) and − 0.07 (− 0.19, 0.05) in patients with eGFR < 60 ml/min/1.73 m^2 and ≥ 60 ml/min/1.73 m^2, respectively ($p = 0.626$). Annual decrease of T-scores at the lumbar spine was − 0.04 (− 0.18, 0.11) and − 0.04 (− 0.22, 0.12) in patients with eGFR < 60 ml/min/1.73 m^2 and ≥ 60 ml/min/1.73 m^2, respectively ($p = 0.494$). There was no correlation between annual bone lost at total hip and age ($r = -0.60$, $p = 0.501$), although there was a significant correlation between annual bone lost at the lumbar spine and age ($r = -0.343$, $p = 0.0001$). There was no demographic, clinical, or biochemical characteristic that distinguished patients who had worsened BMD from the others.

Discussion

The present study included a large sample size of individuals with stages 1–5 CKD providing several insights about the features of BMD in this population. First, we confirmed that patients with low BMD were more likely to be women and older, findings similar to those in the general population. In

Table 2 Characteristics of patients according to renal function, measured by estimated glomerular filtration rate (eGFR)

eGFR (ml/min/1.73 m^2)	> 90 (*N* = 434)	60–90 (*N* = 323)	30–60 (*N* = 253)	15–30 (*N* = 91)	< 15 (*N* = 71)	*p*
Age (years)	43 ± 14	54 ± 14*	59 ± 16*#a	64 ± 16*#a	52 ± 12*	*0.0001*
Male gender (*n* (%))	37.4	26.9	21.9	7.7	6.2	0.819
Creatinine (mg/dl)	0.7 ± 0.1	0.9 ± 0.1* #	1.4 ± 0.3* # a	2.4 ± 0.5* # a	7.2 ± 2.9*	*0.0001*
eGFR (ml/min/1.73 m^2)	109.2 ± 17.5	74.9 ± 8.9* #	45.6 ± 8.6* # a	22.9 ± 4.0* # a	7.5 ± 4.2*	*0.0001*
PTH ≥ 65 pg/ml (%)	14.7	22.5	51.1	78.7	85.5	*0.0001*
Total hip T-score	− 0.9 (− 1.4, − 0.3)	− 0.9 (− 1.5, − 0.2) #	− 1.0 (− 1.8, − 0.3)#	− 1.2 (− 1.8, − 0.7)* a	− 1.4 (− 2.4, − 0.8)*	*0.0001*
Total hip Z-score	− 0.2 (− 0.9, 0.4)	0 (− 0.5, 0.6)* #	0 (− 0.7, 0.7)* #	− 0.09 (− 0.8, 0.6) #	− 0.9 (− 1.5, − 0.2)*	*0.0001*
Spine T-score	− 2.0 (− 2.6, − 1.4)	− 2.0 (− 2.5, − 1.5)	− 1.9 (− 2.4, − 1.2)	− 1.5 (− 2.5, − 0.6) * a	− 1.8 (− 2.6, − 0.7)	*0.016*
Spine Z-score	− 1.2 (− 1.9, − 0.4)	− 0.8 (− 1.6, 0)	− 0.4 (− 1.4, 0.5)* # a	− 0.1 (− 1.1, 1.1)* a	− 0.7 (− 1.8, 0.2)	*0.0001*
Total hip, DXA results (%)						
Normal	78.9	75.4	63.7	50.5	53.6	0.0001
Osteopenia	20.4	23.4	28.7	40.7	30.5	
Osteoporosis	0.7	1.2	7.6	8.8	15.9	
Spine, DXA results (%)						
Normal	60.1	50.6	43.5	48.4	50.7	*0.002*
Osteopenia	24.2	29.2	37.9	30.8	23.9	
Osteoporosis	15.7	20.2	18.6	20.9	25.4	

Values are expressed as mean ± SD, median (25,75) or percentage. Normal was defined if T-score was ≥ − 1 SD at one or more skeletal sites, osteopenia if T-scores was between − 1 SD and − 2.4 SD at one or more skeletal sites, and osteoporosis if T-score was ≤ − 2.5 SD at least one skeletal sites

