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Original Article

Bone Quality Assessment as Measured by Trabecular Bone Score in Patients With End-Stage Renal Disease on Dialysis

Maria P. Yavropoulou,[1] Vasilios Vaios,[2] Maria Pikilidou,[3] Ioannis Chryssogonidis,[4] Melina Sachinidou,[4] Symeon Tournis,[5] Konstantinos Makris,[5] Kalliopi Kotsa,[1] Michalis Daniilidis,[3] Afroditi Haritanti,[4] and Vassilios Liakopoulos[,2]*

[1]Division of Endocrinology and Metabolism, 1st Department of Internal Medicine, AHEPA University Hospital, Aristotle University of Thessaloniki, Greece; [2]Nephrology Division, 1st Department of Internal Medicine, AHEPA University Hospital, Aristotle University of Thessaloniki, Greece; [3]1st Department of Internal Medicine, AHEPA University Hospital, Aristotle University of Thessaloniki, Greece; [4]Radiology Unit AHEPA University Hospital, Aristotle University of Thessaloniki, Greece; and [5]Laboratory of Research of Musculoskeletal System "Th. Garofalidis", Medical School, KAT Hospital, University of Athens, Athens, Greece

Abstract

Patients with end-stage renal disease (ESRD) on maintenance hemodialysis (HD) exhibit osteoporosis and increased fracture risk. Dual-energy X-ray absorptiometry scan measurements and calculation of fracture risk assessment toll score underestimate fracture risk in these patients and do not estimate bone quality. Trabecular bone score (TBS) has been recently proposed as an indirect measure of bone microarchitecture. In this study, we investigated alterations of bone quality in patients with ESRD on HD, using TBS. Fifty patients with ESRD on HD, with a mean age 62 years, and 52 healthy individuals matched for age, body mass index, and gender, were enrolled. All participants had a bone mineral density (BMD) measurement by dual-energy X-ray absorptiometry scan at the lumbar spine, femoral neck, total hip, and 1/3 radius. TBS was evaluated using TBS iNsight. Serum fetuin-A and plasma fibroblast growth factor-23 (FGF-23) (C-terminal) were also measured. Patients on dialysis had significantly lower BMD values at all skeletal sites measured. Plasma FGF-23 levels significantly increased and serum fetuin-A significantly decreased in patients on dialysis compared with controls. TBS was significantly reduced in patients on dialysis compared with controls (1.11 ± 0.16 vs 1.30 ± 0.13, $p < 0.001$, respectively) independently of age; BMD; duration of dialysis; and serum levels of alkaline phosphatase, 25-OH-vitamin D, parathyroid hormone, fetuin-A, or plasma FGF-23. Patients on HD who were diagnosed with an osteoporotic vertebral fracture had numerically lower TBS values, albeit without reaching statistical significance, compared with patients on dialysis without a fracture (1.044 ± 0.151 vs 1.124 ± 0.173, respectively, $p = 0.079$). Bone microarchitecture, as assessed by TBS, is significantly altered in ESRD on patients on HD independently of BMD values and metabolic changes that reflect chronic kidney disease-mineral and bone disorder.

Key Words: Bone mineral density; chronic kidney disease; hemodialysis; osteoporosis; trabecular bone score.

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*Address correspondence to: Vassilios Liakopoulos, MD, PhD, Nephrology Division, 1st Department of Internal Medicine, AHEPA Hospital, School of Medicine, Aristotle University of Thessaloniki, 1 St. Kyriakidi Street, 54636, Thessaloniki, Greece. E-mail: liakopul@otenet.gr

Introduction

Chronic kidney disease (CKD) is frequently associated with low bone mass and increased risk of fragility fractures *(1,2)*. Especially for patients with CKD on dialysis, recent studies have reported that the prevalence of osteoporosis ranges between 13% and 35% *(3)*.

