Bone mass measurement by DXA should be interpreted with caution in the CKD population with vascular calcification

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ABSTRACT

Background: KDIGO guidelines suggest the use of dual-energy X-ray absorptiometry (DXA) to assess bone mineral density (BMD) in patients with CKD 3a-5D. Previous studies have demonstrated an association between trabecular bone mass loss and coronary artery calcification (CAC) progression. This study aimed to prospectively investigate the relationship between BMD changes, quantified by DXA, and CAC progression in the non-dialyzed CKD population.

Methods: In this post hoc study, BMD by DXA was measured at the lumbar spine and total hip at baseline and 12-months. Patients were categorized according to BMD changes into 3 different groups: LOSS, UNCHANGED and GAIN. CAC quantification was obtained by multislice computed tomography at baseline and 12-months.

Results: 87 patients (55.6 ± 10.7 years, 62% males, 30% diabetic, eGFR = 39.2 ± 18.1 mL/min/1.73m²) were enrolled. CAC was found in 41 (47%) of the patients at baseline and CAC progression in 25 (64%) of them. Considering the lumbar spine and total hip BMD changes together, 24%, 48%, and 25% of the patients were in the LOSS, UNCHANGED and GAIN groups, respectively. Compared to the UNCHANGED or LOSS groups, the GAIN group had an increase in calcium score (p = 0.04) and a higher proportion of patients with CAC progression (p = 0.01). In the logistic regression analysis, CAC progression was 4.5 times more likely to be in the GAIN group.

Conclusions: The association between the increase in BMD values and the progression of vascular calcification was the result of two concomitant processes overlapping, leading to a misinterpretation of DXA results. Thus, the use of DXA for the evaluation of bone mass, especially at the lumbar spine, must be applied with restraint and its results very carefully interpreted in CKD patients.

1. Introduction

Bone loss and fractures are frequent findings in patients with chronic kidney disease (CKD) (Nickolas et al., 2006; Fried et al., 2007; Ensrud et al., 2007; Nickolas et al., 2008). The use of dual-energy X-ray absorptiometry (DXA) is recommended for the assessment of bone mineral density (BMD) and fracture risk in the general population (Kanis et al., 2008). The current KDIGO guideline suggests the use of DXA for patients with CKD 3a-5D (Kidney Disease, 2017). The current KDIGO guideline suggests the use of DXA for patients with CKD 3a-5D (Kidney Disease, 2017). This recommendation is based on 4 prospective studies (Yenchek et al., 2012; Naylor et al., 2015; limori et al., 2012; West et al., 2015), and in 2 of them, most participants were in the elderly, in the CKD 3a stage and DXA was just analyzed in the femoral neck (Yenchek et al., 2012; Naylor et al., 2015). Besides, in the other 2 studies there was controversy regarding the impact of BMD change over time in predicting fracture risk (limori et al., 2012; West et al., 2015).

Considering the current knowledge, one should consider if BMD assessment by DXA has enough accuracy for measuring BMD in CKD patients. This imaging method may overestimate bone density measurements especially due to the presence of calcified plaques in the adjacent aorta, which are incorporated in the region of interest (Babayev and Nickolas, 2015; Jannot et al., 2017). Indeed, the presence of vascular calcification is frequent and increases the risk of cardiovascular events and mortality among CKD patients (Watanabe et al., 2010; Chen et al., 2017). It is well established that bone abnormalities and vascular calcification share several common molecular mechanisms and pathways (Chen and Moe, 2012). Vascular calcification coexisting with low bone mass is frequently seen in CKD (Adragao et al., 2009; Asci et al., 2011; Tomiyama et al., 2010). Noteworthy, methods other than DXA, such as computed
tomography (CT) and bone biopsy, have shown the cross-talking between bone mass and vascular calcification (Barreto et al., 2008; Filgueira et al., 2011). Studies have consistently demonstrated that vertebral bone density loss by CT is associated with coronary artery calcification (CAC) progression (Mallucio et al., 2015; Watanabe et al., 2012), while the relationship using DXA has not yet been established in the CKD. Thus, this study aimed to prospectively investigate the relationship between BMD change by DXA and CAC progression in the non-dialyzed CKD population.

