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Original Article

Bone Density Is Directly Associated With Glomerular Filtration and Metabolic Acidosis but Do Not Predict Fragility Fractures in Men With Moderate Chronic Kidney Disease

Guilherme Alcantara Cunha Lima,[*,1] *Francisco de Paula Paranhos-Neto,*[1] *Luciana Colonese Silva,*[1] *Laura Maria Carvalho de Mendonça,*[2] *Alvimar Gonçalves Delgado,*[3] *Maurilo Leite Jr,*[3] *Carlos Perez Gomes,*[3] *and Maria Lucia Fleiuss Farias*[1]

[1]*Division of Endocrinology, Universidade Federal do Rio de Janeiro, Hospital Universitário Clementino Fraga Filho, Rio de Janeiro, Brazil;* [2]*Division of Rheumatology, Universidade Federal do Rio de Janeiro, Hospital Universitário Clementino Fraga Filho, Rio de Janeiro, Brazil; and* [3]*Division of Nephrology, Universidade Federal do Rio de Janeiro, Hospital Universitário Clementino Fraga Filho, Rio de Janeiro, Brazil*

Abstract

Hyperparathyroidism, vitamin D deficiency, increased fibroblast growth factor-23 (FGF-23), and metabolic acidosis promote bone fragility in chronic kidney disease (CKD). Although useful in predicting fracture risk in the general population, the role of dual-energy X-ray absorptiometry (DXA) in CKD remains uncertain. This cross-sectional study included 51 men aged 50−75 yr with moderate CKD. The stage 4 CKD patients had higher levels of parathyroid hormone ($p < 0.001$), FGF-23 ($p = 0.029$), and lowest 25-hydroxyvitamin D ($p = 0.016$), bicarbonate ($p < 0.001$), total femur ($p = 0.003$), and femoral neck ($p = 0.011$) *T*-scores compared with stage 3 CKD patients. Total femur and femoral neck *T*-scores were directly correlated with serum bicarbonate ($p = 0.003$, $r = 0.447$ and $p = 0.005$, $r = 0.427$, respectively) and estimated glomerular filtration rate ($p = 0.024$, $r = 0.325$ and $p = 0.003$, $r = 0.313$, respectively) but were not significantly associated with parathyroid hormone, 25-hydroxyvitamin D, or FGF-23. Only 3.9% of the participants had osteoporosis on DXA scan, whereas 31.4% reported a low-impact fracture. Our data point to a pivotal role of metabolic acidosis for bone impairment and to the inadequacy of DXA to evaluate bone fragility in CKD patients.

Key Words: Chronic kidney disease; dual-energy X-ray absorptiometry; FGF-23; fractures; metabolic acidosis.

Introduction

Chronic kidney disease-mineral and bone disorder (CKD-MBD) is the term used for the set of changes in bone mineral metabolism as well as its skeletal and cardiovascular complications in chronic renal patients, such as blood vessel calcifications *(1)*, deformities, fractures, and immobilization *(2−4)*.

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*Address correspondence to: Guilherme Alcantara Cunha Lima, MD, Departamento de Endocrinologia, Hospital Universitário Clementino Fraga Filho, Universidade Federal do Rio de Janeiro, Rua Prof. Rodolpho Paulo Rocco, 255 - Cidade Universitária - Ilha do Fundão, Rio de Janeiro-RJ, CEP: 21941-913, Brazil. E-mail: gaclima@yahoo.com.br

Several factors are involved in CKD-MBD pathophysiology, among them secondary hyperparathyroidism, vitamin D deficiency, increased fibroblast growth factor-23 (FGF-23), and metabolic acidosis *(5)*.

Secondary hyperparathyroidism is a major component of CKD-MBD *(5)*, and its origin is multifactorial, including vitamin D deficiency and increased FGF-23 *(6−8)*. The sustained elevation of parathyroid hormone (PTH) results in bone resorption, particularly at sites rich in cortical bone, such as femur and radius *(9)*. Another factor involved in bone disease is chronic metabolic acidosis, which leads to dissolution of bone mineral for buffering acidemia, resulting in bone fragility and malnutrition *(10)*.

Bone densitometry using dual-energy X-ray absorptiometry (DXA) is a practical and widely used method for measuring bone mass and determining fracture risk, with high accuracy in the general population *(11)*. However, the use of DXA in CKD remains uncertain *(12)*. This is explained by the fact that numerous factors correlated with CKD-MBD result in significant deterioration of bone quality, which stands beyond the amount of bone and hence cannot be quantified by DXA *(13)*.