Values lower than 0.05 is considered significant

eGFR estimated glomerular filtration rate, *PTH* parathyroid hormone, *DXA* dual X-ray absorptiometry

*$p < 0.005$ vs. > 90; [a] $p < 0.005$ vs. 60–90; #$p < 0.005$ vs. < 15

addition, we demonstrated the association between low BMD and impaired renal function, since osteopenia/osteoporosis seems to be more prevalent as CKD progresses. Second, in patients with eGFR < 60 ml/min/1.73 m^2, hip is the elected bone site for osteopenia/osteoporosis, which is closely related to the presence of hyperparathyroidism.

In patients with CKD, mineral and bone disease (CKD-MBD) is a common complication that begins early in the course of the disease, causing high morbidity and mortality.

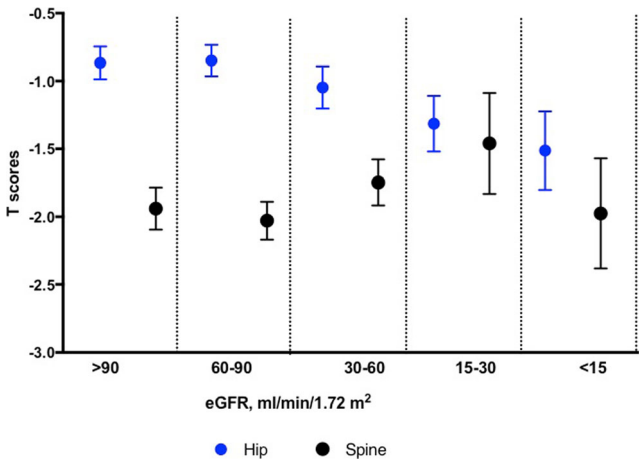

Fig. 1 Bone mineral density according to estimated glomerular filtration rate (eGFR). Symbols are mean and 95% confidence interval. Blue and black circles represent T-scores at the total hip and spine, respectively

Several hormonal and biochemical abnormalities occur as CKD progresses including hyperphosphatemia, increased fibroblast growth factor − 23 (FGF-23) and PTH levels, hypocalcemia, and decreased renal synthesis of $1,25(OH)_2D_3$, chronic metabolic acidosis, chronic inflammation, and premature hypogonadism. Renal osteodystrophy (ROD) is a nomenclature used to describe the abnormalities seen on bone histomorphometry, which are totally independent of BMD. ROD included abnormalities that impair bone remodeling and mineralization and result in cortical and trabecular defects [21]. The diagnosis of osteoporosis in the context of CKD is controversial since the ROD classification has not been designed for the osteoporosis diagnosis. BMD does not predict the type of ROD since different histological causes of bone disease in CKD patients may lead to similar low BMD values. In this context, patients suffering from high-turnover bone disease, low turnover bone disease, or age- or sex-related osteoporosis may all show equal densitometric values [22]. A potential limitation of BMD by DXA at traditional sites (i.e., the hip and spine) is the inability of DXA to discriminate between cortical and trabecular bone compartments. This limitation is particularly relevant in patients with CKD and in those who have high serum PTH, because of an anabolic effect on trabecular bone and a catabolic effect on cortical bone [23]. Knowing that the spine is about 95% trabecular bone and the total hip about 50% cortical/trabecular bone, while DXA's lower resolution is a limitation, it should not be an excuse to

Table 3 Multivariate analyses on the risk of osteoporosis/osteopenia at hip and spine