2. Materials and methods

2.1. Patients

This study is a post hoc analysis of the first year of a prospective 2-year follow-up study that evaluated the effect of rosuvastatin and sevelamer on the progression of CAC in non-dialyzed CKD patients (Lemos et al., 2013). Briefly, 117 patients with CKD stage 2-5NDD, followed for at least 3 months at the outpatient clinic of the Federal University of São Paulo, were screened for eligibility. Those who were less than 18 years of age, had chronic inflammatory disease, active malignancy, HIV, viral hepatitis, or were on chronic steroid therapy, were excluded. None of the patients were using anti-osteoporotic drugs during the study.

The study was approved by the Ethical Advisory Committee of the Federal University of São Paulo (0308/2007; 1297/2020). Additional informed consent was obtained from all individual participants for whom identifying information is included in the study.

2.2. Study protocol

In this prospective study, all patients underwent clinical evaluation, laboratory tests, assessment of calcium score by CT, and BMD by DXA at baseline and after 12 months of follow-up. Eighty-seven out of 117 patients concluded the 12-month study protocol. The reasons for dropout during follow-up are shown in Fig. 1. Demographic and laboratory characteristics, calcium score, and BMD at baseline were similar between the drop-out patients and those who completed the study.

2.3. Measurement of calcium score

Patients underwent CAC quantification using a multislice CT scanner (Light-Speed Pro - GE Healthcare, Milwaukee, USA), as described elsewhere (Lemos et al., 2013). The images were scored by a single radiologist blinded to the clinical parameters of the patients. The calcium score was expressed in Agatston Units (AU) (Agatston et al., 1990) and the presence of calcification was defined as a CAC score > 10 AU and severe calcification as a CAC score > 400 AU. CAC progression was calculated as the difference between 12-month and baseline scores/baseline score*100 and was considered when its value was greater than 0.

2.4. Measurement of bone mineral density

BMD by DXA, expressed in g/cm², was measured at the lumbar spine (L1-L4) and total hip on the same densitometer (LUNAR DPX-MD+, GE Medical Systems, Madison, WI, USA). The tests were scored by a single specialist according to standard methods, blinded to the clinical parameters of the patients. As recommended by the World Health Organization, osteoporosis was defined as a T-score below −2.5 SD of the BMD, while osteopenia was defined as a T-score between −1.0 and −2.5 SD (Lewiecki et al., 2016).

BMD changes were calculated as the difference between 12-month and baseline values. The interpretation of the results took into account the least significant change, as described elsewhere (Lewiecki et al., 2016). The least significant change obtained from our technologist and instrument was 0.034 g/cm² at the lumbar spine and 0.028 g/cm² at the total hip. A net loss or gain in BMD was considered when the absolute value of BMD change was below or above the least significant change value, respectively. Considering the net BMD lumbar spine and total hip changes together, patients were categorized into three different groups: LOSS: loss of BMD in both sites or loss in one and no change in the other site; UNCHANGED: no change of BMD in both sites; and GAIN: gain of BMD in both sites or gain in one and no change in the other site.

2.5. Biochemical measurements

Besides routine chemistry and hematological parameters, intact parathyroid hormone (iPTH), fibroblast growth factor 23 ([FGF-23] ELISA Kairos Laboratories, Tokyo, Japan) and high-sensitivity C-reactive protein ([CRP] immunochemiluminescence) were measured in blood samples collected in a fasting state at baseline and 12-month.