In the present study, we tested the hypothesis that men aged 50−75 yr with moderate CKD presents decreased bone mineral density (BMD), particularly at sites rich in cortical bone, and that hyperparathyroidism, increased FGF-23, vitamin D deficiency, and metabolic acidosis can be related to DXA findings. We also evaluated the correlation between BMD, biochemical data, and low-impact fractures reported by patients to compare the prevalence of the diagnosis of osteoporosis by BMD vs based on historical low-impact fractures, as well as to assess the ability of these factors in predicting fractures in this population.

Materials and Methods

Study Design and Subjects

This is a cross-sectional observational study, in which the study population was composed of 51 men between 50 and 75 yr, with moderate renal impairment (estimated GFR [eGFR] 15−59 mL/min/1.73 m^2 according to the Modification of Diet in Renal Disease [MDRD] study equation) and followed as outpatients at the Nephrology and Cardiology Divisions of the Federal University of Rio de Janeiro Hospital. Men were chosen to avoid the effect of menopause on BMD. We excluded patients with a history of dialysis or transplantation, chronic smoking, previous parathyroid surgery, and other chronic diseases (such as rheumatoid arthritis, systemic lupus erythematosus, cancer, hyperthyroidism, and primary hyperparathyroidism) or medication (glucocorticoids, anticonvulsants, sodium bicarbonate, anticoagulants, bisphosphonates, and immunosuppressive drugs) directly related to the gain or loss of bone mass. The selected criteria aimed to minimize the influence of important confounding factors in bone mass. All participants underwent a prior interview about primary cause of CKD, low-impact fractures and for anthropometric measurements (weight, height, and body mass index) and were included in the study after signing the agreement and informed consent. This study was approved by the local research ethics committee.

Biochemical Data

Mean values of serum creatinine, calcium, phosphorus, alkaline phosphatase (ALP), bicarbonate, and serum intact PTH (iPTH) of the previous 6 mo were obtained for analysis. The eGFR was estimated by the MDRD formula (GFR [mL/min/1.73 m^2] = 175 × [serum creatinine—mg/dL]$^{-1.154}$ × [age—yr]$^{-0.203}$ × [1.210 if black]) *(14)*. The participants were divided in 2 groups according to their eGFR: stage 3 CKD (eGFR: 30−59 mL/min/1.73 m^2, n = 29 patients) and stage 4 CKD (eGFR: 15−29 mL/min/1.73 m^2, n = 22 patients) (*see* details in Table 1).

Creatinine, calcium, phosphorus, and ALP were measured by routine methods. Serum bicarbonate was obtained by venous gasometry. Serum iPTH was measured by chemiluminescent Immulite 2000 kit (Siemens, CA), normal range 11−67 pg/mL. Serum samples for 25-hydroxyvitamin D (25(OH)D) and FGF-23 were collected after overnight fast in the same morning DXA was performed, and aliquots were stored at −70°C until analysis. 25(OH)D was measured by electrochemiluminescent Elecsys 2010 kit (Roche, Berlin, Germany), normal range 30−100 ng/mL and FGF-23 by enzyme-linked immunosorbent assay (Millipore, Billerica, MA).

Dual-Energy X-ray Absorptiometry

BMD of lumbar spine, proximal femur, and radius was performed at a Prodigy Advance GE device (General Electric, Madison, WI), and the results were analyzed by the same experienced physician. Values were expressed by the *T*-scores.

Low-Impact Fractures

Fractures caused by major impact (e.g., automobile accident, run over, physical aggression), extremities (fingers and toes), and skull were not considered. Only low-impact fractures occurred after 50 yr and referred by the patients were considered. No active search for nonclinical vertebral fractures by X-rays or vertebral fracture assessment using DXA was done.

Statistical Analysis

Comparisons between the 2 groups were performed by using nonpaired Student's *t* test and Mann-Whitney *U*-test for parametric and nonparametric values, respectively. Categorical variables were compared by the Chi-square and Fisher exact tests. Pearson product moment correlation was used for correlation analyses. Multiple linear regression and multiple logistic regression were performed to predict quantitative and qualitative dependent variables from observations of more than 2 independent variables, respectively. Differences were considered significant when $p < 0.05$ (2-sided).

Results

The groups were comparable for primary cause of CKD, age, body mass index, and low-impact fractures reported by patients. The stage 4 CKD exhibited significant higher levels of iPTH, FGF-23, and ALP and lower serum levels of 25(OH)D and bicarbonate, in comparison to the stage 3 CKD. BMD *T*-scores were also lower in the stage 4 CKD in comparison to the stage 3 CKD for femoral neck and total femur values; no differences were found at radius 33% and lumbar spine (Table 1).