	Relative risk	95% CI lower-upper	*p*
Total HIP			
Entire group			
Age (each year)	1.043	1.031–1056	*0.0001*
Female gender	1.141	0.755–1.723	0.532
iCa	1.206	0.759–1.917	0.427
PTH ≥ 65 pg/ml	1.954	1.355–2.819	*0.0001*
eGFR (each ml/min)	0.997	0.991–1.003	0.301
eGFR < 60 ml/min/1.73 m^2			
Age (each year)	1.046	1.028–1.063	*0.0001*
Female gender	1.451	0.807–2.609	0.214
iCa	1.168	0.661–2.065	0.592
PTH ≥ 65 pg/ml	2.238	1.324–3.783	*0.003*
eGFR, each ml/min	0.997	0.983–1.012	0.693
SPINE			
Entire group			
Age (each year)	1.043	1.032–1.055	*0.0001*
Female gender	1.511	1.034–2.208	*0.033*
iCa	1.596	1.021–2.497	*0.040*
PTH ≥ 65 pg/ml	1.205	0.857–1.694	0.284
eGFR (each ml/min)	1.000	0.995–1.006	0.871
eGFR < 60 ml/min/1.73 m^2			
Age (each year)	1.024	1.009–1.040	*0.001*
Female gender	1.550	0.881–2.729	0.129
iCa	1.681	0.945–2.991	0.077
PTH ≥ 65 pg/ml	1.650	1.008–2.701	*0.046*
eGFR (each ml/min)	1.014	1.000–1.028	0.058

Values lower than 0.05 is considered significant

iCa ionized calcium, *PTH* parathyroid hormone, *eGFR* estimated glomerular filtration rate

discourage its use in patients with CKD, as it gives information on both cortical and trabecular compartments based on which skeletal site is imaged. Indeed, DXA is recognized to predict fracture in patients with CKD, and so far, it is the recommended method of screening in this population [16].

Spinal fracture in patients with mild CKD, evaluated by lateral radiograph, showed prevalence comparable to the general population [24], whereas hip fracture is far more frequent among patients with CKD [7, 25–27]. In a recent study, 65% of all major bone fractures in a sample of patients on hemodialysis were at the hip [28].

In agreement with these findings, we observed low hip BMD mostly in patients with eGFR < 60 ml/min/1.73 m^2. This result can be explained by a greater impairment of cortical than trabecular bone in patients with CKD, a finding already demonstrated by peripheral quantitative computed tomography (HRpQCT) [29].

We found that hyperparathyroidism was associated with low BMD in patients with CKD. The fact that hip is a more cortical bone than spine explains, at least in part, the higher prevalence of fracture in this site among patients with CKD [30, 31]. This information is of extreme importance since hip fractures are most serious and costly [32]. Levels of PTH were associated with low BMD in a previous study [33], although the association of this hormone with a fracture is more controversial and described mostly in patients on dialysis [15, 34, 35]. It is known that high concentration of PTH predicts loss of cortical area, density, and thickness, and increases the cortical porosity, while it decreases bone strength, which constitutes osteoporosis [23]. Taken together, our results point to an important impact of hyperparathyroidism on low BMD, mostly at the hip in patients with CKD. It should be noted that for the same age, the risk of having osteoporosis/osteopenia is much higher in the presence of hyperparathyroidism. As an example (Fig. 2), the probability of having low BMD of a given patient with 60 years old is close to 20% in the absence of hyperparathyroidism and increases to 40% if hyperparathyroidism is present. Looking at it in another way, we can say that a 40% probability of having low BMD is the same for a patient with 50 years old and 70 years old in the presence and absence of hyperparathyroidism, respectively. Although renal function does have a role in low BMD at spine, this association does not seem to be strong. Though the current KDIGO guidelines recommend using DXA for predicting fractures, the relationship between low BMD at lumbar spine and fracture in patients with CKD has not been established [36–38]. Taken together, our data suggest that hip fracture might be associated with hyperparathyroidism and low BMD in patients with CKD, whereas spine fractures are similar to those observed in the general population and cannot be predicted by low BMD.

The present study does have limitations given its observational single-center nature. Although we have included a large cohort of patients with CKD and demonstrated a high prevalence of reduced BMD in this population, it is important to acknowledge that the current results cannot address causality. Another limitation, which should be mentioned, is that patients selected from a tertiary hospital might not represent the entire population of CKD worldwide. We are also aware of the possible bias of selection inherent to a retrospective study, the lack of ascertaining while describing medications in use and compliance to the prescription, and the exclusion of patients with missing key data. Finally, other limitations included the lack of formal protocols to request DXA, which was a decision of each physician, the lack of forearm DXA imaging, and other factors that might play a role in the increased fracture risk among patients with CKD such as acidosis, inflammation, and hypogonadism that were not evaluated in the current study.