2.6. Statistical analysis

Mean, Standard deviation (SD), median and interquartile values, or frequencies (proportions) were calculated for all variables. Comparison of baseline and follow-up data were done by using paired student’s t-test or Wilcoxon signed-rank test, as appropriate. The analysis of proportions was done by the MacNemar test. Comparisons of two different groups were done by using a non-paired student’s t-test or Mann-Whitney U test for normally distributed data and skewed data, respectively. The comparison of continuous variables among the groups LOS, UNCHANGED and GAIN was performed using the ANOVA or Kruskal-Wallis test. For categorical variables we used x²-test or Fisher exact test, when appropriate. Variables selected in univariate analyses were fed into multivariate logistic regression models to verify their independent association with the BMD change groups, adjusted for age, gender, eGFR, and intervention. p < 0.05 was considered statistically significant. All statistical analysis was performed using SPSS for Windows (version 19; SPSS, Chicago, IL, USA).

3. Results

Table 1 shows the characteristics of the patients at baseline and 12-month. The patients were predominantly middle-aged males and had been followed by a nephrologist for a median of 16 months. Diabetes mellitus was found in 30% of the patients, obesity in 25% [body mass index (BMI) ≥ 30 kg/m²], overweight in 36% (BMI ≥ 25 kg/m²) and
Bone Reports 16 (2022) 101169

15% had a BMI < 22 kg/m². At baseline, eGFR was 39.2 ± 18.1 mL/min/1.73m². According to the CKD classification, 15 patients (17%) were in stage 2, 13 (15%) in stage 3a, 25 (29%) in stage 3b, 32 (37%) in stage 4 and 2 (2%) in stage 5ND. Twenty-four patients (28%) had proteinuria above 500 mg/24 h. Hemoglobin < 10 g/dL was found in 2% of the patients, while serum bicarbonate < 22 mmol/L and CRP > 0.3 mg/dL were both found in 45% of the patients. Concerning bone mineral metabolism, none of the patients had a serum ionized calcium < 1.11 mmol/L, 9% had a serum phosphorus > 4.6 mg/dL and 70% had iPTH levels > 65 pg/mL at baseline. Over 12 months of follow-up, there was an increase in proteinuria (p < 0.01) and a trend toward the reduction of eGFR (p = 0.06). Serum levels of hemoglobin (p < 0.01), calcium (p < 0.01) and FGF-23 (p < 0.01) increased, while a reduction in serum levels of CRP (p = 0.04) and LDL and HDL-cholesterol (p < 0.01) was observed.

There were no differences in other laboratory parameters. Besides the prior protocol drugs, statin and sevelamer which doses were not modified, there was an increase in the proportion of patients using erythropoietin, calcium carbonate, and calcitriol (from 3 to 14%, 6 to 14% and 4 to 10%, respectively) during the study.

At baseline, CAC was found in 41 patients (47%), while severe calcification was observed in 19 (46%) of them. During the follow-up, only 2 patients (4%) from the non-calcified group had an increase in calcium score. In contrast, the progression of CAC was observed in 25 out of 41 patients (64%) of the calcified group (Fig. 2). The group of patients who showed CAC progression was older (61.2 ± 8.9 vs 53.2 ± 10.6 years; p < 0.01) and had higher proportion of diabetes (44 vs 22%; p = 0.04) and males (85 vs 52%; p < 0.01) compared to those without CAC progression. The group of patients who showed CAC progression was older (61.2 ± 8.9 vs 53.2 ± 10.6 years; p < 0.01) and had higher probability of diabetes (44 vs 22%; p = 0.04) compared to those without CAC progression. In this group, most of the patients were male (85%). No other variable, including drug intervention, was different between the groups.

