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Original Investigation

Diagnostic Accuracy of Bone Turnover Markers and Bone Histology in Patients With CKD Treated by Dialysis

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Background: The management of chronic kidney disease–mineral and bone disorder requires the assessment of bone turnover, which most often is based on parathyroid hormone (PTH) concentration, the utility of which remains controversial.

Study Design: Cross-sectional retrospective diagnostic test study.

Setting & Participants: 492 dialysis patients from Brazil, Portugal, Turkey, and Venezuela with prior bone biopsy and stored (−20°C) serum.

Index Tests: Samples were analyzed for PTH (intact [iPTH] and whole PTH), bone-specific alkaline phosphatase (bALP), and amino-terminal propeptide of type 1 procollagen (P1NP).

Reference Test: Bone histomorphometric assessment of turnover (bone formation rate/bone surface [BFR/BS]) and receiver operating characteristic curves for discriminating diagnostic ability.

Results: The biomarkers iPTH and bALP or combinations thereof allowed discrimination of low from nonlow and high from nonhigh BFR/BS, with an area under the receiver operating characteristic curve $>$ 0.70 but $<$ 0.80. Using iPTH level, the best cutoff to discriminate low from nonlow BFR/BS was $<$103.8 pg/mL, and to discriminate high from nonhigh BFR/BS was $>$323.0 pg/mL. The best cutoff for bALP to discriminate low from nonlow BFR/BS was $<$33.1 U/L, and for high from nonhigh BFR/BS, 42.1 U/L. Using the KDIGO practice guideline PTH values of greater than 2 but less than 9 times the upper limit of normal, sensitivity and specificity of iPTH level to discriminate low from nonlow turnover bone disease were 65.7% and 65.3%, and to discriminate high from nonhigh were 37.0% and 85.8%, respectively.

Limitations: Cross-sectional design without consideration of therapy. Potential limited generalizability with samples from 4 countries.

Conclusions: The serum biomarkers iPTH, whole PTH, and bALP were able to discriminate low from nonlow BFR/BS, whereas iPTH and bALP were able to discriminate high from nonhigh BFR/BS. Prospective studies are required to determine whether evaluating trends in biomarker concentrations could guide therapeutic decisions. *Am J Kidney Dis.* 67(4):559-566. © *2016 by the National Kidney Foundation, Inc.*

INDEX WORDS: Sensitivity and specificity; alkaline phosphatases; bone-specific alkaline phosphatase (bALP; BSAP); bone histomorphometry; chronic kidney disease–mineral bone disorder (CKD-MBD); parathyroid hormone (PTH); procollagen type 1 N propeptide (P1NP); renal osteodystrophy.

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Chronic kidney disease (CKD) is a significant public health problem, afflicting ∼11% of the American adult population[1] with a similar prevalence worldwide.[2] Disturbances of mineral metabolism, which occur in nearly all patients with CKD stages 3 to 5D, are associated with bone loss and fractures, cardiovascular disease, inflammation, abnormal immune function, and increased mortality.[3] Mineral abnormalities and renal osteodystrophy in CKD and more recently, their association with extraosseous calcifications, have been topics of great interest and controversy.[4-8]

In 2006, KDIGO (Kidney Disease: Improving Global Outcomes), an international initiative with a key mission of developing clinical practice guidelines concerning CKD, published a position statement proposing a new approach to classifying bone and mineral disorders termed CKD–mineral and bone disorder (CKD-MBD).[9] This was defined as a systemic disorder, with renal osteodystrophy being redefined as one

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of the components of CKD-MBD, and the recommendation was to only use this term to delineate bone histopathologic findings. The gold standard for the diagnosis and specific classification of renal osteodystrophy is a bone biopsy with bone histomorphometry.[9,10] There is heterogeneity of histologic abnormalities observed in patients with CKD,[11] and patients may develop different lesions as CKD progresses. The classic description of the histologic abnormalities includes hyperparathyroid bone disease, adynamic bone disease, osteomalacia, and mixed uremic osteodystrophy.[11-14] The KDIGO consensus conference agreed on a new classification of renal osteodystrophy that addresses the most important bone abnormalities, which include changes in bone turnover (T), mineralization (M), and volume (V).[9] The TMV classification is consistent with the classically used classification system.[11-14]