In summary, we have demonstrated that osteopenia and osteoporosis were highly prevalent in patients with CKD and seem to be more likely to occur as the renal function

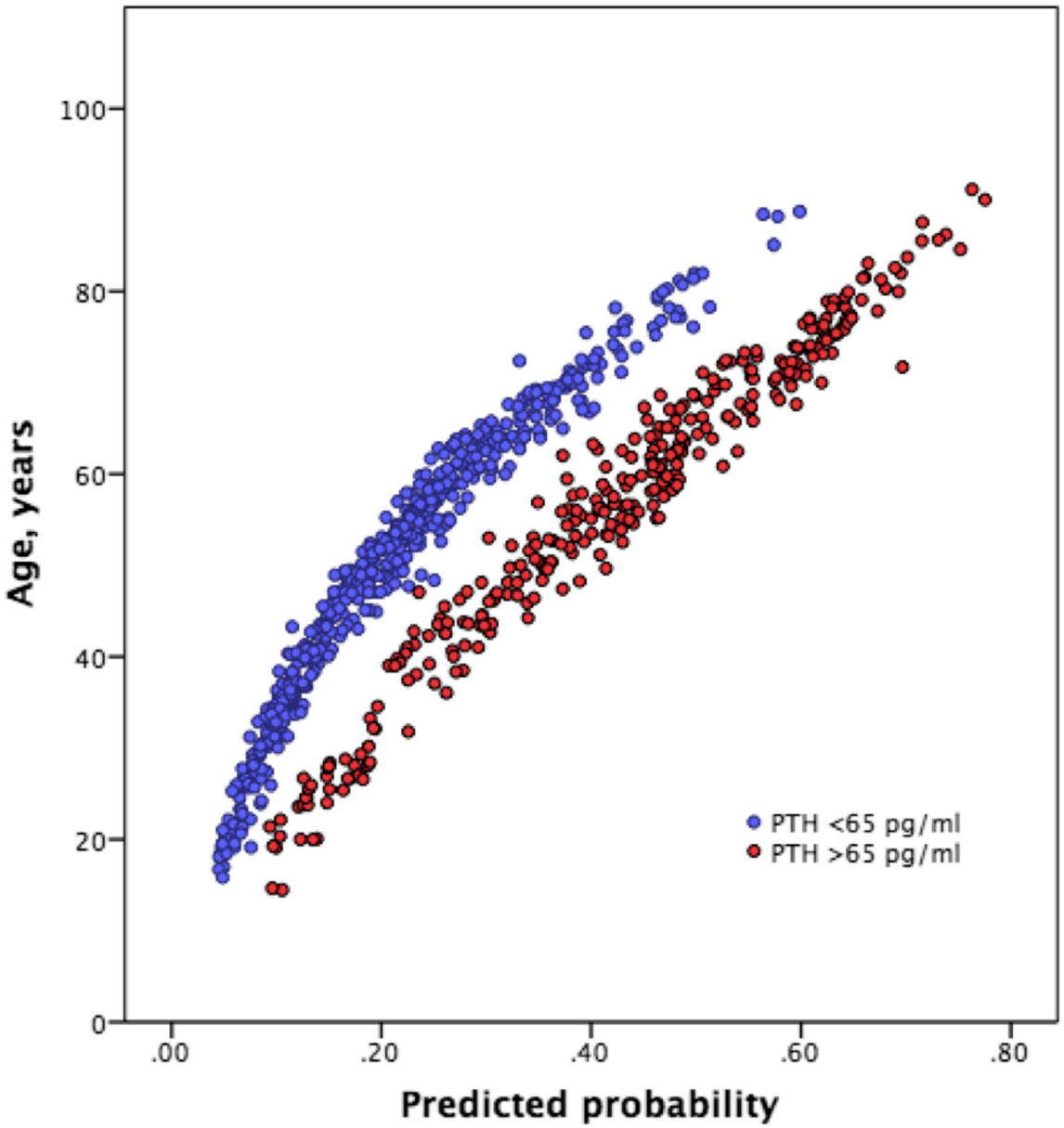

Fig. 2 Probability risk of osteoporosis/osteopenia at the total hip according to age and presence of hyperparathyroidism. Model also adjusted for gender and ionized calcium. Blue circles symbolize patients without hyperparathyroidism (PTH < 65 pg/ml) and red circles symbolize patients with hyperparathyroidism (PTH > 65 pg/ml). PTH, parathyroid hormone

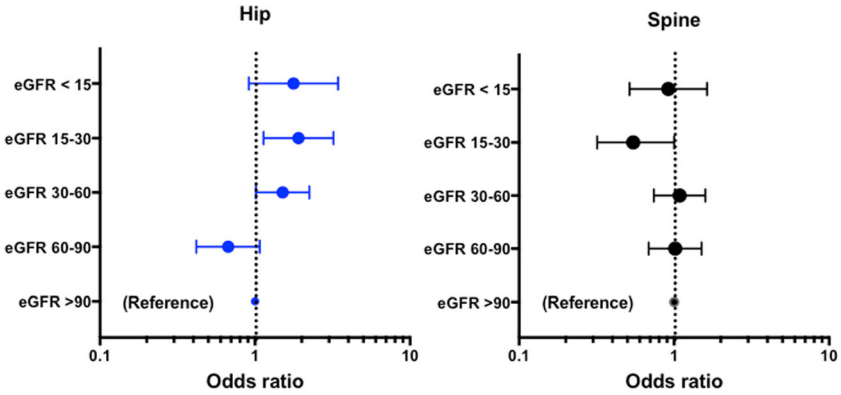

Fig. 3 Risk of osteopenia/osteoporosis at the hip (blue circles) and at the spine (black circles) according to chronic kidney disease stage, measured by estimated glomerular filtration rate (eGFR). Model adjusted for age, gender, pratahyroid hormone, and ionized calcium. Reference was set at eGFR > 90 ml/min/1.73 m^2

deteriorates, with aging, and in patients with PTH higher than 65 pg/ml. Indeed, hyperparathyroidism was associated with high risk of reduced BMD, particularly at the hip, opening a new avenue for research. Whether this finding explains the high prevalence of hip over spine fracture in patients with CKD deserves further studies. Knowing that reduced BMD in patients with CKD, as measured by DXA, can predict the risk of fracture, and in face of