Osteopenia was found in 45% and osteoporosis in 13% of the patients at baseline. Compared to the patients with normal BMD, those with T-score < −1.0 (58%) showed lower BMI (25.8 ± 4.2 vs 28.6 ± 5.5 kg/m²; p < 0.01), a trend toward older age (57.2 ± 11.3 vs 52.9 ± 9.1 years; p = 0.06) and a higher percentage of Caucasians (55 vs 47%; p = 0.06). Considering the least significant change, 25% of the patients had a gain (from 0.034 to 0.112 g/cm²) and 22% had a loss (from 0.034 to 0.115 g/cm²) of BMD at the lumbar spine. At the total hip, 9% of the patients had a gain (from 0.032 to 0.074 g/cm²) and 14% had a loss (from 0.030 to 0.065 g/cm²) of BMD.

Out of the 85 participants in the study sample, 20 (24%), 41 (48%), and 21 (25%) patients were in the LOSS, UNCHANGED and GAIN groups, respectively. Three patients were excluded from the analysis due to presenting simultaneously gain of BMD at the lumbar spine and loss at

Table 1

| Characteristics of the patients at baseline and 12 months (n = 87). | Baseline | 12 months | p |
|---|---|---|---|
| **Age (years)** | 55.6 ± 10.7 | | |
| **Gender males (%)** | 54 (62) | | |
| **Caucasians (%)** | 45 (52) | | |
| **CKD etiology** | | | |
| Hypertension (%) | 24 (28) | | |
| Diabetes (%) | 21 (24) | | |
| Others (%) | 42 (48) | | |
| **Hypertension (%)** | 83 (95) | | |
| **Diabetes (%)** | 26 (30) | | |
| **Sedentary lifestyle (%)** | 65 (75) | | |
| **Smoking (%)** | 44 (51) | | |
| **Alcoholism (%)** | 8 (9) | | |
| **Medication (%)** | | | |
| ACE-inhibitor and ARB | 80 (92) | | |
| Thiazide diuretic | 24 (28) | | |
| Loop diuretic | 47 (54) | | |
| Calcium channel blocker | 32 (37) | | |
| Statin | 28 (32) | | |
| Calcium carbonate | 5 (6) | | |
| Sevelamer | 22 (25) | | |
| Calcitriol | 4 (4) | | |
| Erythropoietin | 3 (3) | | |
| **Laboratory parameters** | | | |
| Creatinine (mg/dL) | 2.04 ± 0.67 | 2.21 ± 0.94 < 0.01 |
| eGFR (mL/min/1.73m²) | 39.2 ± 18.1 | 37.8 ± 19.6 0.06 |
| Proteinuria (g/24 h) | 0.22 (0.0-0.63) | 0.41 (0-0.89) < 0.01 |
| Hemoglobin (g/dL) | 12.9 ± 1.8 | 13.5 ± 1.7 < 0.01 |
| Blood glucose (mg/dL) | 88 (81-106) | 89 (81-99) 0.62 |
| Ionized calcium (mmol/L) | 1.29 ± 0.06 | 1.31 ± 0.06 < 0.01 |
| Phosphorus (mg/dL) | 4.07 ± 0.7 | 4.07 ± 0.7 0.78 |
| Total alkaline phosphatase (U/L) | 81 (63-101) | 79 (62-99) 0.38 |
| iPTH (pg/mL) | 97 (61-152) | 101 (65-168) 0.33 |
| Bicarbonate (mmol/L) | 22.0 ± 3.1 | 22.5 ± 3.3 | |
| Total cholesterol (mg/dL) | 189 ± 38 | 169 ± 43 < 0.01 |
| LDL-cholesterol (mg/dL) | 105 ± 29 | 90 ± 35 < 0.01 |
| HDL-cholesterol (mg/dL) | 50 ± 13 | 46 ± 13 < 0.01 |
| Triglycerides (mg/dL) | 139 (99-218) | 133 (99-217) 0.27 |
| CRP (mg/dL) | 0.27 | 0.25 (0.08-0.58) 0.04 |
| Calcium score at baseline and 12 months in non-calcified and calcified groups. | | | |
| Calcium score (AU) | 378 (123-914) | 463 (134-1143) 0.04 |
| Calcium score (AU) in calcified group | 463 (134-1143) | | |
| Bone mineral density | | | |
| L1-L4 (g/cm²) | 1.147 ± 0.180 | 1.150 ± 0.182 0.59 |
| Total hip (g/cm²) | 0.990 ± 0.164 | 0.989 ± 0.166 0.59 |