The pathologic changes that occur in bone structure as kidney function deteriorates are complex and include a wide spectrum of abnormalities in bone and mineral metabolism. Patients with CKD usually present with renal osteodystrophy, which includes the traditional histomorphometric forms of osteitis fibrosa cystica, osteomalacia, mixed renal bone disease, and adynamic bone disease *(4,5)*. A more recent term of chronic kidney disease-mineral and bone disorder (CKD-MBD) is currently used to describe the systemic disorder of the bone–vascular axis that except for the increased risk of fractures is also linked to vascular calcification, cardiovascular disease, and increased mortality *(6)*. In this more systemic concept of CKD-MB, other factors such as the phosphate regulator fibroblast growth factor-23 (FGF-23) and the calcification inhibitor fetuin-A are also involved. Elevated FGF-23 level is suggested to be an early biomarker of altered phosphorus metabolism in the initial stages of CKD, develops earlier than increased phosphate or parathyroid hormone (PTH) *(7)*, and acts as a strong predictor of mortality in patients on dialysis *(8)*. In bone biopsies of patients on dialysis, serum FGF-23 levels were significantly correlated with dynamic parameters such as mineralization lag time, activation frequency, and bone formation rate, but not with static, structural parameters such as osteoid maturation *(9)*. In addition, in in vivo studies with CKD mice models, neutralization of FGF-23 improved significantly histomorphometric parameters of bone quality, suggesting a link between FGF-23 and CKD-MBD *(10)*. Fetuin-A is a serum glycoprotein that apart from its anti-calcification activity is also a regulator of bone remodeling. Although most of fetuin-A is synthesized in the liver, recent data have shown that it is also produced by osteocytes and to a lesser extent by osteoblasts *(11)*. Low fetuin-A levels in patients with uremia have been associated with bone mineral density (BMD), fracture risk, vascular calcification, and cardiovascular disease *(12)*. In addition, it has been demonstrated that at cellular level FGF-23 produced by osteocytes regulates the expression of fetuin-A, linking the 2 proteins in the complex network of bone and vascular pathology *(11)*.

BMD measurement with dual-energy X-ray absorptiometry (DXA) for the diagnosis of osteoporosis and fracture risk assessment is currently recommended in patients with stages 1–3 of CKD *(4)*, but not in later stages of 4 or 5 and in patients on dialysis. However, recent evidence supports some predictive value of BMD on fracture risk in patients with end-stage renal disease (ESRD) on dialysis *(13–15)*, and a revision of Kidney Disease: Improving Global Outcomes (KDIGO) recommendations regarding the use of DXA in this population is being prepared *(16)*.

Trabecular bone score (TBS) has been recently introduced into clinical practice and is considered an indirect 2-dimensional measurement of bone microarchitecture at the appendicular skeleton that can be calculated by specific software installed in DXA *(17)*. Clinical studies assessing 3-dimensional bone microarchitecture parameters of the trabecular bone have demonstrated significant correlations with TBS, confirming its value in assessing bone quality and fracture susceptibility *(18–20)*. In addition, cross-sectional studies in postmenopausal women with osteoporosis have shown that TBS can add significant information on top of BMD measurement in assessing fracture risk *(21–24)*.

The value of TBS in evaluating fracture risk has also been tested and proven in secondary causes of osteoporosis such as diabetes mellitus type 2 and primary hyperparathyroidism *(25,26)*, but data are scarce in patients with CKD on dialysis *(27)*.

To investigate bone quality in patients with ESRD on hemodialysis (HD) by noninvasive methods, we calculated TBS in these patients and correlated its values with BMD, age, duration of dialysis therapy, and laboratory abnormalities. We also measured serum fetuin-A and plasma FGF-23 levels in an attempt to have the full picture of the possible associations of bone microarchitecture, as assessed by TBS, with other factors that reflect bone and vascular abnormalities in these patients.

We hypothesized that TBS values could add significant information on the evaluation of bone disease in these patients and could be easily obtained in routine clinical practice.

Patients and Methods

Study Population

This is a cross-sectional case-control study in which we screened all patients with ESRD undergoing chronic HD and were under regular follow-up in the Dialysis Unit of AHEPA University Hospital. Eligible patients were postmenopausal women and men aged >40 years old. Exclusion criteria were impaired liver function; malignancy; diabetes mellitus type 1 or type 2; the presence of diseases known to affect bone turnover other than osteoporosis, such as Paget's disease of bone; primary hyperparathyroidism; hypo- or hyperthyroidism; medication known to affect bone metabolism such as bisphosphonates and/or calcimimetics; and the use of glucocorticoids at any dosage or form at the last 6 months before enrollment. Healthy individuals matched for age, body mass index (BMI), and gender were recruited as controls from the personnel of AHEPA University Hospital.

All participants had a BMD measurement by DXA (Lunar Prodigy, General Electric, San Francisco, CA) at the lumbar spine in posterior-anterior projection (L1–L4) (LS-BMD, at 2 femoral sites: femoral neck [FN-BMD] and total femur [TH-BMD]) and in the nondominant forearm at the