accumulated evidence to date, complacency with a contemplative care practice regarding osteoporosis needs to change. There is a need for a placebo-controlled prospective study to assess the effect of treatment of these conditions on mineral density, quality of life, fracture risk, and mortality.

Acknowledgments We thank Fatima Libânio for her assistance in collecting the electronic data.

Author contributions Authors' roles: Study design: KSBC, and RME. Study conduct: KSBC, RFVV, MRC, VJ, RMAM, and RME. Data collection: KSBC, RFVV, and RME. Data analysis: KSBC, RMAM, and RME. Data interpretation: KSBC, MRC, VJ, RMAM, and RME. Drafting manuscript: KSBC, RMAM and RME. Revising manuscript content: KSBC, MRC, VJ, RMAM, and RME. Approving final version of manuscript: KSBC, RFVV, MRC, VJ, RMAM, and RME. RME takes responsibility for the integrity of the data analysis.

Compliance with ethical standards

Conflicts of interest KSBC, MRC, and RME have nothing to declare. VJ and RMAM are financially supported by CNPq, Conselho Nacional de Desenvolvimento Científico e Tecnológico (grant numbers 303684/2013-5 and 304249/2013-0, respectively). This financial support had no role in study design; collection, analysis, and interpretation of data; writing the report; and the decision to submit the report for publication.

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