Legend: Results are presented as mean ± SD, median (interquartile range), or n (%). CKD, chronic kidney disease; BMI, body mass index; ACE-inhibitor, angiotensin converting enzyme inhibitor; ARB, angiotensin-receptor blocker; eGFR, glomerular filtration rate estimated; iPTH, parathyroid hormone; LDL-cholesterol, low-density lipoprotein; HDL-cholesterol, high-density lipoprotein; CRP, high-sensitivity C-reactive protein; FGF-23, fibroblast growth factor 23; AU, Agatston units; L1-L4: lumbar spine.

Fig. 2. Calcium score at baseline and 12 months in non-calcified and calcified groups.

Legend: 0 mo., baseline; 12 mo., 12 months; AU, AU, Agatston units.
the total hip. Table 2 depicts the comparison among the BMD change groups. The GAIN group had a higher proportion of males compared to the UNCHANGED or LOSS groups (86 vs 54 vs 52%, respectively; \( p = 0.03 \)). During the follow-up, patients of the GAIN group had a reduction in serum alkaline phosphatase levels \([-8 \pm 17; 0 \text{ U/L}]\) compared to the UNCHANGED \([-2 \pm 9; 6 \text{ U/L}]\) or LOSS groups \([4 \pm 5; 15 \text{ U/L}]\), \( p = 0.01 \).

Fig. 3 shows the variation of calcium scores among the groups. The patients of GAIN group had an increase of calcium score \((17.5\% \pm 0; 56.4)\) compared to those of the UNCHANGED \((0\% \pm 0; 2)\) or LOSS groups \((0\% \pm 6; 2,3)\), \( p = 0.04 \). Additionally, the CAC progression was more frequent in the GAIN group compared to the UNCHANGED or LOSS groups \((57 \text{ vs } 22 \text{ vs } 25\%, \text{ respectively}; \ p = 0.01)\). Table 3 depicts the logistic regression analysis model. Male patients were found to be 5.7 and those with CAC progression 4.5 times more likely to be into the GAIN group. The decrease of 10 U/L in the levels of alkaline phosphatase increases by 40% the chance to be into the GAIN group.

4. Discussion

In this study half of the CKD patients changed bone mass evaluated by DXA after one year of follow-up. Unexpectedly, an increase of BMD values associated with a progression of vascular calcification was observed. However, one could consider that this association mirrors no actual increase in bone mass gain but rather increase of calcium deposits in the vessels.

Previous studies of our group have demonstrated that the loss of trabecular bone mass, evaluated by methods other than DXA, has been associated with vascular calcification progression in the CKD population (Barreto et al., 2008; Watanabe et al., 2012). Moreover, other authors showed that BMD loss evaluated by DXA at total hip was associated with CAC progression in the general population (Campos-Obando et al., 2015). To the best of our knowledge, the present study is the first one that prospectively investigated the BMD change by DXA and its association with CAC progression in CKD patients. Although DXA is the most common and available method to assess bone mass, it has several limitations, especially in patients with kidney dysfunction (Babayev and Nickolas, 2015; Jannot et al., 2017; Salam et al., 2014; Khairallah and Nickolas, 2018).

There is a relevant concern in the literature regarding the use of DXA, particularly analyzing the lumbar spine due to vascular calcification.