The main focus on renal osteodystrophy has been to assess bone disease based on bone turnover, from low to high. Because bone turnover is a function in large part of the degree of hyperparathyroidism, circulating parathyroid hormone (PTH) levels have traditionally been used as a surrogate indicator of bone turnover. Intact PTH (iPTH), together with PTH ratio, has been studied for the diagnosis of bone turnover in dialysis patients,[15,16] and differences between whites and blacks have been shown.[16] However, the assay for determining PTH ratio is not widely available. Together with serum calcium, phosphorus, and total alkaline phosphatases or bone-specific alkaline phosphatase (bALP), PTH levels are used to guide the pharmacologic treatment of CKD-MBD. However, using PTH levels from random serum samples as the primary criteria for defining and monitoring bone turnover alterations in CKD is an oversimplification of the complexity that governs this process. In addition, differences in intermethod (assay) PTH standards, variability, and reference ranges[17-19] have led to confusion about the use of PTH as a bone biomarker. Additional bone biomarkers have also been evaluated for their predictive value in assessing renal osteodystrophy, but sample sizes of these studies were small and inconclusive.[20,21] Information evaluating renal bone disease with the currently used PTH assays alone or in combination with other bone biomarkers and the utility of classifying renal osteodystrophy with the TMV system are limited.[22,23] Thus, in order to better define the relative diagnostic value of various circulating biomarkers that are currently in clinical use alone or as a panel, KDIGO led an international consortium in a cross-sectional retrospective diagnostic test study. The goal of this study was to determine the predictive value of serum levels of PTH (determined by both iPTH and whole PTH assays), bALP, and amino-terminal propeptide of type 1 procollagen (P1NP) as markers of bone turnover.

METHODS

Study Population and Data Collection

Data and serum samples were obtained from clinical programs in Brazil, Portugal, Turkey, and Venezuela. All patients from the 4 study sites who had been treated with dialysis for at least 3 months and had a reported histomorphometric analysis of a bone biopsy specimen and stored serum drawn within 30 days of the acquisition of the bone biopsy specimen were included in the study. All blood specimens were obtained from November 1993 through June 2007 and stored frozen at below −20°C until analyzed in November 2008. Additional data collected included demographics (age, sex, ethnicity, country of origin, and dialysis modality and vintage), biopsy technique, health history (cause of CKD, time since first diagnosis of CKD, history of diabetes mellitus, parathyroidectomy, or previous kidney transplantation), biochemical parameters (calcium, phosphorus, and iPTH), and treatment information (vitamin D, type of vitamin D, phosphate binder, and type of binder) at the time of the biopsy (Table 1).

Serum Biochemistry

All serum biomarkers were measured by a single central laboratory (Nordic Biochemical Research Laboratory, Herlev, Denmark). Reference ranges for P1NP were 13.9 to 85.5 ng/mL for men, 15.1 to 58.6 ng/mL for premenopausal women, and 20.3 to 76.3 ng/mL for postmenopausal women. The laboratory measured iPTH using a chemiluminescence immunoassay on a Roche Elecsys 2010 Analyzer; this assay detects both iPTH and a fragment containing amino acids 7 to 84; the reference range is 15.0 to 65.0 pg/mL. The laboratory measured whole PTH with an immunoradiometric assay kit from Scantibodies Laboratories; this assay is specific for PTH isoforms containing amino acids 1 to 84, and the reference range is 6.0 to 32.0 pg/mL. bALP was measured by an immunoassay from Quidel (reference range, 15.0-41.3 U/L for men, 14.2-42.7 U/L for postmenopausal women, and 11.6-29.6 U/L for premenopausal women). All serum samples were stored at below −20°C for various periods. Specimen collection and storage condition characteristics, temperature settings (−80°C vs −20°C), and specimen age were recorded.

Bone Biopsy and Histomorphometry

Histologic interpretation of bone biopsy specimens were completed at the Bone Diagnostic and Research Laboratory, University of Kentucky, Lexington (for biopsies from patients from Turkey); Federal University of São Paulo, São Paulo, Brazil; University of São Paulo Renal Physiopathology Laboratory, São Paulo, Brazil (for biopsies from Brazil and Portugal); and University Hospital of Caracas, Caracas, Venezuela (for biopsies from Venezuela) The histomorphometric parameter used for analysis of bone turnover is bone formation rate/bone surface (BFR/BS). Each laboratory used their normative data to classify BFR/BS as either low, normal, or high (Table S1, available as online supplementary material).

Statistical Analysis

Descriptive statistics were presented as mean ± standard deviation and median; frequency and percentage were presented for data with tabulation. Correlations between biomarkers were assessed by computing a Spearman correlation coefficient. Analysis of variance (ANOVA) or nonparametric counterpart Kruskal-Wallis test was used to detect between-group difference; post hoc pairwise comparison was Bonferroni adjusted (for ANOVA) or by Terpstra permutation test (for nonparametric test). Logistic regression analysis was conducted to derive the area under the receiver operating characteristic (ROC) curve (AUROC) to determine the diagnostic ability for bone turnover of the biomarkers. AUROC $>$ 0.7 is very good, $>$0.8 is excellent, and $>$0.9 is