### Table 2

Characteristics of LOSS, UNCHANGED and GAIN groups.

|                  | LOSS \((n = 20)\) | UNCHANGED \((n = 41)\) | GAIN \((n = 21)\) | \( p \) |
|------------------|------------------|-----------------------|------------------|-----|
| Age (years)      | 58.1 ± 10.8      | 53.6 ± 11.5           | 57.9 ± 9.3       | 0.19 |
| Gender males (%) | 10 (50)          | 22 (54)               | 18 (86)          | 0.03 |
| Causcetans (%)   | 14 (70)          | 21 (51)               | 8 (38)           | 0.12 |
| Diabetes (%)     | 5 (25)           | 13 (32)               | 5 (24)           | 0.76 |
| Calcium score (AU at baseline) | 20 (0.356) | 0 (0.218) | 123 (0.704) | 0.53 |
| Laboratory changes |                  |                       |                  |     |
| eGFR (ml/min/1.73m²) | -1.9 ± 6.7 | -1.4 ± 5.6 | -0.9 ± 8.9 | 0.88 |
| Ionized calcium (mmol/L) | -0.01 ± 0.07 | 0.04 ± 0.05 | 0.02 ± 0.05 | 0.07 |
| Phosphorus (mg/dL) | 0.1 ± 0.5 | 0 ± 0.6 | -0.1 ± 0.5 | 0.67 |
| Total alkaline phosphate (U/L) | 4 \((–15)\) | -2 \((-9)\) | 8 \((-17)\) | 0.01 |
| iPTH (pg/mL) | 15 (0.45) | 3 \((-13)\) | -4 \((-49)\) | 1.17 |
| Bicarbonate (mmol/L) | -0.2 ± 3.0 | 1.3 ± 3.4 | 0.3 ± 3.0 | 0.19 |
| FGF-23 (pg/mL) | 7.0 \((-9.8\text{-}32.0)\) | 46.4 | 27.9 | 0.13 |

Legend: Results are presented as mean ± SD, median (interquartile range), or n (%). iPTH, parathyroid hormone; FGF-23, fibroblast growth factor 23.
progression. Reinforcing these findings, we recently showed that cortical, unlike trabecular bone loss, was not associated with vascular calcification progression in CKD patients (Costa et al., 2020). Moreover, an interesting study in end-stage renal disease patients showed that low trabecular bone analyzed by CT was better than DXA in predicting the presence of CAC at baseline and cardiovascular mortality (Chen et al., 2016). Thus, the sum of cortical and trabecular bone density by DXA might have jeopardized the interpretation of the results of our study.

Another finding in this study should be mentioned. There was a reduction of serum total alkaline phosphatase in the bone mass gain group which simultaneously had CAC progression. One could speculate that the reduction of alkaline phosphatase could reflect transition to low bone activity. Moreover, previous reports showed an association between low bone turnover disease with the development and progression of vascular calcification (Asci et al., 2011; Tomiyama et al., 2010; London et al., 2004).

It is important to mention some limitations of the present study. It is a post hoc analysis with a relatively small sample size and short follow-up. We could not analyze the skeletal sites separately due to the small sample of patients who changed bone mass at one unique site. Other BMD testing methods such as trabecular bone scans and central quantitative CT scans should be done to better evaluate bone mass in CKD population.

5. Conclusion

The increase in the value of BMD is likely no actual gain of bone mass but rather false results in CKD patients with vascular calcification. Thus, the use of DXA for the evaluation of bone mass, especially at the lumbar spine, must be applied with restraint and its results very carefully interpreted in that population.

CRediT authorship contribution statement

Layon S. Campagnaro: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Visualization. Alulzo B. Carvalho: Conceptualization, Methodology, Investigation, Writing – review & editing, Visualization, Supervision. Paula M. Pina: Investigation. Renato Watanabe: Investigation, Resources. Maria Eugenia F. Canziani: Conceptualization, Methodology, Investigation, Writing – review & editing, Visualization, Supervision, Project administration.

Declaration of competing interest

The authors have no conflicts of interest to declare. All co-authors have seen and agree with the contents of the manuscript and there is no financial interest to report. The results presented in this paper have not been published previously in whole or part.

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